Institute of Digestive Disease

Department of Medicine and Therapeutics

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The Chinese University of Hong Kong

Study Protocol

Study Title

Comparison of second forward view examination and conventional withdrawal examination in the right colon on polyp detection in screening and surveillance colonoscopies: A randomized controlled study (SFVRC Study)

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BACKGROUND

It is estimated that there are about 1.4 million patients with colorectal cancer (CRC) worldwide, with a rising trend in CRC incidence in many Asian Pacific countries [1]. In Hong Kong, colorectal cancer ranks first in cancer incidence and second in cancer mortality based on data from 2013 [2].

CRC is one of the most preventable cancers because its development in general follows an adenoma-carcinoma sequence [3,4]. Adenomas are considered precursor lesions for CRC. Recent guidelines from USA, Europe and Asia Pacific region recommend CRC screening for average-risk asymptomatic individuals starting at age 50 [5-7]. Modalities such as guaiac-based fecal occult blood tests (gFOBT), fecal immunochemical tests (FIT), flexible sigmoidoscopy (FS), and colonoscopy are among the acceptable options for CRC screening [5-7].

While early detection and removal of colorectal adenoma by screening colonoscopy with polypectomy reduce CRC incidence and mortality, interval cancers (cancers that develop after a colonoscopy and before the next scheduled colonoscopy) may still occur and were reported to account for up to 10.5% of CRC [8-9]. The protective effect of colonoscopy against cancer in the right colon has not been consistently demonstrated [9-12]. Interval CRC has been associated with proximal colon location, small lesion, flat lesion, missed lesion, inadequate examination, incomplete resection of lesion, tumor biology, and low adenoma detection rate (ADR) [12-15].

High ADR (eg, $\geq$ 20%) has been associated with a reduced risk of interval CRC [14,15]. Methods that can improve polyp detection in the right colon such as retroflexed examination of the right colon, second forward view examination of the right colon, use of colonic fold flattening device, colonoscope with an increased field of view may potentially reduce the risk of interval CRC, but data is still limited [16-20]. Performance of a second forward view (SFV) examination of the right colon may be the easiest and safest from a practical standpoint when compared to other options (eg, additional training is often needed for retroflexed examination of the right colon since there may be a potentially higher risk of perforation in endoscopists not familiar with the technique, additional equipment is needed when using a colonic fold flattening device, or a colonoscope with an increased field of view). In a recent randomized control study comparing retroflexed examination and SFV examination in the right colon in patients undergoing screening or surveillance colonoscopy, high ADRs were achieved by both methods (47% in retroflexed group vs 46% in SFV group, $p = 0.75$) [17]. A recent single arm prospective cohort study of 280 male veteran patients in USA showed that additional adenomas were detected in 15.4% of the patients after a SFV examination of the right colon [18]. The overall ADR increased by 3.2% and the ADR for the right colon increased by 6.7% after SFV examination of the right colon [18]. 3.6% of the patients had a change in their screening / surveillance interval with the addition of findings on the SFV examination of the right colon [18]. Of note, the overall ADR in this cohort of male veteran patients was very high and up to 71.8% on conventional withdrawal exam [18]. It is unclear whether a SFV examination of the right colon would still be beneficial in populations with both males and females and a lower overall ADR (eg, closer to the

recommended colonoscopy quality indicator of an ADR of 20% by the American Society of Gastrointestinal Endoscopy). To date, there has been no dedicated randomized controlled study comparing the yield of SFV examination in the right colon to that of conventional withdrawal examination of the right colon on adenoma /polyp detection in patients undergoing screening and surveillance colonoscopies. Our current study aims to determine whether a routine SFV examination in the right colon can lead to an increase in adenoma / polyp detection when compared to conventional withdrawal examination in the right colon in both male and female patients undergoing screening and surveillance colonoscopies.

HYPOTHESIS

Performance of a SFV examination in the right colon can increase adenoma / polyp detection when compared to conventional withdrawal examination of the right colon in patients undergoing screening and surveillance colonoscopies.

AIM

To investigate the impact of a SFV examination in the right colon on the right-sided and overall adenoma / polyp detection in patients undergoing screening and surveillance colonoscopies in a randomized controlled study.

METHODOLOGY

Study Design

It is an international multi-centre randomized controlled study

Setting

Endoscopy centers in Prince of Wales Hospital, combined endoscopy unit in Alice Ho Miu Ling Nethersole Hospital, and partner institutes of Asia-Pacific Working Group on Colorectal Cancer.

Study Population

The study protocol, risks and benefits of procedures, and informed consent would be discussed either in a pre-colonoscopy clinic visit or on the day of scheduled colonoscopy procedure at two endoscopy centres in Prince of Wales Hospital and combined endoscopy unit in Alice Ho Miu Ling Nethersole Hospital, and partner institutes of Asia-Pacific Working Group on Colorectal Cancer based on the local institutional guidelines. After informed consent form is signed by the patient, patient will be enrolled into the study, with study randomization conducted on the day of procedure (see endoscopic procedure description below).

Eligibility

Inclusion Criteria

- Patients undergoing colonoscopy for CRC screening or polyp surveillance
- Age 50 - 75 years
- Written informed consent available

Exclusion Criteria

- Contraindications for endoscopy due to comorbidities
- Unable to provide written informed consent
- Personal history of prior resection of any portion of the colon, familial polyposis syndrome, inflammatory bowel disease
- Patients with incomplete colonoscopy (i.e, inability to achieve cecal intubation), a Boston Bowel Preparation Scale (BBPS) score of 0 in either right colon, transverse colon, or left colon at the time of colonoscopy
- Known history of coagulopathy and thrombocytopenia
- Pregnant patients

Study Flow

Patients who fulfill inclusion criteria and sign informed consent form for the study will be assessed for the followings:

- Demographics: age, gender, height, weight
- Clinical Conditions: indication for colonoscopy, family history of CRC, personal history of colonic polyp, history of prior CRC screening, comorbidities (eg, diabetes, etc), smoking history, use of antiplatelets and antithrombotic medications

Standard colonoscopy will be performed. The only intervention in the study is the SFV in the right colon. The additional risk of SFV should be minimal and similar to standard colonoscopy since it does not involve a new endoscopic skill or new equipment. Patients' vital signs will be monitored during colonoscopy. Data such as cecal intubation time, total procedure withdrawal time, the size, morphology, and location of each polyp, bowel preparation quality assessment by BBPS, additional withdrawal time for the SFV in the right colon, presence of immediate complications such as perforation, bleeding, hypotension, etc and final histology of the removed polyps will be collected.

After colonoscopy, patients will be monitored for any immediate complications. If no sign of immediate complication is detected, patient will be discharged according to standard discharge protocol for sedated procedure. Oral intake will be resumed with diet advancement as tolerated after discharge. Patients will be given a designated telephone line for post-colonoscopy adverse events reporting and follow up during office hours within 30 days. They will be instructed to attend the nearby Accident and Emergency Department for serious adverse events out of office hours. All information about post-colonoscopy serious adverse events will be retrieved from hospital record system on day 30.

Patients will be followed up at their original clinic after colonoscopy. The interval for next screening or surveillance colonoscopy will be determined based on findings of colonoscopy, number and histology of polyp removed during colonoscopy, patient's clinical and family history accordingly to regional and international guidelines [5]. This follow up is not the study procedure but standard care.

Endoscopic Procedures

Colonoscopy will be performed by investigators in their standard sessions. Olympus (Tokyo, Japan) high definition colonoscopes will be used in this study. Narrow band imaging (NBI), an image enhanced function on the endoscope, may be used for characterization of an identified polyp at the discretion of the endoscopist but not routinely for polyp detection during entire examination. In addition, chromoendoscopy can be used when sessile serrated adenoma is suspected. Conscious sedation with intravenous administration of midazolam and pethidine would be used during the procedure with regular monitoring of vital signs. A digital rectal (PR) examination will be performed before insertion of the endoscope. The colonoscope will be passed to cecum. A colonoscopy would be considered incomplete if cecal intubation cannot be achieved. Distal attachment (also known as a cap or hood) would not be used routinely during colonoscopy to enhance colonic fold flattening / exposure.

Standard Colonoscopy Procedure (Conventional group)

The colonoscope will then be withdrawn from the cecum with irrigation and aspiration of any residual colonic contents for careful examination of the colonic mucosa for polyps. During the initial colonoscope withdrawal from cecum to hepatic flexure (ie, the first forward view examination of the right colon), polyps detected in the right colon (ie, cecum and ascending colon) will be removed and sent for histopathological examination. Once the colonoscope is withdrawn to the level of hepatic flexure, patients will be randomized to either a SFV examination of the right colon, or continuation of the conventional colonoscope withdrawal for examination of colonic mucosa for polyps. In the conventional group, colonoscope withdrawal will be continued from hepatic flexure to rectum after randomization. Examination of colonic mucosa for polyps from hepatic flexure to rectum will be performed per standard of care. Polyps detected in these areas will be removed and sent for histopathological examination accordingly. Risks of colonoscopy such as perforation, bleeding, or infection were reported to be less than 1%.

Second Forward View Colonoscopy Procedure (SFV group)

During the initial colonoscope withdrawal from cecum to hepatic flexure (ie, the first forward view examination of the right colon), polyps detected in the right colon (ie, cecum and ascending colon) will be removed and sent for histopathological examination. Once the colonoscope is withdrawn to the level of hepatic flexure, patients will be randomized to either a SFV examination of the right colon, or continuation of the conventional colonoscope withdrawal for examination of colonic mucosa for polyps. For the SFV group, the colonoscope will be advanced to the cecum again when hepatic flexure was reached the first time, where a SFV examination of the right colon will be

performed. Additional polyps removed in the right colon during the SFV examination will be sent for histopathological examination in separate specimen containers to avoid being confused with the polyps removed during the first forward view examination of the right colon. Examination of colonic mucosa for polyps from hepatic flexure to rectum will follow standard practice.

The risk of harm or discomfort of the second forward view examination of the right colon is similar to the risks of standard colonoscopy (less than 1% chance of perforation, bleeding, etc) because it does not involve a new endoscopic skill or new equipment. Based on local data at the Prince of Wales Hospital, the second forward view examination of right colon takes about an additional 2 minutes. No additional sedation medication was needed for the added time based on the local data.

Randomization Method

Block randomization generated by a computer program will be used at study site. Randomization will be in 1:1 ratio.

OUTCOME MEASURES

Primary Outcomes

1) Per-patient ADR in the right colon in each group. For the SFV group, it is defined as the number of patients with at least 1 adenoma identified in the right colon on either the first or second examination of the right colon divided by the total number of patients in the SFV group. Thus, if a patient has at least 1 adenoma detected on both the first examination and the second examination of the right colon, then this patient will be counted once only. For the conventional group, it is defined as the number of patients with at least 1 adenoma identified in the right colon on the conventional withdrawal examination of the right colon divided by the total number of patients in the conventional withdrawal group.

Secondary Outcomes

1) Increase in per-patient ADR in the right colon in the SFV group.
    - It is defined as the difference between the new ADR in the right colon after the first examination and SFV (again, if a patient has at least 1 adenoma detected on both the first examination and the second examination of the right colon, then this patient will be counted once only) and the ADR in the right colon after the first examination.
2) Overall ADR for the entire colon in each group.
    - For the SFV group, it is defined as the number of patients with at least 1 adenoma identified on either the second examination of the right colon or on the first examination of the right + examination from hepatic flexure to rectum, divided by the total number of patients in the SFV group. Thus, if a patient has at least 1 adenoma detected on both the first examination and

the second examination of the right colon, then this patient will be counted once only. For the conventional group, it is defined as the number of patients with at least 1 adenoma identified in the whole colon on the conventional withdrawal examination divided by the total number of patients in the conventional withdrawal group.

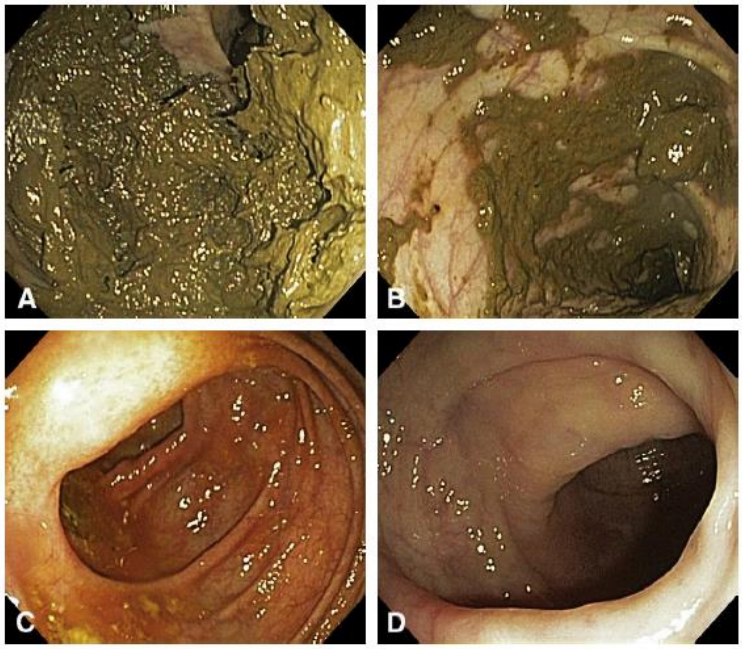
3) The number of patients with at least 1 additional adenoma detected in right colon in the SFV group
4) Adverse events during colonoscopy and up to 30 days post colonoscopy (eg, perforation, bleeding, etc)
5) Total number of adenomas found on the first and second examinations of the right colon in the SFV group, and that on the examination of the right colon in the conventional group
6) Total number of polyps (all pathological type) found on the first and second examinations of the right colon in the SFV group, and that on the examination of the right colon in the conventional group

Bowel preparation quality assessment:

Endoscopists will rate the quality of bowel preparation using the Boston bowel preparation scale (BBPS), a quantitative scale that assesses bowel preparation after all cleansing maneuvers are completed by the endoscopist [21]. A 4-point scoring system will be used to rate the following three main regions of the colon: right colon (ie, cecum, ascending colon), transverse colon (ie, hepatic flexure, transverse colon, splenic flexure), and left colon (ie, descending colon, sigmoid, rectum).

Figure 1: A, Segment score 0, unprepared colon segment with mucosa not seen because of solid stool that cannot be cleared. B, Segment score 1, portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen because of staining, residual stool, and/or opaque liquid. C, Segment score 2, minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well. D, Segment score 3, entire mucosa of colon segment seen well with no residual staining, small fragments of stool and/or opaque liquid [21]. Therefore, the maximum BBPS score for a perfectly clean colon without any residual liquid is 9, and the minimum BBPS score for an unprepared colon is 0.

Figure 1: (reference 21)



SAMPLE SIZE CALCULATION

Based on an ADR in the right colon of 16.0% from a screening colonoscopy cohort in Hong Kong, and assuming a SFV examination of the right colon would give a 6.7% increase in ADR in the right colon [18], we would need 502 patients per study group (ie, a total of 1004 patients for the study) in order to give a power of 80% at a type 1 error of 5%.

STATISTICAL ANALYSIS

Categorical variables will be analyzed using chi-square test or Fisher's exact test. Continuous variables will be analyzed using Student's t-test or Mann-Whitney U test. $P < 0.05$ is considered to be statistically significant.

TIME TABLE OF WORK

The ethics committee's approval of the study will be sought. The study will commence in November / December 2016 upon ethics committee's approval. The expected project duration is 24 months.

DATA HANDLING AND DISSEMINATION OF INFORMATION

All data obtained from the study will be kept confidential and be available only to personnel involved in the study and patient care. Case report forms and other documents will be kept in designated area of the Institute of Digestive Disease and retained for 7 years after study completion. The results of this study will be presented in scientific meetings and medical journals.

DISCLOSURE

The study would be conducted in compliance with the Declaration of Helsinki.

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