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Comparison of Adenoma Detection Rate Between Three-dimensional and Standard Colonoscopy: A Multicenter Randomized Controlled Trial

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Abstract:

Background and study aim:

Improvement of adenoma detection rate (ADR) effectively reduces the subsequent incidence of colorectal cancer (CRC). Three-dimensional (3D) colonoscopy provided more anatomical details than standard two-dimensional (2D) colonoscopy and improved ADR in a simulation study. We aimed to compare the ADR between 2D and 3D colonoscopy.

Patients and methods:

In this multicenter randomized controlled trial, subjects aged ≥ 40 years who underwent colonoscopy for screening, surveillance, or symptoms were consecutively enrolled between February 2022 and June 2023 and randomized into 2D or 3D groups with a 1:1 ratio. The primary outcome was ADR. The secondary outcomes included the detection rates of flat adenoma, right-sided adenoma, proximal adenoma, sessile serrated lesion and advanced adenoma.

Results:

Of the 348 participants recruited, 158 and 160 were allocated to 2D and 3D colonoscopy, respectively. The mucosa inspection time was comparable between the 3D (9.8±2.6 minutes) and 2D (9.4±3.1 minutes) groups (p=.21). The 3D group had significantly higher ADR (53.1% vs. 38.6%, difference (95% confidence interval, CI): 14.5% (3.7-25.4), p=.0094), as well as higher detection rates for flat adenoma (35.0% vs. 21.5%, difference: 13.5% (3.7-23.3), p=.0076), right-sided adenoma (26.3% vs. 15.2%, difference: 11.1% (2.2-19.9), p=.015), proximal adenoma (38.1% vs. 23.4%, difference: 14.7% (4.7-24.7), p=.0045) and adenoma sized 5-9mm (45.0% vs. 31.0%, difference: 14.0% (3.4-24.5), p=.010). However, there was no difference in the detection rate of sessile serrated lesion and advanced adenoma.

Conclusions:

3D colonoscopy improved the detection of adenomas without significantly increasing the mucosa inspection time. (ClinicalTrials.gov: NCT05153746)

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Comparison of Adenoma Detection Rate Between Three-dimensional and Standard Colonoscopy: A Multicenter Randomized Controlled Trial

Short title: Adenoma Detection Rate with 3D colonoscopy

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Drafting and revision of the manuscript: Wei-Yuan Chang, Li-Chun Chang, Wei-Chih Liao, Han-Mo Chiu

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Data Transparency Statement:

Appropriate academic parties may contact Li-Chun Chang (lichunchang@ntu.edu.tw) for the statistical code, and de-identified participant dataset that underlies the results reported in this article, per the data sharing policies of the National Taiwan University Hospital and the Ministry of Health and Welfare of the Taiwanese Government, with input from the investigator group where applicable after receipt of the research proposal.

Abstract

Background and study aim:

Improvement of adenoma detection rate (ADR) effectively reduces the subsequent incidence of colorectal cancer (CRC). Three-dimensional (3D) colonoscopy provided more anatomical details than standard two-dimensional (2D) colonoscopy and improved ADR in a simulation study. We aimed to compare the ADR between 2D and 3D colonoscopy.

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In this multicenter randomized controlled trial, subjects aged ≥ 40 years who underwent colonoscopy for screening, surveillance, or symptoms were consecutively enrolled between February 2022 and June 2023 and randomized into 2D or 3D groups with a 1:1 ratio. The primary outcome was ADR. The secondary outcomes included the detection rates of flat adenoma, right-sided adenoma, proximal adenoma, sessile serrated lesion and advanced adenoma.

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Of the 348 participants recruited, 158 and 160 were allocated to 2D and 3D colonoscopy, respectively. The mucosa inspection time was comparable between the 3D (9.8±2.6 minutes) and 2D (9.4±3.1 minutes) groups (*p*=.21). The 3D group had significantly higher ADR (53.1% vs. 38.6%, difference (95% confidence interval, CI): 14.5% (3.7-25.4), *p*=.0094), as well as higher detection rates for flat adenoma (35.0% vs. 21.5%, difference: 13.5% (3.7-23.3), *p*=.0076), right-sided adenoma (26.3% vs. 15.2%, difference: 11.1% (2.2-19.9), *p*=.015), proximal adenoma (38.1% vs. 23.4%, difference: 14.7% (4.7-24.7), *p*=.0045) and adenoma sized 5-9mm (45.0% vs. 31.0%, difference: 14.0% (3.4-

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Conclusions:

3D colonoscopy improved the detection of adenomas without significantly increasing the mucosa inspection time. (ClinicalTrials.gov: NCT05153746)

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide[1]. Most sporadic CRCs arise from pre-existing adenomas[2], and removal of these precancerous lesions has been shown to effectively reduce both the incidence and mortality of CRC[3,4]. Therefore, the effectiveness of colonoscopy in protecting against CRC hinges on the detection and removal of adenomas, and adenoma detection rate (ADR) is the most important quality indicator of colonoscopy. Previous research showed that a 1% increase in ADR can reduce CRC incidence and mortality by 3% and 5%, respectively[5]. Therefore, various modalities have been developed to improve ADR, including image-enhancing technologies[6], chromoendoscopy[7], and devices enhancing exploration of the mucosa[8,9].

Despite improvements in ADR conferred by those modalities, post-colonoscopy colorectal cancer (PCCRC) remains a concern[10]. The incidence of PCCRC has been reported at 8.6% within three years[11], with more than 80% of PCCRCs being attributed to missed adenomas[12,13]. Notably, flat and proximal adenomas are independently associated with the development of PCCRC and particularly difficult to detect, posing significant challenges in improving ADR[12,14,15].

Three-dimensional (3D) endoscopy provides 3D visualization with superior depth perception over conventional two-dimensional (2D) endoscopy and may thereby enhance detection of flat/superficial lesions and subtle mucosal changes. 3D endoscopy has shown promise in enhancing the detection of

superficial gastric neoplasms and accuracy in assessing morphology[16]. 3D endoscopy had also been proposed to enhance the detection of colonic adenomas, showing a 25% increase in adenoma detection in a study using simulated 3D colonoscopy in a synthetic colon model[17,18]. However, whether 3D colonoscopy could improve ADR and facilitate detection of flat polyps compared with standard 2D colonoscopy in clinical colonoscopic practice remains to be studied.

MonoStereo 3D endoscopic visualization system (MedicalTek Co. Ltd, Taichung, Taiwan) is a novel 3D endoscopy system which performs real-time conversion of standard 2D images to realistic 3D visualization during endoscopy and has been approved for clinical use[19,20]. We hypothesized that the 3D endoscopic visualization system could enhance polyp detection during colonoscopy, especially for flat/superficial polyps. Therefore, we conducted a randomized controlled trial (RCT) to investigate whether 3D colonoscopy improved adenoma detection over standard 2D colonoscopy.

MATERIAL AND METHODS

Study design

This was a prospective multicenter randomized, open-label, single-blind trial conducted in one referral center and two regional hospitals in Taiwan. Complying with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, this trial was approved by the institutional review board of National Taiwan University Hospital (No.202109112DIPB) and registered at ClinicalTrials.gov (NCT05153746). An independent data and safety monitoring

committee monitored the progress of the trial, with regular assessment of safety outcomes, overall trial integrity, and trial performance.

Participants

Subjects aged 40 or older who were scheduled for colonoscopy for screening, surveillance, or symptoms at outpatient clinics in the participating institutions were consecutively assessed for eligibility. Subjects with a contraindication to colonoscopy or polypectomy or with a history of inflammatory bowel disease and hereditary polyposis syndrome were excluded.

Randomization and masking

The participants were randomized centrally by research assistants at the endoscopy units before the start of colonoscopic examinations in a 1:1 ratio without stratification using a computer-generated randomization sequence with a block size of twenty. Allocation concealment was ensured by storing the group allocation in ordered, sealed, and opaque envelopes. The patients and research assistants who assessed the outcomes were blinded to the group allocation to avoid bias.

Procedures

Three-dimensional colonoscopy

Figure 1a illustrates the MonoStereo 3D endoscopic visualization system (MedicalTek Co. Ltd, Taichung, Taiwan). 2D images (**Figure 1b**, right screen in **Figure 1d**) are converted in 80 milliseconds to images (**Figure 1c**, left screen in **Figure 1d**) which yield immersive 3D images through polarized glasses, providing real-time 3D imagery without perceptible time lag (**Figure 1d**) (**Video**). The system offers three pupillary distance selections to mitigate

eyestrain, and endoscopists are recommended to identify the optimal personal selection before first use by finding the selection yielding the most vivid 3D imagery. The system does not require calibration before examination; endoscopists are advised to place the 3D screen at eye-level and stand in front of the screen at a distance tailored to individual preference (generally 100 cm to 150cm for a 31”/32” screen). Instantaneous switch between 3D and standard 2D displays is achieved by pressing a button. As the polarized glasses do not change the visual perception of the surrounding environment or standard 2D endoscopic images, the endoscopist do not need to remove the glasses when not using the 3D display.

Intervention and colonoscopy

Study colonoscopies were performed by three junior (colonoscopy experience < 5000) and one senior colonoscopist (colonoscopy experience ≥ 5000). Before the commencement of the study, the participating colonoscopists received an introduction on the 3D technology and equipment and performed 3D colonoscopy using a colonoscopy simulator. Each colonoscopist was then requested to use 3D colonoscopy in conjunction with standard 2D colonoscopy for mucosa inspection during colonoscope withdrawal in at least ten colonoscopic procedures (**Figure 1d**).

For the RCT, high definition colonoscopes (290 series, Olympus, Tokyo, Japan) and video processors (EVIS Lucera Elite, Olympus, Tokyo, Japan) were used for colonoscopy. Bowel preparation and image-enhanced endoscopy were performed in the same way in both groups. Standard 2D colonoscopy was used for colonoscope insertion as in routine clinical practice in both groups. The

use of distal attachment devices, such as cap or cuff, was prohibited. After the cecum was intubated, colonoscope withdrawal was performed exclusively with 2D or 3D images as per allocation. A standardized protocol for photo documentation of individual colonic segments and a withdrawal time of 6 minutes or longer were required during colonoscope withdrawal. During withdrawal, image-enhanced endoscopy (narrow-band imaging or chromoendoscopy with indigo carmine) was routinely used for suspicious lesions, and adenomas were removed/resected. The size, morphology, and location of each polyp were recorded, and specimens were sent for histological examination. The time for optic diagnosis and polyp removal was defined as therapeutic time. Mucosa inspection time was defined as withdrawal time minus therapeutic time. Participants were excluded for analysis if the colonoscopic examination was incomplete, defined as a failure of cecal intubation or poor bowel preparation. In line with the established clinical workflow of the participating institutions, bowel preparation was assessed with the modified Aronchick bowel preparation scale[21,22].

Outcomes

The primary outcome was ADR, defined as the proportion of patients with at least one adenoma detected during colonoscopy. Secondary outcomes were flat (Paris classification 0-IIa, 0-IIb, or 0-IIc) ADR (fADR), sessile (Paris classification 0-Is) ADR, right-sided (cecum and ascending colon) ADR (rADR), left-sided (transverse colon to rectum) ADR (lADR), proximal (cecum to splenic flexure) ADR (pADR), distal (descending colon to rectum) ADR (dADR), sessile serrated lesion detection rate (SSLDR), advanced adenoma detection rate

(AADR), ADR stratified by size (<5 mm, 5-9 mm, ≥10 mm), polyp detection rate (PDR), mean adenoma number per patient and mean polyp number per patient. AA was defined as adenomas with size ≥10 mm, villous component, or high-grade dysplasia according to World Health Organization classification[23].

Statistical analysis

A simulation study suggested that 3D colonoscopy could increase the ADR by 60% (from 42.7% to 67.7%) compared to standard colonoscopy[18]. Following international guidelines, we set the ADR with standard colonoscopy at 25%[24]. To detect a 60% increase in ADR between 3D and standard colonoscopy (40% vs. 25%) with an 80% statistical power and a 2-sided significance level of 0.05, a minimum of 150 participants per group was needed. Accounting for potential exclusions or dropouts of approximately 10%, the enrollment target was at least 165 participants for each group. The analysis was by intention-to-treat. Categorical variables were summarized using frequencies and percentages, and continuous variables as means and standard deviations (SDs). Statistical significance for categorical variables was tested using the Pearson chi-square test, and differences between groups for continuous variables were tested using the independent sample t-test. Univariable and multivariable logistic regression analyses were conducted to identify factors predictive of adenoma detection. Variables with a *p* value less than 0.05 in the univariable analysis were included in the multivariable analysis, and variance inflation factor was used to detect multicollinearity. Post-hoc analysis of the temporal changes in ADR and mucosa inspection time was conducted to explore the learning curve of 3D colonoscopy. All analyses were performed using STATA software

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(StataCorp, College Station, TX, USA). All tests were 2-tailed, and differences were considered significant if $p<.05$.

RESULTS

Patients

From February 2022 through June 2023, a total of 348 subjects were screened for eligibility (**Figure 2**), and 339 consented to participate. 334 subjects underwent colonoscopy and were randomly allocated to either the 2D or 3D group (each n=167). After excluding cases with incomplete colonoscopy and inadequate bowel preparation, 158 and 160 subjects in the 2D and 3D groups were analyzed, respectively. There was no crossover between the two groups.

Baseline characteristics

The baseline characteristics and clinical information are summarized in **Table 1**. Among the 318 enrolled participants, 150 (47.2%) were men and the mean age was 61.9±10.6 years. Most (69.8%) of the recruited subjects were asymptomatic, and the major indication for colonoscopy among the asymptomatic patients was positive fecal immunochemical test (FIT) or surveillance colonoscopy. The groups were comparable in age, sex, family history of CRC, cigarette and alcohol consumption, antithrombotic agent use, underlying diseases, colonoscopy indications, and bowel preparation status. There was no significant difference between the two groups in mucosa inspection time among the entire cohort (2D vs. 3D: 9.4±3.1 vs. 9.8±2.6 minutes, $p=.21$).

Outcomes

The 3D colonoscopy function was successfully implemented in all cases allocated to the 3D group without temporary equipment dysfunction during the colonoscopic procedures. For the two groups combined (n=318), PDR and ADR were 54.4% and 45.9%, respectively. ADR was significantly higher in the 3D group compared with the 2D group (53.1% vs. 38.6%, difference (95% confidence interval [CI]: 14.5% (3.7-25.4), odds ratio (OR) (95%CI): 1.80 (95% CI:1.15-2.82), *p*= .0094 (**Table 2**). Regarding the secondary outcomes, the 3D group had higher detection rates of flat adenomas (3D vs. 2D: 35.0%, vs. 21.5%, difference (95% CI): 13.5% (3.7-23.3), OR (95% CI): 1.96 (1.19-3.24), *p*=.0076), right-sided adenomas (3D vs. 2D: 26.3% vs. 15.2%, difference (95% CI): 11.1% (2.2-19.9), OR (95% CI): 1.98 (1.14-3.48), *p*=.015), proximal adenomas (3D vs. 2D: 38.1% vs. 23.4%, difference (95% CI): 14.7% (4.7-24.7), OR (95% CI): 2.02 (1.24-3.28), *p*=.0045), and small-sized adenomas (5-9mm) (3D vs. 2D: 45.0% vs. 31.0%, difference (95% CI): 14.0% (3.4-24.5), OR (95% CI): 1.82 (1.15-2.88), *p*=.010) compared with the 2D group. The number of adenoma per patient was also higher in the 3D group (median (interquartile range, IQR), 2D vs. 3D: 0 (0-1) vs. 1 (1-2), *p*=.028). As all individuals with adenomas had at least one left-sided adenoma (adenomas at transverse, descending, sigmoid colon, or rectum), the left-sided ADR was equivalent to overall ADR in both groups. There was no significant difference in the detection rate of sessile adenoma, distal adenoma, AA and SSL.

Factors associated with adenoma detection

In the univariable logistic regression analysis, age, hypertension, FIT positivity, bowel preparation (excellent/good vs fair), mucosa inspection time,

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and 3D colonoscopy were significantly associated with adenoma detection (**Table 3**). The multivariable analysis showed that 3D colonoscopy was independently associated with adenoma detection (adjusted OR (aOR) (95%CI): 1.76 (1.09-2.83)) after adjusting for FIT positivity, mucosa inspection time, and other confounders. Age (aOR: 1.03 (1.01–1.06)) and mucosa inspection time (aOR: 1.16 (1.06–1.28)) were also independently associated with adenoma detection.

Temporal changes in ADR and mucosa inspection time

Compared with the 2D group, the mean mucosa inspection time in the 3D group was significantly longer in the first 40 exams (11.1±2.6 vs. 9.6±2.6 minutes, p=.012) but became comparable afterward (**Table 1** & **Figure 3a**). Similar trends were observed in each endoscopist with inter-endoscopist variations. The learning curve, as inferred by the difference in mucosa inspection time between 3D and 2D colonoscopy, seemed shortest for the senior colonoscopist, with the time difference reduced from 2.8 minutes for procedure 1~10 to 0.5 minute for procedure 11~ 20. By contrast, one junior endoscopist appeared to have the longest learning curve (time difference: 1.9, 0.9, and 0.5 minutes for procedure 1~10, 11~20, and 21~30, respectively). On the other hand, ADR in the 3D group was consistently higher than that in the 2D group by approximately 15% throughout the study, even among the first 40 exams (**Figure 3b**). All endoscopists achieved numerically higher ADR with 3D colonoscopy (difference in ADR, 3D minus 2D: senior endoscopist: 12%; junior endoscopists: 12.5%, 21.6%, and 50%, respectively). However, per-endoscopist analyses on differences in mucosa inspection time and ADR were

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post-hoc and had limited sample size and thus should be interpreted as exploratory.

DISCUSSION

This RCT conducted in individuals aged 40 or older showed that 3D colonoscopy resulted in a significant 15% increase in ADR, as well as in the detection rates of small, flat, right-sided and proximal neoplasms which are commonly overlooked by standard 2D colonoscopy. Notably, 3D colonoscopy enhanced polyp detection without increasing the mucosa inspection time and could be used in conjunction with other image-enhancing modalities such as narrow-band imaging and chromoendoscopy.

Enhancing the ADR is crucial for reducing the incidence of PCCRC and associated mortality[5]. Despite the multitude of advanced image processing technologies that have been developed to improve adenoma detection[6], the incidence of PCCRC remains as high as 8% in Asia and Europe and is mainly attributed to missed neoplasms during colonoscopy[11,25,26]. Neoplasms with flat morphology, particularly those located in the proximal colon, are more likely to be overlooked[27]. The larger colonic folds in the proximal colon where neoplasms are more often flat further compound adenoma detection[28]. This study corroborated the notion that 3D colonoscopy enhances anatomical details and depth perception and thereby facilitates identification of those hard-to-detect neoplasms. Our finding that 3D colonoscopy improved ADR and detection for flat, right-sided or proximal adenomas supported for its potential to reduce PCCRCs, warranting further long-term follow-up research. Multicenter clinical trials and real-world studies, advocacy by gastroenterology societies

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and opinion leaders, regulatory approval, and education/training are crucial for the dissemination of 3D colonoscopy.

The finding that 3D colonoscopy mainly enhanced the detection of polyps 5-9 mm in size might be attributed to that such polyps were on the verge of being missed or detected (i.e., near the threshold of detection) on 2D colonoscopy; therefore, enhanced depth perception conferred by 3D colonoscopy significantly increased the ability to detect those polyps. By contrast, polyps 1-5 mm might remain difficult to detect despite enhanced depth perception and thus 3D colonoscopy did not significantly improve detection. In line with this notion, studies on chromoendoscopy using indigo carmine found no or minimal improvement in detecting adenomas 1-5mm [29,30]. On the other hand, polyps >10 mm could be easily detected on 2D colonoscopy, with limited room for further improvement by 3D colonoscopy.

It is worth noting that while high ADRs (ADR 38.6%, rADR 15.2%, pADR 23.4%, fADR 21.5%) were achieved by standard 2D colonoscopy with a mean mucosa inspection time of approximately 9 minutes, 3D colonoscopy could further increase the ADRs by approximately 15% (ADR 53.1%, rADR 26.3%, pADR 38.1%, fADR 35.0%). The ADRs of the 2D group in our study was in line with a recent RCT by Zhao et al. which showed that 2D white light colonoscopy with a mucosa inspection time of 9 minutes achieved ADR, pADR, and fADR of 36.6%, 21.4%, and 27.4%, respectively[31]. An odds ratio of 1.76 for detecting adenomas after adjusting for mucosa inspection time and other confounders firmly supported that 3D colonoscopy provided distinctive advantage over 2D colonoscopy in adenoma detection that cannot be provided by alternative

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means such as increasing the mucosa inspection time. Whether 3D colonoscopy could provide greater benefit over standard 2D colonoscopy in real clinical settings where the mucosa inspection time is shorter than 9 minutes warrants further study.

Our exploratory analysis supported that 3D colonoscopy has a short learning curve and consistently confers an improvement in ADR even during the learning phase. The finding suggested a learning curve between 10 and 20 procedures for 3D colonoscopy with inter-endoscopist variation. Taken together, the consistent benefit in ADR and short learning curve supported that 3D colonoscopy could be easily adopted by endoscopists in routine colonoscopy practice.

A recent cross-over RCT including patients younger than 40 years compared 2D then 3D vs. 3D then 2D colonoscopy (i.e., tandem colonoscopy) and showed that ADR in the first exam was comparable between 3D and 2D colonoscopy (24.7% vs. 23.8%), whereas in the second exam ADR was significantly higher with 3D compared with 2D (13.8% vs. 9.9%)[32]. However, the tandem colonoscopy design could introduce bias, because the diagnostic performance of the latter exam was influenced by the findings of the first one. In contrast, the parallel design of this study minimized bias, better reflected clinical reality, and used ADR, the surrogate for PCCRC, as the primary outcome. Notably, the ADR of the first colonoscopy in the previous study did not differ between 2D and 3D and seemed lower than that in the current study, probably due to the shorter withdrawal time (<6 minutes) and the inclusion of younger patients (aged 18 to 40) in that study. In contrast, the current study enrolled

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individuals aged over 40 and thus the results should be more generalizable to the examinees of clinical colonoscopy practice, and the ability to further improve ADR where colonoscopy quality assurance measures were rigorously implemented highlighted the benefit of 3D colonoscopy in enhancing adenoma detection. The use of different 3D endoscopy systems could have also contributed to the differences between the two studies, as the vividness of 3D visualization might differ between systems depending on the image reprocessing algorithms employed.

This study had several notable strengths. This RCT is the first to demonstrate the ability of 3D imaging in improving ADR and enhancing detection of flat and proximally located adenomas which are challenging to detect with standard 2D colonoscopy. Second, this study ensured high-quality colonoscopy thorough measures such as attention to bowel cleansing and photodocumentation and maintaining a withdrawal time exceeding 6 minutes in accordance with the international benchmarks. Third, this study enrolled individuals aged over 40 to align the study population with the examinees in general colonoscopic practice, enhancing the relevance and generalizability of the results. Last, this study conducted stratified comparisons according to polyp morphologies and location, revealing the advantage of 3D colonoscopy in enhancing detection of flat and proximal adenomas.

This study also had limitations. Given the apparent differences between 2D and 3D colonoscopy, it was not possible to blind the colonoscopists to group allocation. However, the quality assurance program including standardized photodocumentation in participating institutions ensured that the mucosa

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inspection time was comparable between the two groups and >6 minutes, refuting the possibility that colonoscopists tried harder to find polyps in the 3D group. Therefore, non-blinding of endoscopists should not have introduced significant bias. While the endoscopists' ADR might have been affected by study participation (i.e., Hawthorne effect), the potential influence should occur in both 2D and 3D groups to a similar degree; therefore, the observed difference in ADR should be little influenced by the Hawthorne effect and remain valid. The comparability in other procedural factors and randomization minimized the possibility of confounding, and regression analysis adjustment for potential confounders further supported that the observed improvement in adenoma detection was attributed to 3D colonoscopy. Second, given the limited availability of the newly developed 3D colonoscopy equipment, this RCT included only a limited number of institutions and colonoscopists. A larger trial including more institutions/colonoscopists and diverse patient populations is warranted to further ascertain the potential benefit conferred by wide implementation of 3D colonoscopy. Third, this study did not evaluate the endoscopists' burden such as eye strain because of the lack of a well-established objective evaluation tool/method. However, none of the participating endoscopists reported fatigue or eye strain after performing 3D colonoscopy, probably because this 3D endoscopy system uniquely considers pupillary distance. Tailoring the 2D to 3D conversion process according to pupillary distance is crucial for mitigating visual discomfort when watching 3D imagery[33]. The finding that a significant increase in ADR with 3D colonoscopy was not accompanied by an increase in the mucosa inspection time compared

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421 with 2D colonoscopy also supported that processing the 3D images did
422 significantly increase endoscopist burden. Whether more prolonged use of this
423 3D system for colonoscopy might increase endoscopist burden remains to be
424 evaluated. Lastly, given the relatively low prevalence of SSL and AA, this study
425 was not powered to detect potential differences in the rate of SSL and AA
426 between 3D and 2D colonoscopy. The numerically higher detection rates of
427 SSL and AA with 3D colonoscopy observed in this study warrants confirmation
428 by further research with a larger sample size.

429 In conclusion, this RCT demonstrated that for individuals aged 40 and
430 above, 3D colonoscopy significantly increased the detection rates of
431 adenomas, particularly small, flat, and proximal adenomas, compared with
432 standard 2D colonoscopy. The sizable increases in ADR suggested that
433 implementing 3D colonoscopy in clinical practice might deliver significant
434 improvement in patient outcomes.

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FIGURE LEGENDS

Figure 1. Schematic representation of the MonoStereo 3D endoscopic visualization system (a) (provided by MedicalTek Co. Ltd). The endoscopic display can be switched from standard 2D images (b) to reconstructed images (c) which transform into real-time fully immersive 3D images when viewed with polarized 3D glasses. Employing 3D colonoscopy during routine colonoscopic examinations (d).

Figure 2. Screening, recruitment, randomization, and analysis of the study participants.

Figure 3. Temporal changes between 2D and 3D colonoscopy in mean mucosa inspection time (a) and adenoma detection rate (b).

538 **VIDEO LEGENDS**

539 **Video title:** Demonstrative video: 2D and 3D colonoscopy.

540 Legend: 2D images are converted to left/right images which yield 3D images

541 using 3D monitors and polarized glasses. Deliberate endoscope movement

542 demonstrates minimal time-lag. The seeming difference in polyp shape on 3D

543 images will disappear with 3D monitors and polarized glasses.

Table 1. Demographics and clinical characteristics of study subjects

	2D colonoscopy n=158	**3D colonoscopy n=160**	***p***
Age - years, mean (SD)	62.4 (11.2)	61.4 (9.9)	.40
Male, n (%)	79 (50.0)	71 (44.4)	.32
Body weight – kg, mean (SD)	65.4 (12.2)	66.4 (13.2)	.48
Body height – cm, mean (SD)	164.2 (9.7)	162.9 (7.8)	.19
Body mass index, kg/m^2, mean (SD)	24.2 (4.2)	24.9 (4.1)	.13
Family history with CRC, n (%)	17 (10.8)	27 (16.9)	.11
Ever smoking, n (%)	39 (24.7)	32 (20.0)	.32
Alcohol consumption, n (%)	14 (8.9)	11 (6.9)	.51
Anti-thrombotic agent use, n (%)	21 (13.3)	27 (16.9)	.37
Diabetes mellitus, n (%)	24 (15.2)	25 (15,6)	.91
Hypertension, n (%)	52 (32.9)	64 (40.0)	.19
Indication, n (%)			.35
FIT positivity	44 (27.8)	50 (31.3)	
Post-polypectomy surveillance	59 (37.3)	45 (28.1)	
Symptoms	43 (27.2)	53 (33.1)	
Others	12 (7.6)	12 (7.5)	

(To be continued)

Table 1. Demographics and clinical characteristics of study subjects (continued)

	2D colonoscopy n=158	3D colonoscopy n=160	*p*
Modified Aronchick bowel preparation scale*,			.085
n (%)	100 (63.3)	87 (54.4)	
Excellent/Good	58 (36.7)	73 (45.6)	
Fair	11.0 (5.2)	12.5 (5.0)	.0092
Withdrawal time (min)**, mean (SD)			
Mucosa inspection time (min)***, mean (SD),	9.4 (3.1)	9.8 (2.6)	.21
Entire cohort	9.6 (2.6)	11.1 (2.6)	.012

Case number 1-40	10.0 (3.6)	10.1 (2.5)	.89
Case number 41-80	9.5 (3.4))	9.9 (2.1)	.53
Case number 81-120	8.3 (2.6)	8.0 (2.2)	.58
Case number 121-160			

2D/3D: 2-dimensional/3-dimensional, SD: standard deviation, CRC: colorectal cancer, FIT: Fecal immunochemical test, min.: minute

* Subjects rating poor or inadequate bowel preparation had been excluded from the study.

**Withdraw time = the total time from cecum to anus

***Inspection time = withdraw time – time for observing and removing polyp

Table 2. Comparison of primary and secondary outcomes between 2D and 3D colonoscopy

	2D colonoscopy n=158	3D colonoscopy n=160	Difference in detection rate % (95%CI)	Odds ratio (95% CI)	*p*
Primary outcomes					
Patients with adenoma, n (%)	61 (38.6)	85 (53.1)	14.5 (3.7-25.4)	1.80 (1.15-2.82)	.0094
Secondary outcomes					
Patients with flat adenoma, n (%)	34 (21.5)	56 (35.0)	13.5 (3.7-23.3)	1.96 (1.19-3.24)	.0076
Patients with sessile adenoma, n (%)	44 (27.8)	47 (29.4)	1.6 (-8.4-11.5)	1.08 (0.66-1.75)	.76
Patients with right-sided adenoma, n (%)	24 (15.2)	42 (26.3)	11.1 (2.2-19.9)	1.98 (1.14-3.48)	.015
Patients with left-sided adenoma, n (%)	61 (38.6)	85 (53.1)	14.5 (3.7-25.4)	1.80 (1.15-2.82)	.0094
Patients with proximal adenoma, n (%)	37 (23.4)	61 (38.1)	14.7 (4.7-24.7)	2.02 (1.24-3.28)	.0045
Patients with distal adenoma, n (%)	48 (30.4)	53 (33.1)	2.7 (-7.5-12.8)	1.11 (0.68-1.82)	.66

(To be continued)

Table 2. Comparison of primary and secondary outcomes between 2D and 3D colonoscopy (continued)

	2D colonoscopy n=158	3D colonoscopy n=160	Difference in detection rate % (95%CI)	Odds ratio (95% CI)	*p*
Patients with sessile serrated lesions, n (%)	8 (5.1)	11 (6.9)	1.8 (-3.4-7.0)	1.38 (0.54-3.54)	.50
Patients with advanced adenoma, n (%)	11 (7.0)	15 (9.4)	2.4 (-3.6-8.4)	1.38 (0.61-4.11)	.43
Patients with adenoma, n (%)					
< 5mm	14 (8.9)	13 (8.1)	0.7 (-6.9-5.4)	1.10 (0.50-2.42)	.81

5-9mm	49 (31.0)	72 (45.0)	14.0 (3.4-24.5)	1.82 (1.15-2.88)	.010
≥10mm	15 (9.5)	25 (15.6)	6.1 (-1.1-13.4)	1.77 (0.89-3.49)	.10
Patients with polyps, n (%)	73 (46.2)	100 (62.5)	16.3 (5.5-27.1)	1.94 (1.24-3.04)	.0035
No. of adenoma per patient, median (IQR)	0 (0-1)	1 (1-2)	-	-	.028
No. of polyp per patient, median (IQR)	0 (0-1)	1 (0-2)	-	-	<.0001

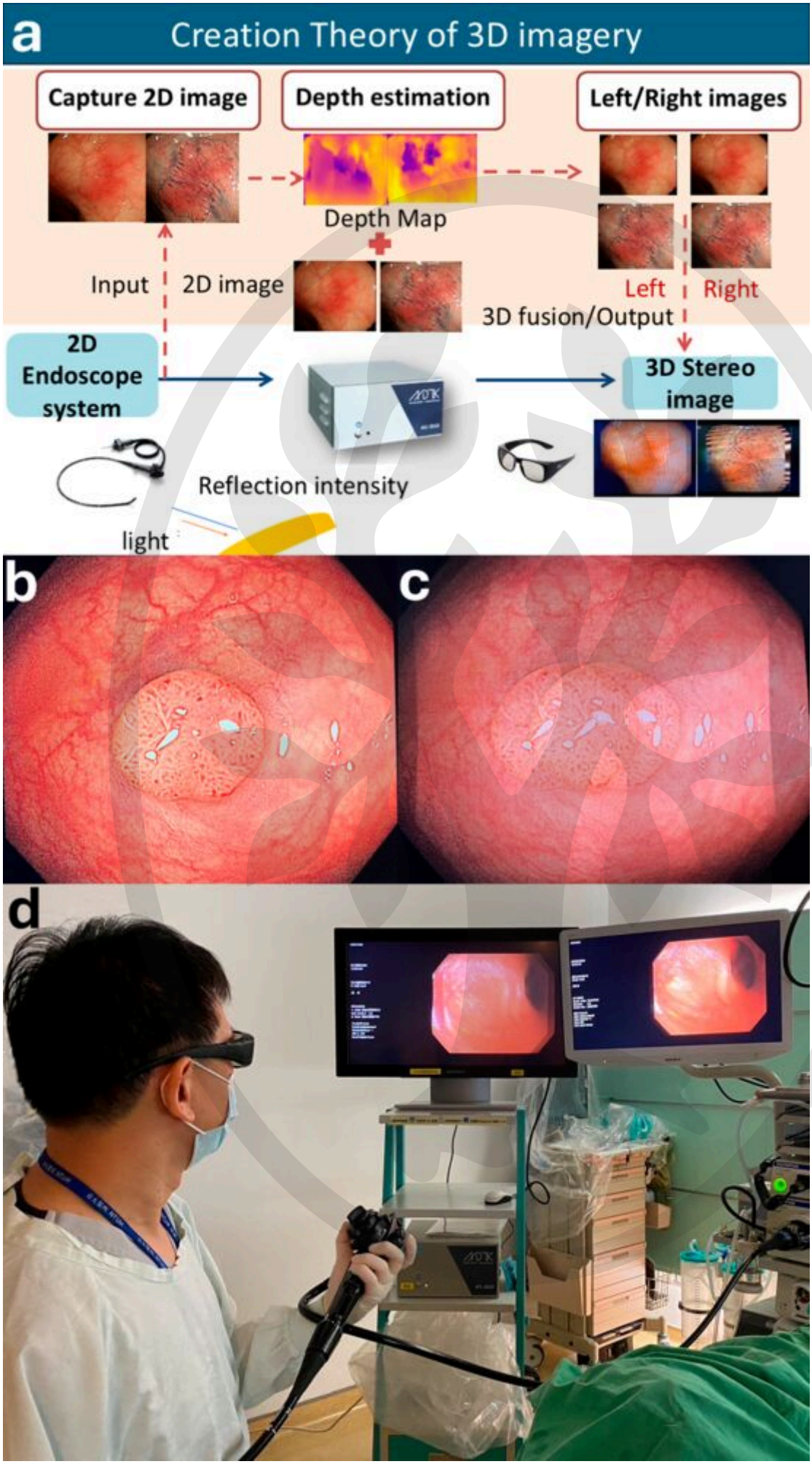
2D/3D: 2-dimensional/3-dimensional, OR: Odds ratio, no.: number, CI: confidence interval, SD: standard deviation, IQR: interquartile range

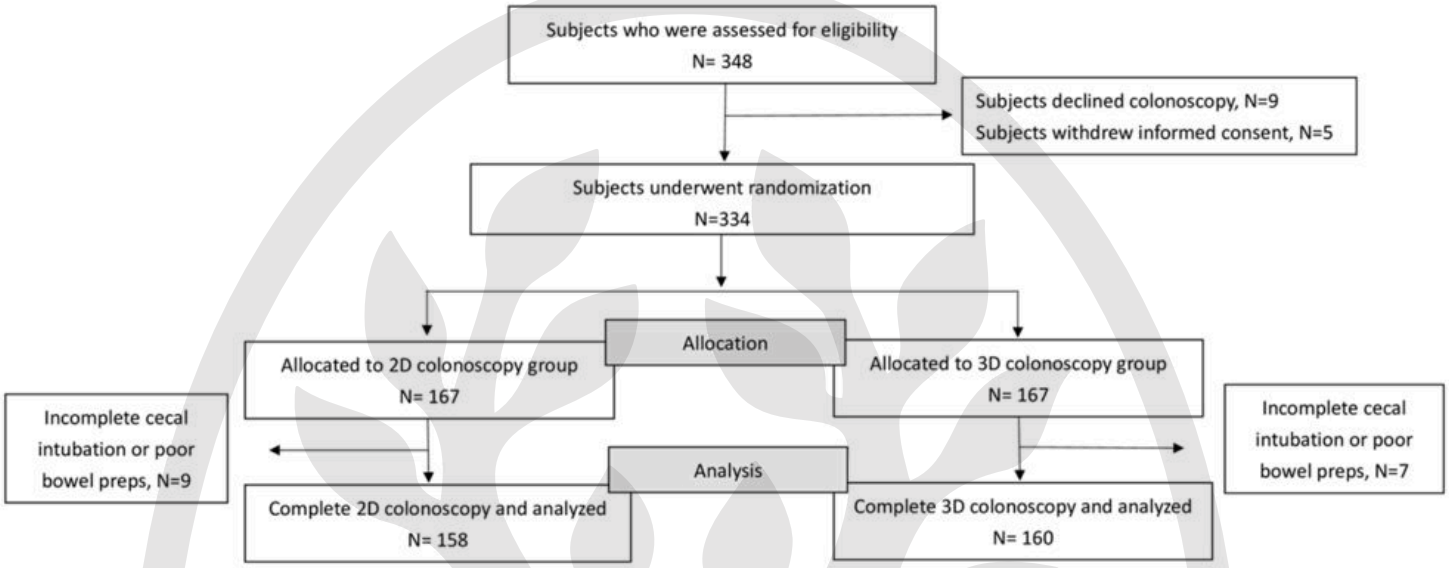
Right-sided adenoma: Adenoma at cecum or ascending colon; Left-sided adenoma: Adenoma at transverse colon, descending colon, sigmoid colon or rectum; Proximal adenoma: Adenoma at cecum, ascending colon, or transverse colon; Distal adenoma: Adenoma at descending colon, sigmoid colon or rectum; Flat adenoma: Paris classification 0-IIa, 0-IIb, or 0-IIc; Sessile adenoma: Paris classification 0-Is

Table 3. Factors associated with detection of adenoma

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*	aOR (95% CI)	*p*
Age, per 1-year increment	1.04 (1.02-1.06)	<.0001	1.03 (1.01-1.06)	.0080
Male sex	1.44 (0.92-2.24)	.11		
BMI, per 1 kg/m^2 increment	1.04 (0.98-1.10)	.16		
Ever smoking	1.70 (1.00-2.90)	.050		
Alcohol consumption	1.30 (0.57-2.93)	.54		
Anti-thrombotic agent use	1.79 (0.96-3.34)	.066		
Diabetes mellitus	1.40 (0.76-2.58)	.28		
Hypertension	1.90 (1.20-3.02)	.0060	1.32 (0.79-2.20)	.29
Family history of CRC	0.63 (0.33-1.21)	.17		
FIT positivity	1.90 (1.17-3.10)	.010	1.46 (0.86-2.47)	.16
Good or excellent bowel preparation	0.60 (0.38-0.94)	.025	0.89 (0.54-1.47)	.67
Mucosa inspection time, per 1 minute increment	1.20 (1.10-1.31)	<.0001	1.16 (1.06-1.28)	.0010
3D colonoscopy use	1.80 (1.15-2.81)	.0093	1.76 (1.09-2.83)	.021

OR: odds ratio, aOR: adjusted odds ratio, CI: confidence interval; BMI: body mass index; CRC: colorectal cancer, FIT: fecal immunochemical test, 3D: 3-dimensional





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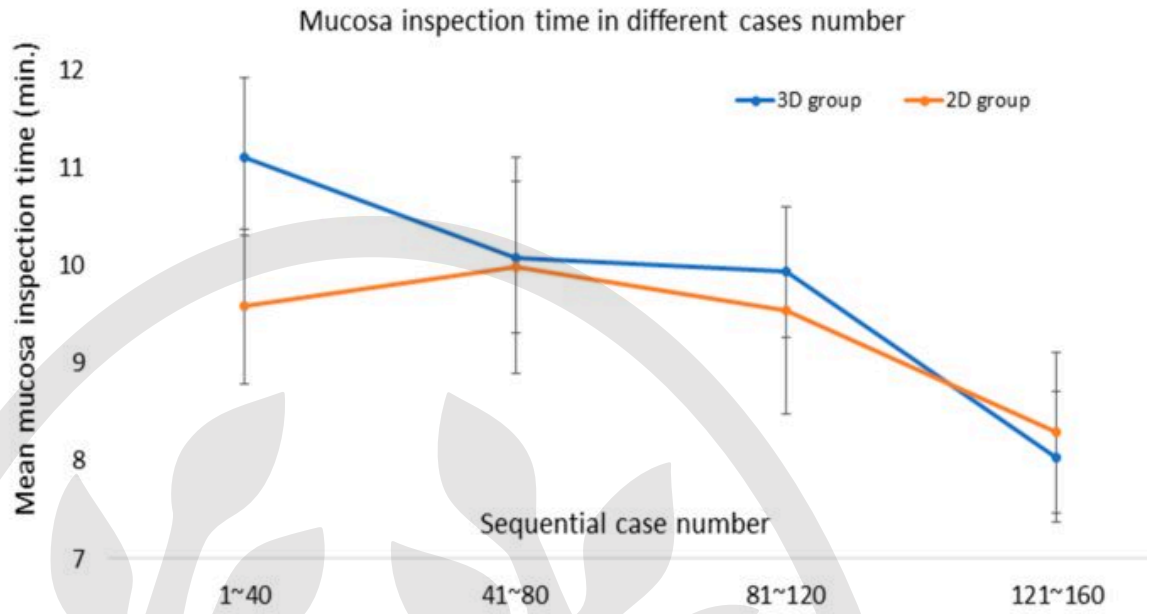

		1~40	41~80	81~120	121~160
Mean mucosa inspection time ,min, mean(SD)	3D group	11.11 (2.57)	10.08 (2.48)	9.93 (2.13)	8.04 (2.16)
	2D group	9.58 (2.56)	9.99 (3.57)	9.54 (3.43)	8.29 (2.58)
	p value	<.01	.90	.54	.64

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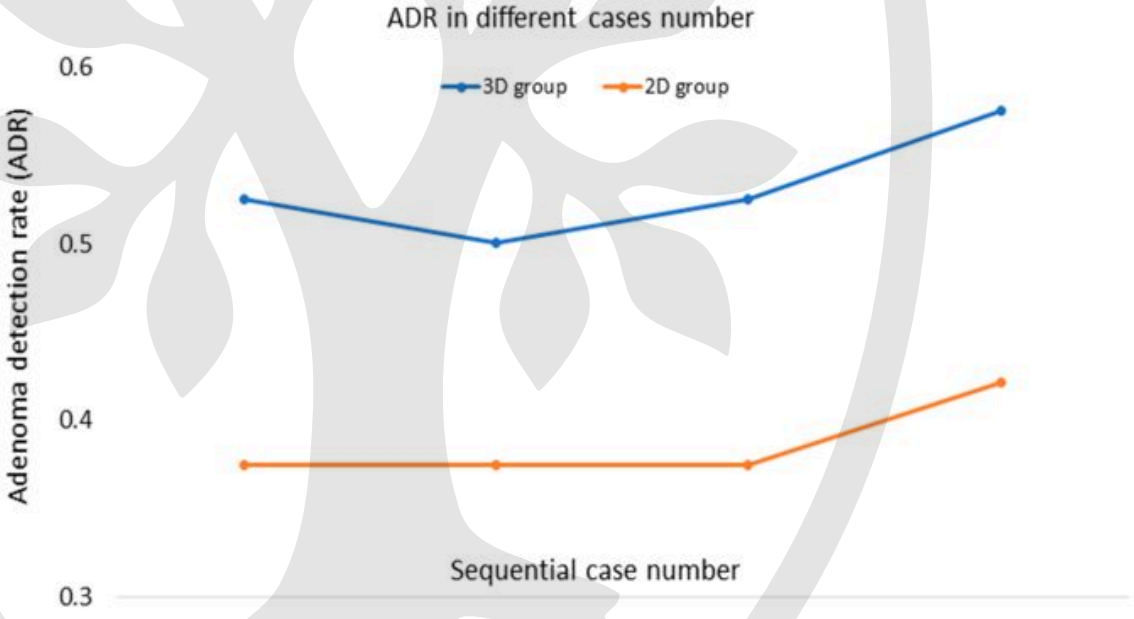

		1~40	41~80	81~120	121~160
Adenoma detection rate (ADR)	3D group	0.53	0.5	0.53	0.58
	2D group	0.38	0.38	0.38	0.42