The Impact of Repeat Colonoscopy Insert Method on the Detection Rate of Adenomas in the Sigmoid Colon.

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1. Research Title

The Impact of Repeat Colonoscopy Insert Method on the Detection Rate of Adenomas in the Sigmoid Colon.

2. Research Background

(1) High-quality colonoscopy is key to preventing colorectal cancer.

Colorectal cancer (CRC) is a malignant tumor originating from the colorectal mucosal epithelium, with rising incidence and mortality rates[1]. Currently, CRC ranks third in incidence and second in mortality among all cancers worldwide, making it the leading cancer in terms of global incidence and mortality[2, 3]. According to GLOBOCAN2018, the estimated new cases and deaths from colorectal cancer globally were 1.85 million and 0.88 million respectively, accounting for 28% each in China, and it has become the second most common digestive system cancer and the most prevalent cancer in China. As shown in the "Henan Cancer Registry Annual Report" (2013-2020), colorectal cancer has also been one of the high-incidence malignant tumors threatening the health of the population in our province. Approximately 90% of CRC develops from colorectal polyps, which are considered precancerous lesions of CRC, especially adenomatous polyps[4, 5]. If removed endoscopically during the polyp stage, 70%-90% of CRC can be prevented[6]. With the enhancement of people's health awareness, the number of colonoscopies performed annually is increasing. Taking our hospital as an example, the annual growth rate of colonoscopies exceeds 30%, with over 30,000 colonoscopies completed in 2021. However, current colonoscopy examinations have a high miss rate for polyps. Studies have shown that the miss rates for polyps and adenomas after colonoscopy can reach 22%-28% and 12%-26%, respectively[7]. These missed polyps and adenomas increase the risk of CRC and may be an important cause of interval CRC after colonoscopy, which can account for 0.6% to 9% of all CRC[8, 9]. A study on the Polish colonoscopy screening program found that the risk of detecting CRC was 10 times higher for those with an adenoma detection rate (ADR) of <20% compared with ≥20%[10]. Therefore, the ADR is universally recognized as a reliable indicator for measuring colonoscopy quality, and is inversely correlated with the risk of interval CRC[10, 11]. It can be seen that high-quality colonoscopy and sufficient adenoma detection rate are key to preventing CRC[12], which can greatly reduce the incidence of colorectal cancer while lowering the miss rate of polyps.

(2) Insufficiencies in the traditional observation method during colonoscopy.

According to the "2014 Chinese Guidelines for Early Screening and Endoscopic Diagnosis and Treatment of Colorectal Cancer", the observation method during colonoscopy starts from the rectum and progresses forward to the cecum, with observations made during withdrawal: from the cecum, ascending colon, transverse colon, descending colon, sigmoid colon to the rectum. Current quality control of colonoscopy mainly focuses on controlling withdrawal time exceeding 6 minutes, controlling cecal intubation rate, and ensuring adenoma detection rate[13], without specific requirements on the observation method. However, in actual clinical practice, it is found that single withdrawal observation is not enough, as this examination approach is prone to many missed polyps. The likely reason is that the colon is in a compressed state during withdrawal observation. Conventional colonoscopy with two

operators used to be widely adopted internationally. Single-operator colonoscopy has become the mainstream insertion method internationally due to its advantages of operational safety, simplicity, high success rate, saving manpower resources and facilitating chromoendoscopy. The core technique of single-operator method is "short-axis reduction", meaning that the colonoscope maintains a straight configuration throughout the examination. The average adult colon length is about 1.5m, but the distance reached during single-operator technique is often between 70-80cm, indicating compression of the colon. In addition, colonic folds become more dense when compressed, making it easier for lesions like polyps to hide within or near folds, leading to misses. Currently in clinical practice of colonoscopy, only withdrawal observation is performed, and only once, on a compressed colon. Many lesions can be easily missed, compromising colonoscopy quality. The sigmoid colon has the most turns in the entire large intestine, and is also the part most prone to compression during colonoscopy insertion. Correspondingly, it is also more prone to misses during withdrawal observation. Although some scholars proposed repeating withdrawal to improve lesion detection rates, observation is still made on a compressed colon regardless of two or three withdrawals. In actual clinical work, many polyps can only be found during advancement.

(3) Status of domestic and international studies

Recently, some studies have reported that Endocuff, full-spectrum endoscope examination, water-assisted colonoscopy and repeated examinations, including retroflexion or anteversion, can effectively increase the overall colon ADR[14-18]. Among these methods, repeated colonic examination may be the simplest and most convenient method for endoscopists, as it does not require additional equipment, personnel or costs. In recent years, domestic and international researchers have done a lot of work on repeated colonoscopy insertion examinations. The most studied is repeated antegrade and retrograde withdrawal observation. A meta-analysis including 6 studies involving 3,901 patients showed[19]: compared with the normal withdrawal group, the right colon ADR and PDR in the double withdrawal group were significantly higher: ADR (RR [95% CI] 1.39 [1.22,1.58]) and PDR (RR [95% CI] 1.47 [1.30,1.65]), and there was no significant difference in right colon withdrawal time (SMD [95% CI] 1.54 [-0.20,3.28]) or total withdrawal time (SMD [95% CI] 0.37 [-0.39,1.13]) between the two groups. Some studies compare adenoma detection rates of repeated antegrade and retroflexion methods[20]. A meta-analysis including 4 studies involving 1,882 patients showed that repeated right colon antegrade and retroflexion were both associated with improved ADR, and one of the techniques should be considered to increase ADR and improve colonoscopy quality[21]. In terms of feasibility, though retroflexion has a higher success rate and lower risk of adverse events, endoscopists are more likely to perform antegrade examinations in routine clinical practice. In addition, some domestic studies have investigated the effect of number of insertions on polyp detection rates. The studies by Feng Yan et al. compared 2 or 3 insertions with 1 insertion and concluded that polyp detection rate with 2 insertions was significantly higher than with 1 insertion. Recently, a domestic study proposed that the focus of observation in different colonic locations during withdrawal and insertion should be different, and the second insertion should focus on locations easily ignored during withdrawal. The results showed that the second insertion method had a higher detection rate for multiple polyps, small polyps, ascending colon polyps, transverse colon polyps, sigmoid colon polyps and sessile polyps ($P < 0.05$) . However, these studies only

observed again based on the original examination, and the colon observed was still compressed. Based on our previous mention that colonic compression can lead to missed polyps, we proposed performing a second insertion specifically for the easily compressed sigmoid colon. During the second insertion, the "short-axis reduction" technique should not be used. Instead, the folds should be deliberately advanced into to fully extend the compressed sigmoid colon and shallow or eliminate the folds, allowing observation during insertion to achieve effects beyond multiple withdrawals and find hidden lesions within or near folds, thereby improving colonoscopy quality. Therefore, to explore whether observing during a second sigmoid colon insertion can further improve the adenoma detection rate (ADR) to improve colonoscopy quality and reduce interval cancers, we conducted this study.

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3. Objectives

(1) To further explore the impact of a second sigmoid colon insertion on the adenoma detection rate (ADR), analyze factors associated with missed adenomas, and improve clinicians' understanding of the second insertion method;
(2) To further improve the quality of colonoscopy and the early screening positivity rate for colorectal cancer in China.

4. Research Content

(1) Subjects and clinical data

A prospective study was conducted on patients undergoing painless colonoscopy at the First Affiliated Hospital of Zhengzhou University from December 1, 2023 to March 1, 2024 (including outpatients and inpatients). According to the random number table method, patients were divided into two groups: the routine insertion group, where patients underwent a single insertion with observation during withdrawal only; the second insertion group, where after the first withdrawal observation, a second insertion was performed from the rectum through the colonic lumen with deliberate folds advancement in the sigmoid colon, with observation during both insertion and withdrawal. The adenoma detection rate (ADR) and polyp detection rate (PDR) in the sigmoid colon were calculated and compared between the two groups.

(2) Inclusion criteria:

1) Patients who underwent painless colonoscopy at the Gastrointestinal Endoscopy Center of the

First Affiliated Hospital of Zhengzhou University and signed the informed consent for the clinical trial;

2) Aged at age 45 and above with BMI >24.

(3) Exclusion criteria:

1) Patients with contraindications to colonoscopy: patients with acute diverticulitis, patients with known or suspected perforation, patients with severe cardiovascular and cerebrovascular lesions, patients with severe hepatic or renal insufficiency, patients with abdominal aneurysm of large arteries, patients with active hemorrhagic descending colonic lesions, patients with acute radiological colorectal inflammation, patients with advanced carcinomas with pelvic metastases or obvious ascites, patients with severe and extensive intestinal adhesions after abdominal or pelvic surgery;

2) Patients with inflammatory bowel disease, colorectal cancer, familial adenomatous polyposis, Peutz-Jeghers syndrome, abdominal wall hernia, patients with a history of colorectal surgery;

3) Patients with incomplete colonoscopy, i.e., those in whom the endoscopist has failed to successfully cannulate the cecum due to technical difficulties;

4) Patients with poor bowel preparation, i.e., patients with a total score of <6 or any bowel segment of <2 on the Boston Bowel Preparedness Scale score for poor bowel preparation).

(4) Research methods and contents:

1) Preparation for colonoscopy: Routine ECG, infectious disease screening were performed before examination. Patients were advised liquid diet 1 day before and fasted from food and water on the day of examination according to the "Chinese Guidelines for Gastrointestinal Tract Preparation for Endoscopy (2019, Shanghai)". Patients were advised to take oral polyethylene glycol electrolyte powder or sodium phosphate solution for bowel preparation. The last bowel movement should be clear liquid stool before examination.

2) Colonoscopy: All patients took left lateral position with flexed knees close to abdomen. Olympus CF-H290 high definition electronic colonoscope was used under general anesthesia. The endoscopist advanced the colonoscope to the cecum and started withdrawal observation of the colon and rectum mucosa. Polyp lesions found were photographed, removed with biopsy forceps and sent for pathology. When the colonoscope was withdrawn to the rectum after the first examination, patients were randomly allocated to the standard group or second insertion group. Computer-generated randomization numbers divided patients into two groups with allocation information sealed in numbered, opaque envelopes. The endoscopist was blinded to group assignments until completion of first examination of the proximal rectum when the envelope was opened. For the second insertion group, the sigmoid colon was re-inserted with deliberate folds advancement to unfold the folds, and further observations were made during both insertion and withdrawal, polyp lesions found were photographed, removed and sent for pathology. Withdrawal to the anus was then performed in standard manner. The standard group had standard withdrawal observation from rectum to anus for polyp detection and removal.

3) Collection of patient data:

General information: height, weight, gender, age, smoking, drinking, abdominal circumference, hypertension, diabetes, family history of colorectal cancer etc.

Special data: number, location, morphology (pedunculated, sessile), size (<5mm,

5-10mm, >10mm) of polyps, pathology of polyps (inflammatory, hyperplastic, adenomatous); BBPS score for bowel cleanliness; time of first withdrawal, second sigmoid insertion, withdrawal (excluding time for polyp biopsy or treatment); vital signs like blood pressure, heart rate, oxygen saturation (recorded every 5 minutes) of patients during colonoscopy; adverse reactions after procedure (abdominal pain, bloating, nausea, vomiting).

4) Calculation and analysis of data:

① Separately calculate and compare the ADR of sigmoid colon between standard and second insertion groups: ADR= number of patients with detected sigmoid adenoma / total number of patients in each group.

② Separately calculate and compare the PDR of sigmoid colon between standard and second insertion groups: PDR= number of patients with detected sigmoid polyps / total number of patients in each group

③ Calculate and compare the postoperative adverse reaction rate between two groups: Adverse reaction rate= number of patients with adverse reactions / total number of patients in each group.

5) Statistical methods: Analysis was performed using SPSS 26.0 software. Counting data were expressed as cases (n) and percentage (%), inter-group comparison was performed using $\chi 2$ test, $\chi 2$ correction or Fisher's exact test. Measurement data were expressed as Mean ± SD, inter-group comparison was performed using t test, t' test or non-parametric test (U test). $P < 0.05$ was considered statistically significant.

5. Expected research outcomes

(1) Analyze the impact of a second sigmoid colon insertion on the adenoma detection rate (ADR) and related risk factors for missed adenomas, thereby improving clinicians' understanding of the second insertion method;

(2) Publish 1 sci paper.

6. Other ethical issues

(1) Privacy protection: Patient data collected will only be used for this study. Personal information of patients collected during the study will be kept confidential. For example, patients' clinical data will be identified by study code number instead of name; information that can identify patient identity will not be disclosed to research group members unless with patient permission; all research members and applicant are required to keep patient identity confidential; patient files will be kept in file cabinets for access by researchers only; government management departments or ethics committees may access personal patient data according to regulations to ensure study is conducted properly; no personal patient information will be disclosed when publishing study results.

(2) Informed consent: All subjects participating in the experiment will be fully informed of risks and benefits and sign an informed consent form.