学位論文
Doctoral Thesis

Colorectal cancer screening at multidetector-row computed tomography: detection of flat- and polypoid lesions with a dedicated workstation
（大腸がんスクリーニングにおけるマルチスライスCT:ワークステーションを用いた平坦型及び隆起型病変の検出）

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2012年3月

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Abstract

Background and Purpose: In recent years, computed tomography colonography (CTC) has been clinically applied to screen for colorectal cancers, and perceived as highly diagnostic, because of the widespread use of multidetector-row CT and increased accuracy of analysis software. In addition, CTC, which yields objective and reproducible results, is a high-potential screening method, in that it is a low-invasive test associated with mild distress, and can be easily normalized. Thus, the purposes of this study are: 1) to compare the detectability of colorectal lesions among 3 different colon cleansing techniques; 2) to evaluate the effect of the use of antispasmodics on colonic dilatation; and 3) to evaluate the detection capability and usefulness of CTC in the screening of flat- and polypoid lesions by comparing CTC- and optic colonoscopy findings.

Materials and Methods: In the first basic study, three preprocessing methods were compared: polyethylene glycol on the previous day, polyethylene glycol on the same day, and a bowel-cleansing tablet on the previous day. In the second basic study, the subjects were 83 patients who underwent CTC screening (40 without antispasmodics, 43 with antispasmodics). Volume rendering images obtained in the supine and prone positions were used for evaluation. In the third clinical study, we evaluated the CTC detection capability for flat colorectal polyps with a flat surface and a height not exceeding 3mm by comparing to conventional polypoid lesions according to the polyp diameter. Four types of reconstruction images including multiplanar reconstruction, volume rendering, virtual gross pathology, and virtual endoscopic images were used for visual analysis. We compared the abilities of the 4 reconstructions for polyp

visualization.

Results: Visual assessment scores were also significantly different between the three methods (p<0.05). The lumen was visualized more clearly when the volume of residual colonic contents was less. Performing polyethylene glycol on the previous day allows blind areas to be reduced with high precision. In the second basic study, Colonic dilatation was significantly greater with antispasmodics than without (p<0.05). In the third clinical study, Detection sensitivity for flat polyps was 31.3%, 44.4%, 87.5% for lesions measuring 2-3 mm, 4-5 mm, and ≥6 mm, respectively; the corresponding sensitivity for polypoid lesions was 47.6%, 79.0%, 91.7%. Virtual endoscopic imaging showed best visualization among the 4 reconstructions.

Conclusion: The virtual endoscopic imaging showed highest visualization score for detection of both flat- and polypoid colorectal polyps. CTC using 64-row multidetector CT is useful for colon cancer screening to detect the lesions measuring 6 mm or more, although the detection of flat lesions is still challenging.

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   The Current Status and Issues of the Screening for Colorectal Cancer with CT Colonography.
   Stomach and Intestine. 47(1): 55-65 2012

Acknowledgements

These academic investigations were done during from 2008 to 2012 at department of Diagnostic Radiology, Graduate School of Medical Sciences, Kumamoto University.

I wish to extend my sincere thanks to Dr. Daisuke Utsunomiya, Department of Diagnostic Radiology, Graduate School of Medical Sciences, Kumamoto University for general guidance and constructive instructions.

I am deeply grateful to Professor Yasuyuki Yamashita, chairman of the Department of Diagnostic Radiology, Graduate School of Medical Sciences, Kumamoto University.

Of course, I owe a great deal to the colleagues of Radiology, Dr. Urata, RT. Kawakami, RT. Matsuda, for their cooperation and helps in my works.

Finally, the greatest gratitude is offered to Dr. Mitsuzaki who motivated me to be engaged in scientific study.

Abbreviations

2D: two-dimensional

3D: three-dimensional

ACR: American College of Radiology

CT: computed tomography

CTC: computed tomography colonography

KV: kilovolt

OC: optic colonoscopy

PPV: positive predictive value

mAs: milliamperesecond

MPR: multiplanar reconstruction

MDCT: multidetector-row CT

NPV: negative predictive value

PEG: polyethylene glycol

VC: virtual colonoscopy

VE: virtual endoscopy

VGP: virtual gross pathology

VR: volume rendering

- Chapter I -

Clinical Role of CT Colonography

1. Background

2. Clinical Application

3. Techniques and protocols

4. Summary

1. BACKGROUND

Colorectal cancer is common malignancy all over the world, and is preventable if detected early at screening examinations. Optic colonoscopy (OC) is a conventional method for screening of colorectal lesions; however, it is relatively invasive and operator-dependent. Computed tomography colonography (CTC) has been introduced as an alternative technique. It is also known as virtual colonoscopy (VC), is a useful technique for the evaluation of the entire colon. It has potential advantages over conventional colonoscopy because of its minimally invasive nature and no need for sedation and recovery time. The examination is based on a helical, thin-section CT of the cleansed and distended colon. Data evaluation is performed with commercially available CTC post-processing software with simultaneously available multiplanar two-dimensional (2D) and virtual endoscopy (VE) three-dimensional (3D) image displays. Also, CTC can be a valuable tool for the identification of extracolonic findings [1, 2]. Yee and colleagues [3] evaluated extracolonic findings in 500 subjects who underwent CTC, and they reported that clinically important extracolonic findings were identified in 9% of patients (45/500).

CTC was first popularized by Vining and colleagues [4] at the Bowman Gray School of Medicine in 1994, where they used helical CT data to provide 3D images, simulating the endoluminal view of traditional OC. They called the technique CTC [5]. The term of "CTC" was later adopted by the American College of Radiology (ACR) because of its more accurate description of the test [6]. Early studies of CTC were performed in the supine position, using prior-generation single- or dual-row CT scanners and 2D imaging. Incorporation of supine and prone positions, multidetector-row CT (MDCT) scanners, and both 2D and 3D imaging has allowed for steady improvement in resolution and detection [6, 7]. The use of the supine- and prone positions in a single CTC test allows for better displacement of fluid and stool to reduce areas of the colon that may be obscured by retained fluid or poorly distended. The clinical use of CTC has been the detection of colon cancer and the surveillance of colorectal polyps, although CTC had not been widely used on prior-generation MDCT with 16- or less detectors. After the introduction of newer-generation MDCT with 64- or more detectors, its use has been growing in popularity among physicians and patients for cancer screening. As opposed to OC, CTC does not require conscious sedation or endoscopy, making it less invasive and less time-consuming. Currently, there are several clinical indications for CTC. They include evaluation of the colon after an incomplete or unsuccessful conventional colonoscopic examination and evaluation of the colon proximal to an obstructing neoplasm [8-10]. Another potential indication for CTC is in the evaluation of frail and elderly patients or patients who would have an increased risk with conventional colonoscopy. The use of CTC to monitor patients after surgery for colorectal cancer is currently under investigation [11, 12]. In addition, CTC may contribute to colorectal screening by providing a safe, effective, and rapid examination that can be used to evaluate the entire colon for clinically significant lesions.

2. CLINICAL APPLICATION

CTC has developed an important role for the evaluation of the colorectal lesions. In some situations it may be a safer method to visualize the colon effectively, or it may be the only available option when other techniques have failed. CTC requires the volumetric acquisition of data using helical CT and is now achieved with MDCT with 64 detectors or more. Post-processing of CT data sets is performed on a computer workstation with specific software to generate axial images, multiplanar reconstruction (MPR) views, and 3D images of the colon. (Fig. 1-4)

Before the patient is scanned, however, several preparatory steps are required to produce an optimally diagnostic study. A well-cleansed colon with good distention is essential to achieve a high-quality study for polyp and cancer detection. A poorly prepared colon may be the cause of both false-negative and false-positive findings [13, 14]. Standard CTC protocol requires scanning the patient in supine- and prone positions, which allows segments of colon with poor cleansing or suboptimal distention in one position to be reevaluated in the opposing position with potentially improved distention and cleansing. The rationale for using various colonic cleansing regimens for CTC is discussed. Positive labeling of residual material and electronic subtraction of tagged material are potential strategies to reduce and possibly eliminate the need for purgatives that would further increase patient acceptance of CTC compared with other techniques. The two distending agents for CTC (room air and carbon dioxide) are discussed, along with practical tips for administration and the role of antispasmodic drugs.

The ability of CTC to detect colorectal polyps has been tested in many previous studies[13, 15, 16]. CTC appeared to be promising in high-risk populations; with a reported sensitivity greater than 90% for polyps ≥10 mm. Recent results in the low

prevalence population were more heterogeneous and less impressive (34–93.8%) [15, 17-19]. This wide range of results may be likely caused by differences in patient selection, examination and evaluation techniques, and reader experience [20, 21]. Also, the detection of flat colorectal polyps is still challenging.

Thus, we consider that the appropriate preparation and the validation of the clinical role of CTC in the large number of patients are critically important.

3. TECHNIQUES AND PROTOCOLS

State-of-the-art CTC requires MDCT and a high-end computer workstation with advanced graphic software that displays 2D and 3D views of the colon. Patients typically are scanned in a craniocaudal direction in both supine and prone positions. Scanning in the supine and left lateral decubitus positions has been proposed as an alternative to supine and prone scanning whenever patients cannot lie prone. Gryspeerdt and colleagues [22] found improvements in colonic distention using either supine/prone or supine/left lateral decubitus. Fewer breathing artifacts were noted with left lateral decubitus imaging in elderly patients.

Intravenous contrast material is not administered routinely for screening CTC. Disadvantages of the use of intravenous contrast include increased invasiveness, the possibility of contrast reactions, higher radiation dose, increased interpretation times, and higher cost. Intravenous contrast should not be administered if patients undergo oral stool and fluid tagging because of the potential difficulty in differentiating an enhancing lesion from tagged material. Morrin and colleagues [23] found that administration of intravenous contrast significantly improved reader confidence for assessment of bowel wall conspicuity and for the detection of medium-sized polyps (6–9 mm) in suboptimally cleansed colonic segments. When the diagnosis of colon

cancer is already established or is suspected based on initial imaging, intravenous contrast should be administered for CTC for staging purposes.

A typical CTC protocol using MDCT consists of a collimation of 0.625 to 2.5 mm with a gantry rotation time of 0.5 seconds resulting in a scan time of less than 10 seconds. MDCT scanners have enabled subcentimeter collimation without compromising z-axis coverage. The volumetric data set is used for traditional 2D axial images and MPR as well as to produce 3D endoluminal views. Motion artifact from peristalsis and respiration is decreased or eliminated with MDCT because scan times are significantly shortened. Several studies have demonstrated that thinner reconstructions allow increased sensitivity for small polyps (< 6mm) and improve specificity in both phantom and human datasets [24-27]. Lui and colleagues [24] performed a study in 25 patients and found increased specificity for polyps 5 mm or larger using a slice thickness of 1.25 mm x 1 mm when compared with thicker slices (5 mm x 2 mm) using a 4-row MDCT.

The ACR practice guidelines for the performance of CTC recommend use of MDCT with a slice collimation of 3 mm or less and a reconstruction interval of 1.5 mm or less [28]. In a recent consensus study a maximum acceptable slice thickness of 3 mm or less was recommended by 88% (22/25) of selected CTC experts [29]. According to the ACR guidelines, we suggest that 64-row MDCT should be appropriate for CTC.

CTC has several limitations such as ionizing radiation and preparation. Because of the intrinsic high contrast between the intraluminal gas and the soft tissue of the colonic wall, dropping the milliamperesecond (mAs) should be performed. Macari and colleagues [30] performed CTC in 105 subjects using 50 mAs, 120 kilovolt (kV), and a 1.25-mm slice thickness with a 1-mm reconstruction interval. Sensitivity of CTC for the detection of polyps 6 to 9 mm and 10 mm or larger were 70% and 93%,

respectively. To obtain diagnostic image quality, the preparation such as colon cleansing and colonic dilatation is especially important. However, the appropriate preparation techniques have been undefined.

4. SUMMARY

For the appropriate performance of CTC in clinical practice, the optimal colonic preparation i.e. bowel cleansing and sufficient colonic distention should be critical. The first purpose of this thesis was to optimize the technique in patient preparation (Chapter II and III). The second purpose was to evaluate the detection capability and usefulness of screening CTC with 4-different reconstruction methods; i.e. MPR, volume rendering (VR), VE, and virtual gross pathology (VGP) images (Chapter IV).

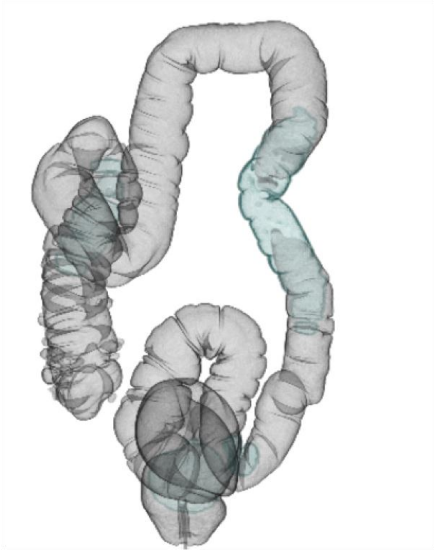

Fig.1 Volume Rendering Image

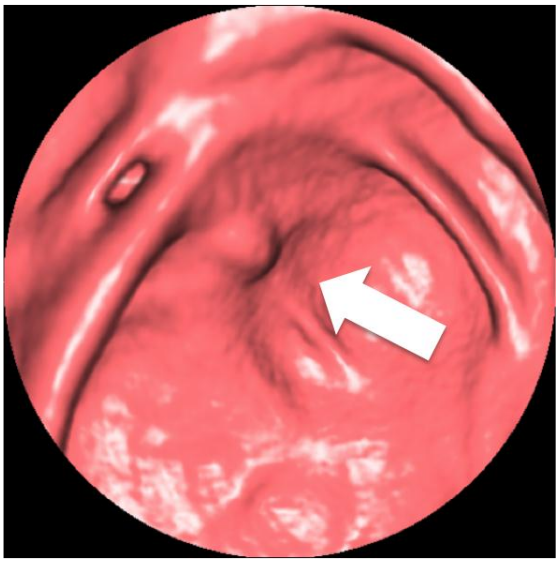

Fig.2 Virtual Endoscopy

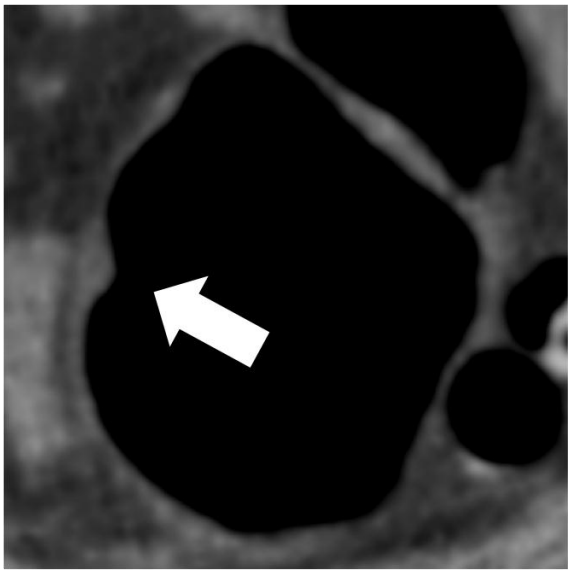

Fig.3 MultiPlanar Reconstruction Image

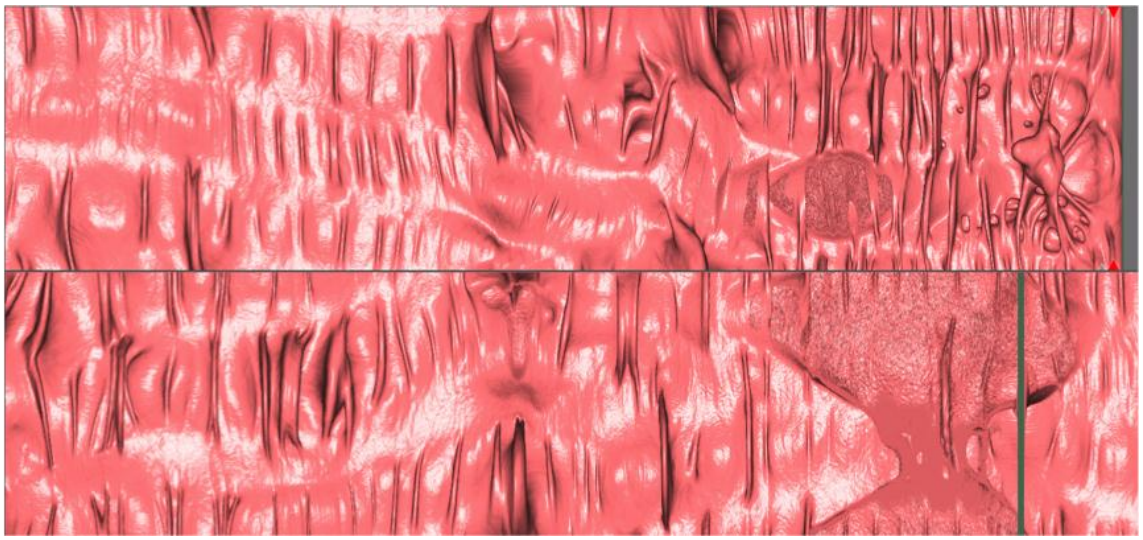

Fig.4　Virtual Gross Pathology

Virtual endoscopy image (Fig.2) shows polypoid lesion (arrow).　MultiPlanar Reconstruction image (Fig.3) shows polypoid lesion of uniform soft tissue density (arrow).

- Chapter II –

Improved image quality at screening CT colonography –
Optimization of the preprocessing for CT colonography

1. Introduction
2. Materials and Methods
3. Results
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1. INTRODUCTION

The introduction of CTC using MDCT has made it possible to acquire high-resolution images over a wide range in a shorter time. Due to the improvements of image processing techniques, the application of CTC as a screening examination has been extensively investigated, mainly in the United States and Europe. [15, 31]

In Japan, on the other hand, the combined use of fecal occult blood testing and total colonoscopy is recommended for screening, and as a result, few studies have been conducted to evaluate the usefulness of CTC as a screening examination. In order for CTC to be employed for screening, bowel preparation protocols that are easy to perform and also ensure accurate examination results must be established. Obtaining images with a consistent level of image quality under conditions in which there is a minimal volume of residual liquid or solid matter in the colon is the most important factor in improving visualization of the intestinal lumen and thus ensuring accurate diagnosis in clinical practice (Fig. 1a. 1b).

In the present chapter, we evaluated the diagnostic accuracy and clinical usefulness of CTC by comparing different bowel-preparation protocols.

2. MATERIALS AND METHODS

Study group

Of 450 patients who underwent total colonoscopy between February 2009 and September 2010, 151 patients who agreed to undergo CTC examination before colonoscopy were enrolled in this study. Three different bowel preparation protocols were developed and randomly employed for CTC examination. In the group A, a bowel cleansing agent (polyethylene glycol [PEG]) was administered on the day before the examination, and CTC was performed on the following day. In the group B, the bowel-cleansing agent was administered in the morning of the day of examination, and CTC was performed in the afternoon. In the group C, a bowel-cleansing agent (Monobasic sodium phosphate monohydrate: Visiclear® Combination Tablets, Zeria Pharmaceutical, Japan [Bowel cleansing tablets]) was administered on the day before the examination, and CTC was performed on the following day (Fig. 2).

Group A and B received 2 liters of the bowel cleansing agent, group C received bowel cleansing tablets 50tablets and 2 liters of the water, which is required for colonoscopy. In addition, water-soluble iodinated contrast medium (sodium amidotrizoate and meglumine amidotrizoate, Gastrografin) was used for fecal tagging. When the remaining amount of bowel cleansing agent had fallen to 380 mL, 20 mL of Gastrografin was added, and the total volume of 400 mL of this mixture was then administered.

The study group included 74 men and 77 women with an average age of 49.1± 9.8 years (age range: 25 to 79 years). The group A included 45 patients and the group B included 60 patients and the group C included 46 patients. The age of the patients was 50.3±12.5 years in the group A, 51.0±8.3 years in the group B and 45.3±7.7 years in the group C. The body weight of the patients was 60.3±12.4 kg in the group A and 63.7±11.2 kg in the group B and 61.7±10.2 kg in the group C. The target lesions were polyps measuring 2 mm or more in diameter detected by colonoscopy. All patients

gave informed consent to undergo CTC examination, which involves X-ray exposure, requires the injection of an antispasmodic agent immediately before colonoscopy as well as the administration of iodinated contrast medium, and may cause a bloated sensation or abdominal pain.

CTC

After bowel preparation was completed, an antispasmodic agent (Sesden, 10 mg) was injected intramuscularly 10 minutes before CTC. CTC was then performed using a 64-row MDCT system (Aquilion 64, Toshiba, Japan). Total colonoscopy was performed after CTC. Image analysis was performed at an image workstation (Ziostation System N610, Version 1.21b, Amin, Japan).

Data Acquisition

A tube voltage of 120 kV, a tube current of 100 mA, and a gantry rotation speed of 0.5 s/rot were employed for scanning. The slice collimation was 0.5 mm × 64 slices, the helical pitch was 0.83, and the couch-top movement speed was 27 mm/rot in all patients.

The patient was placed on the couch top in the left lateral decubitus position and received the antispasmodic agent (Sesden, 10 mg) by intramuscular injection in order to suppress intestinal peristalsis before CTC was started. Rectal examination was performed to check for the presence of lesions in the anus, and a 12-EG Nelaton catheter for insufflation was then introduced via the anus. Air or carbon dioxide was administered with the patient in the left lateral decubitus or prone position using an automatic insufflator with a pressure measurement function. After a scout view was obtained to confirm sufficient dilatation of the colon, image acquisition was performed during breath-holding (at end expiration) in the prone and supine positions. The scan

range extended from the bottom of the diaphragm to the inferior edge of the pubis in both positions, with scanning performed in the foot-to-head direction during breath-holding for 7 s to 10 s. Image reconstruction was performed with a slice thickness of 0.5 mm for the acquired helical data. Images reconstructed at 0.5-mm intervals (900 to 1000 slices) were then transferred to the image workstation.

Total Optic Colonoscopy

After CTC examination was completed, the antispasmodic agent (Sesden, 10 mg) was again injected intramuscularly 10 minutes before total colonoscopy and a sedative (Horizon, 10 mg) was injected intravenously immediately before total colonoscopy. The endoscopist (who was qualified as a supervising physician and had performed more than 5000 colonoscopic examinations) performed colonoscopy (CF endoscope, Fujinon Toshiba, Japan). The colonoscope was first advanced into the cecum and then withdrawn toward the anus while checking for the presence of polyps in each region. The findings such as the region, size, and macroscopic morphological characteristics of the polyps were then recorded on the designated form. The size of the polyps was measured using biopsy forceps inserted via the forceps channel, with the forceps pressed against the polyps closed (2 mm in diameter) and open (5 mm in diameter). Biopsy specimens were generally obtained for polyps measuring 6 mm or more in diameter and polyps characterized as depressed plaques measuring 5 mm or less in diameter.

Image Interpretation

Two physicians (the endoscopist who was qualified as a supervising physician and a board-certified radiologist) interpreted the colonoscopic images independently in a blinded manner. In the event of disagreement regarding the diagnostic findings, the

final diagnosis was reached by discussion and consensus. The patient data was selected at the workstation, and images comparable to those obtained by barium enema were generated using the VR method to check for insufficient dilatation, deformation of the walls, and mucosal irregularities. Dissected colon images (VGP images) were then used to identify the regions containing suspected lesions. In the dissected colon images, the presence of elevated lesions and morphological abnormalities were checked by observing the image of each semilunar fold. All of the regions containing suspected lesions were checked and then evaluated in diagnosis confirmation mode. In diagnosis confirmation mode, the regions containing suspected lesions were observed using VE and MPR images in order to determine whether or not lesions were present. When a lesion was found, its region and size were evaluated. With regard to size, the maximum diameter of the lesion was measured in two-dimensional MPR images. In addition, the VE images were observed from two directions (from the oral end and from the anal end) to check for the presence of lesions. When a suspected lesion was found, the region including the suspected lesion was checked in the VGP image again. The final diagnosis was then established based on the findings identified in the VE, VGP, and MPR images. The images obtained with the patient in the prone and supine positions were interpreted in the manner described above to check for lesions.

Study Items

The results obtained by total colonoscopy were used as the gold standard, and the diagnostic results obtained using the CTC images were compared between the three groups for lesions measuring 2 mm or more in diameter. The colon was divided into six regions: the cecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum. The presence and the location of colonic lesions were visually assessed on the CTC images by the 2 observers. The sensitivity,

specificity, and diagnostic accuracy were then calculated in each group.

Next, the volume of residual liquid in the colon following each of the bowel preparation protocols was evaluated. The volume of residual liquid in each region was evaluated by visual assessment of the VE and MPR images and then rated using a 5-grade scale: 0%, 25%, 50%, 75%, and 100% (Fig. 3). For visual assessment, statistical analysis was performed using the Kruskal-Wallis test. A p value of less than 0.05 was considered to be statistically significant.

3. RESULTS

Of the 151 patients who underwent total colonoscopy and CTC, fecal tagging could not be performed due to iodine hypersensitivity in 15 patients.

Polyps measuring 2 mm or more in diameter were found in 61 (40.4%) of the 151 patients. The total number of polyps that were detected by colonoscopy was 123 lesions: 91 lesions measuring 2-4 mm and 32 lesions measuring 5 mm or more. Of these polyps, the final diagnosis was established by histopathological examination of biopsy or surgical specimens in 20 patients (25 lesions). The numbers of patients and types of polyps were as follows: 4 patients with a hyperplastic polyp (6 lesions) and 16 patients with tubular adenoma (19 lesions).

Comparison of Accuracy Rates among the 3 Groups

The accuracy rates in each group are shown in Table 1. In the group A, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were 80.0%, 83.1%, 42.1%, 96.4%, and 82.6%, respectively. In the group B, the sensitivity, specificity, PPV, NPV and diagnostic accuracy were 50.0%, 87.8%, 47.3%, 88.9%, and 81.0%, respectively. In the group C, the sensitivity, specificity, PPV, NPV and diagnostic accuracy were 58.3%, 76.7%, 22.5%, 94.1% and

74.8%, respectively. A significant difference was observed in sensitivity between the group A and the group B, group C ($p<0.05$). A significant difference in PPV was observed between the group A, group B and the group C ($p<0.05$).

Comparison of Detection Rates According to the Size of the Lesion among the 3 Groups

The detection rates according to the size of the lesion in each group are shown in Table 2. In the group A, the sensitivity and PPV for all lesions were 75.8% and 37.9%, respectively. The sensitivity was 68.4% (13/19) for lesions measuring 2-4 mm and 85.7% (12/14) for lesions measuring 5 mm or more. The sensitivity for lesions measuring 5 mm or more was 85.7%, showing good results. The PPV was 28.8% for lesions measuring 2-4 mm and 57.1% for lesions measuring 5 mm or more. The larger the lesion, the higher the PPV. In the protocol B group, the sensitivity and PPV for all lesions were 49.2% and 47.8%, respectively. The sensitivity was 44.4% (24/54) for lesions measuring 2-4 mm and 72.7% (8/11) for lesions measuring 5 mm or more, showing good results. The PPV was 44.4% for lesions measuring 2-4 mm and 61.5% for lesions measuring 5 mm or more. In the protocol C group, the sensitivity and PPV for all lesions were 53.8% and 16.3%, respectively. The sensitivity was 50.0% (10/20) for lesions measuring 2-4 mm and 66.6% (4/6) for lesions measuring 5 mm or more, showing good results. The PPV was 12.8% for lesions measuring 2-4 mm and 50.0% for lesions measuring 5 mm or more. In all protocols, the tendency was observed that the larger lesions had the higher PPV.

Evaluation of the Volume of Residual Liquid in the Colon in Each Group

The visual evaluation results for the volume of residual liquid in each region of the colon are shown in Fig 4. For the images obtained with the patient in the prone

position, the ratings in the protocol A were 4.48 in the cecum, 4.68 in the ascending colon, 4.31 in the transverse colon, 4.44 in the descending colon, 4.28 in the sigmoid colon, and 4.86 in the rectum, with an overall rating of 4.51, while the ratings in the protocol B were 3.63 in the cecum, 3.91 in the ascending colon, 3.03 in the transverse colon, 3.50 in the descending colon, 2.65 in the sigmoid colon, and 4.21 in the rectum, with an overall rating of 3.49. The ratings in the protocol C were 4.00 in the cecum, 4.34 in the ascending colon, 3.07 in the transverse colon, 4.13 in the descending colon, 3.65 in the sigmoid colon, and 4.52 in the rectum, with an overall rating of 4.06. Significant differences were observed between the three groups in all regions ($p<0.05$). For the images obtained with the patient in the supine position, the ratings in the protocol A were 4.48 in the cecum, 4.66 in the ascending colon, 4.62 in the transverse colon, 4.00 in the descending colon, 4.53 in the sigmoid colon, and 4.75 in the rectum, with an overall rating of 4.51, while the ratings in the protocol B were 4.13 in the cecum, 3.91 in the ascending colon, 3.88 in the transverse colon, 2.26 in the descending colon, 3.20 in the sigmoid colon, and 3.80 in the rectum, with an overall rating of 3.53. The ratings in the protocol C were 4.13 in the cecum, 3.82 in the ascending colon, 3.88 in the transverse colon, 3.30 in the descending colon, 3.91 in the sigmoid colon, and 4.26 in the rectum, with an overall rating of 3.96. Significant differences were observed between the 3 groups in all regions ($p<0.05$).

Bowel preparation protocol A resulted in a smaller volume of residual liquid as compared with protocol B and protocol C.

4. DISCUSSION

The key element of a high quality CTC examination is a well-prepared clean, and well-distended colon. Residual stool and fluid may lead to a false-negative or false-positive diagnosis. Therefore, CTC, at present, requires full bowel preparation, just like colonoscopy and double contrast barium enema examination [32].

The mechanism of action and delivery of the three most commonly used cathartic agents for bowel cleansing differ, explaining their relative advantages and disadvantages in various patient populations. PEG is an osmotically balanced electrolyte lavage solution, which results in minimal water and electrolyte absorption and secretion [33]. Because PEG does not result in internal fluid shifts, it has the advantage of being safe in the vast majority of patients and provides a gentle colonic lavage [34].

The goal of colon preparation is to cleanse the colon and to provide contrast for fecal and fluid tagging. This preparation increases the specificity of CTC by tagging residual or adherent fecal material.

In the assessment of residual liquid with the bowel preparation protocol employing PEG on the previous day (group A), the average scores were 4.51 for the images obtained with the patient in the prone position and 4.51 for the images obtained with the patient in the supine position. In the assessment of residual liquid with the protocol employing PEG on the same day (group B), the average scores were 3.49 for the images obtained with the patient in the prone position and 3.53 for the images obtained with the patient in the supine position. In the assessment of residual liquid with the protocol employing bowel cleansing tablets on the previous day (group C), the average scores were 4.06 for the images obtained with the patient in the prone position and 3.96 for the images obtained with the patient in the supine position. Visualization of the lumen was improved as the volume of residual liquid decreased, with significant

differences observed between groups A and C and group B ($p < 0.05$).

For subjects who received PEG on the previous day (group A), the sensitivity, specificity, PPV, and NPV were 80.0%, 83.1%, 42.1%, and 96.4%, respectively. For subjects who received PEG on the same day (group B), the sensitivity, specificity, PPV, and NPV were 50.0%, 87.8%, 47.3%, and 88.9%, respectively. For subjects who received bowel cleansing tablets on the previous day (group C), the sensitivity, specificity, PPV, and NPV were 58.3%, 76.7%, 22.5%, and 94.1%, respectively. A significant difference was observed in sensitivity between group A and groups B and C ($p < 0.05$).

In the assessment according to the size of the lesion, the protocol employing PEG on the previous day showed excellent results for lesions measuring 4 mm or less in diameter, and a significant difference was observed in sensitivity as compared with the other protocols.

For lesions measuring 5 mm or more in diameter, which are considered the targets for detailed examination, no significant differences were observed between the protocols employing PEG on the previous day and PEG on the same day. Since the protocol employing bowel-cleansing tablets resulted in large amounts of cellulose residue, false positives were increased. As a result, the time required for image interpretation was increased and the examination accuracy (PPV) was reduced.

Patients are required to ingest 2L of PEG the before the study. Although PEG is an effective agent for cleansing the bowel, it is not ideal for CTC because it often results in excessive retained fluid in the colon and is considered a ‘‘wet prep.’’ Excess fluid in the colon limits the diagnostic ability of CTC but is not a limitation during OC, because fluid can be removed at the time of the procedure.

PEG on the previous day was found to minimize blind areas due to the presence of residual liquid in the colon.

5. CONCLUSION

The bowel preparation protocol in which the patient received PEG on the previous day of the CTC examination was found to minimize blind areas due to the presence of residual liquid in the colon. It is therefore considered that this is the most effective bowel preparation protocol for CTC examinations with highest detection capability. With regard to the detectability of lesions measuring 5 mm or more in diameter (which are the targets for detailed examination), PEG on the same day also showed good sensitivity and can be considered as an optional bowel preparation technique.

Table.1 Comparison of Accuracy Rates of CTC in the three Groups

Diagnostic accuracy of CTC in the three groups

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Group A (PEG on the previous day)	80.0*	83.1	42.1	96.4	82.6
Group B (PEG on the same day)	50.0	87.8	47.3	88.9	81.0
Group C (Bowel cleansing tablets on the previous day)	58.3	76.7	22.5**	94.1	74.8

PPV: Positive predictive value, NPV: Negative predictive value

*A significant difference in sensitivity was observed between group A and groups B and C.

**A significant difference in PPV was observed between groups A and B and group C.

Table.2 Comparison of Detection Rates According to the Size of the Lesion between the Three Groups

		Detection rates according to the size of the lesion		
Size of lesion		GroupA	GroupB	GroupC
≥5 mm	Number of lesions	12/14	8/11	4/6
	Sensitivity (%)	85.7	72.7	66.6
	PPV (%)	57.1	61.5	50.0
2 to 4 mm	Number of lesions	13/19	24/54	10/20
	Sensitivity (%)	68.4	44.4	50.0
	PPV (%)	28.8	44.4	12.8
Overall	Number of lesions	25/33	32/65	14/26
	Sensitivity (%)	75.8	49.2	53.8
	PPV (%)	37.9	47.8	16.3

PPV: Positive predictive value

PEG on the previous day resulted in the highest detectability of small lesions measuring 4 mm or less in diameter.

However, no significant differences were seen in the detectability of lesions measuring 5 mm or more in diameter (which are the targets for detailed examination) between PEG on the previous day and PEG on the same day.

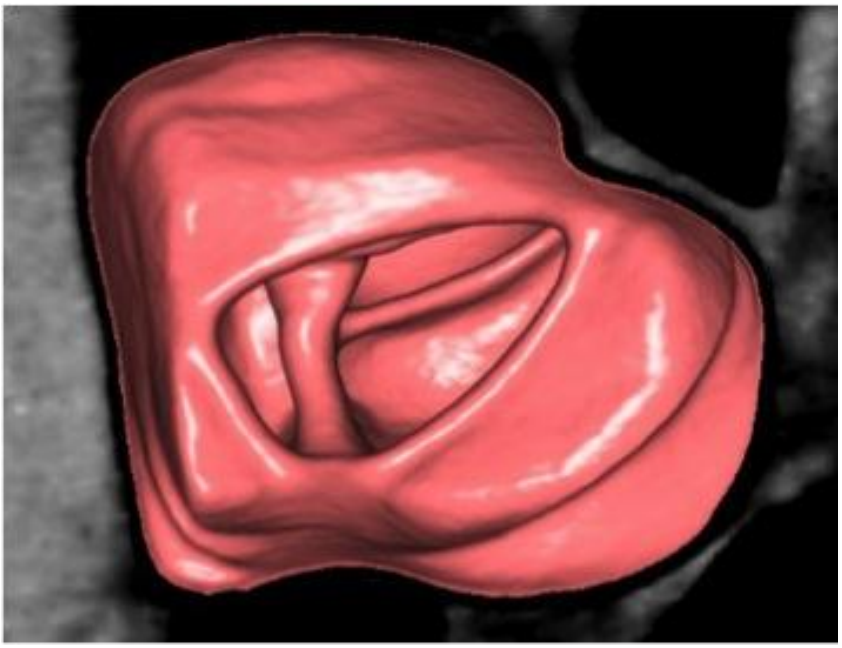


Fig.1a Optimal conditions in which there is almost no residual liquid in the colon

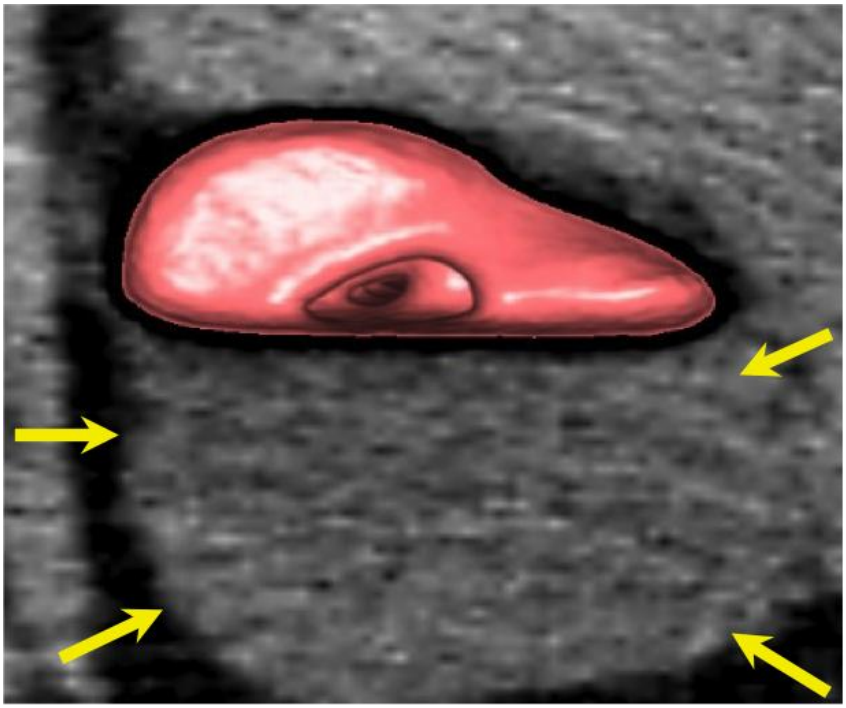
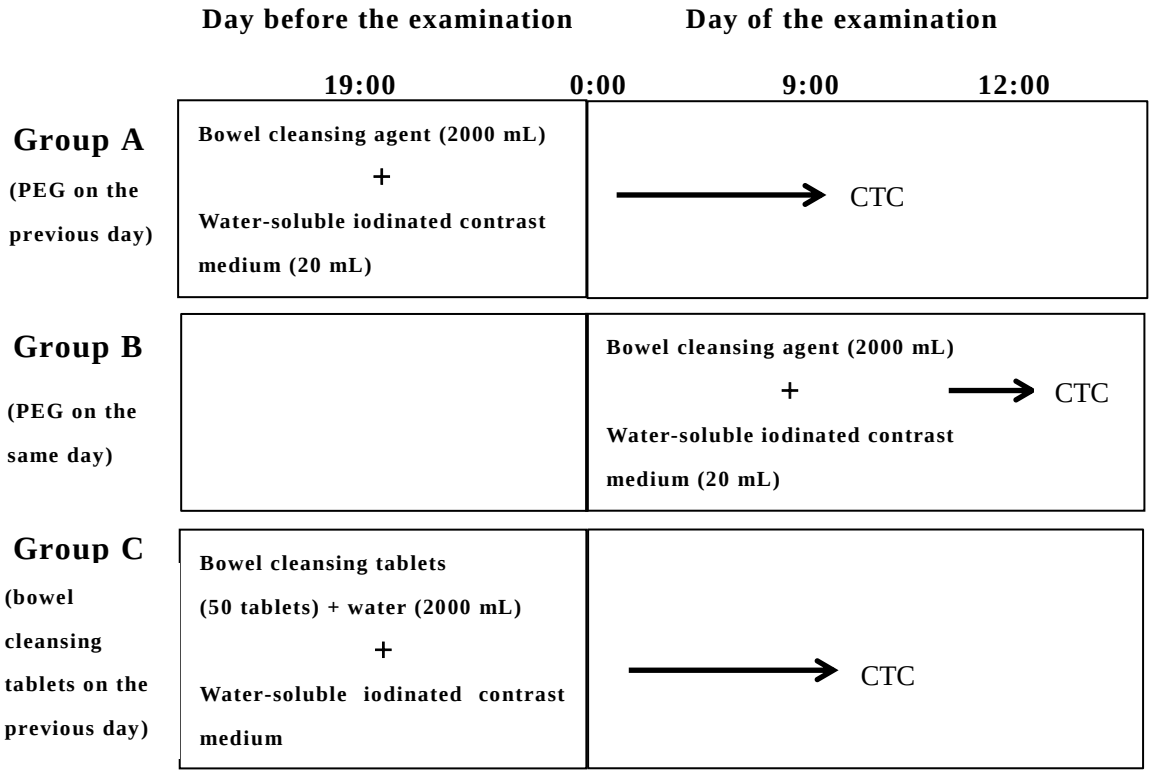


Fig.1b Less favorable conditions in which there is a larger volume of residual liquid in the colon (yellow arrows)



Group A : bowel cleansing agent was administered around 19:00 after dinner on the night before the examination.
CTC was performed in the morning (10:30 to 12:00) of the following day.

Group B: bowel cleansing agent was administered in the morning (9:00 to 10:00) on the day of the examination.
CTC was performed in the afternoon (14:00 to 15:00) on the same day.

Group C : The bowel cleansing tablets were administered around the same time as for Group A

Tagging method: Bowel cleansing agent (1620mL) +
bowel cleansing agent(380mL) + Water-soluble iodinated contrast medium (20 mL)

Fig.2 CTC bowel preparation protocols

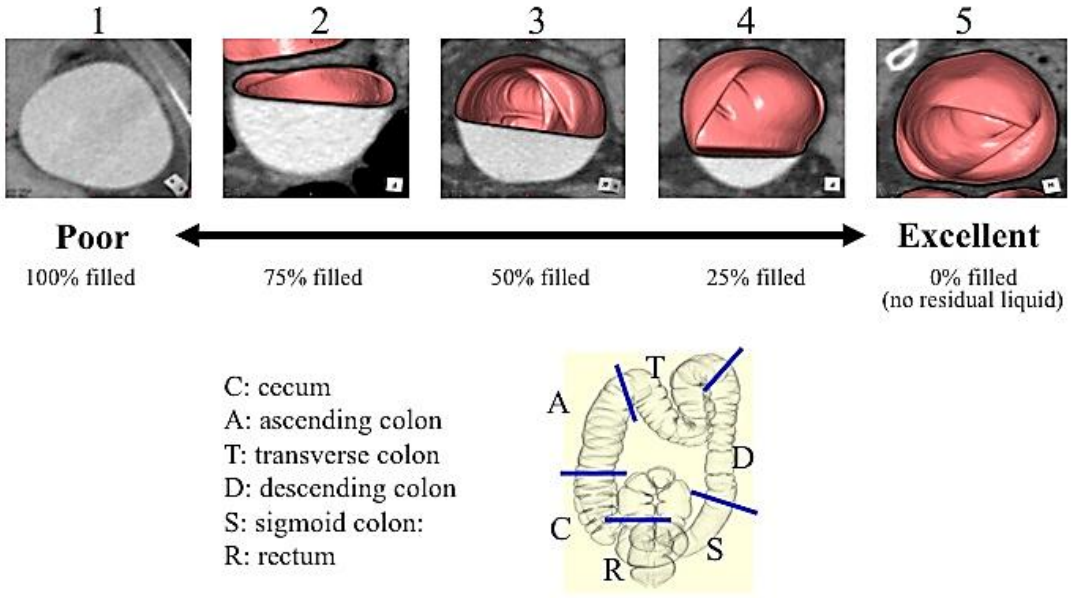


Fig.3 Residual liquid evaluation method and locations

The volume of residual liquid in each of six regions (from the cecum to the rectum) was visually assessed based on the VE and MPR images.

The volume of residual liquid in each region was visually evaluated using a 5-grade scale based on the VE and MPR images obtained with the patient in the prone and supine positions.

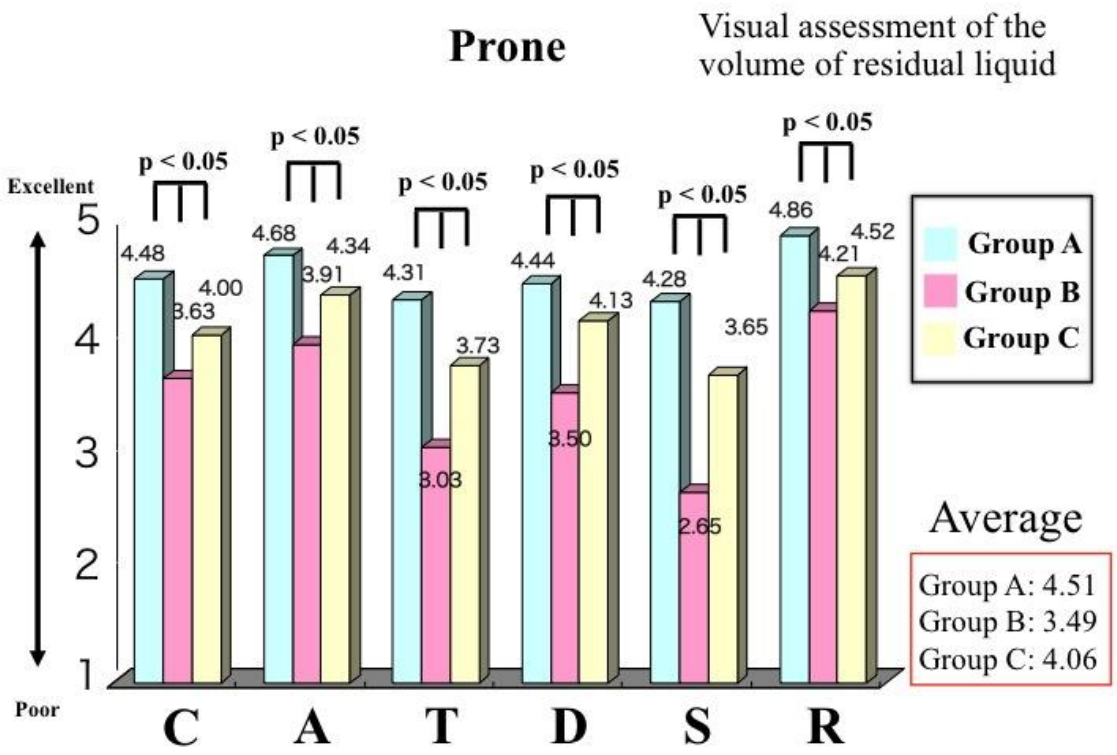


Fig.4-a Visual assessment of the volume of residual liquid (Prone position)

Statistically significant differences were observed in all regions (the cecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum). The values obtained for PEG on the same day were significantly lower.

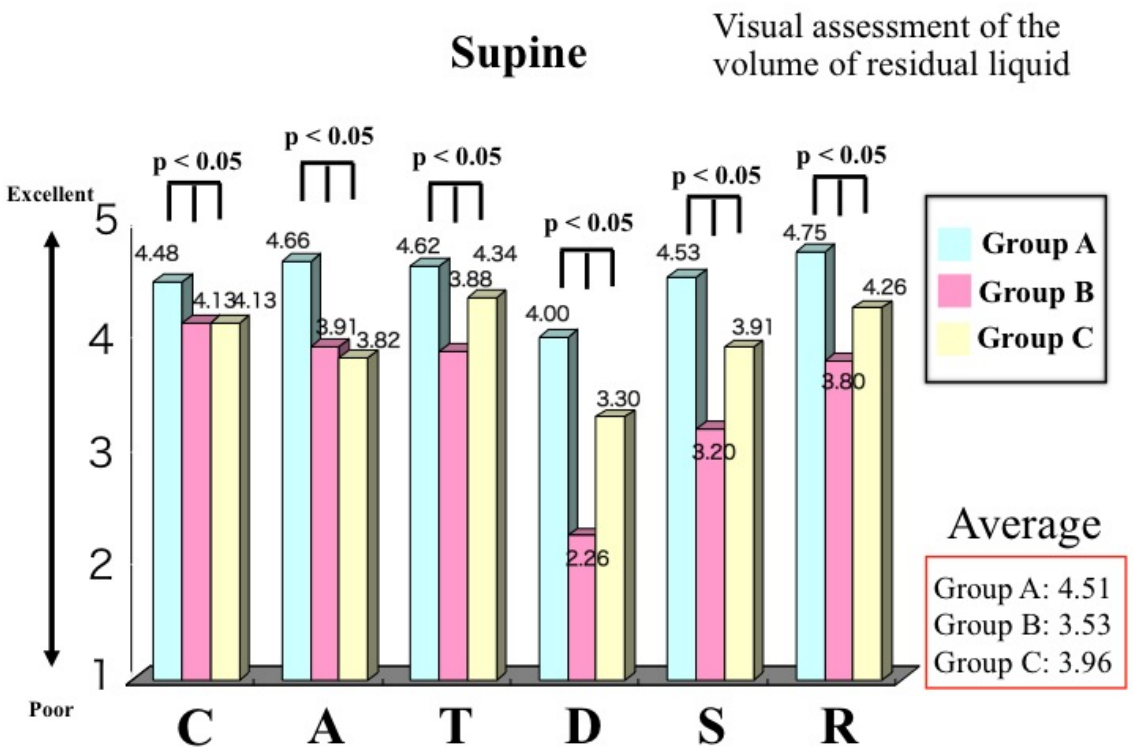


Fig.4-b Visual assessment of the volume of residual liquid (Supine position)

Statistically significant differences were observed in all regions (the cecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum). As was the case for the prone position, the values obtained for PEG on the same day were significantly lower.

- Chapter III -

Evaluation of colonic dilatation by CT colonography: the influence of the antispasmodics and the patient's body size

1. Introduction
2. Materials and Methods
3. Results
4. Discussion
5. Conclusion

1. INTRODUCTION

As MDCT emerged, CTC became capable of acquiring high-resolution images of a broad area within a short period of time, and advancement in image processing techniques facilitated studies on its application for screening mainly in Western countries [15, 16, 31, 35].

Several conditions are required to maintain the high-level accuracy of screening employing CTC, such as appropriate pretreatment, optimizing acquisition conditions, and fecal tagging, and favorable dilatation of the intestinal lumen is also an important factor. Insufficient colonic dilatation reduces the ability to observe lesions, leading to them being overlooked.

In this study, we paid attention to the use of antispasmodics as a factor which influences colonic dilatation on CTC, and compared colonic dilatation with and without the use of antispasmodics. Since, based on our clinical experience, a patient's body size is associated with the degree of colonic dilatation, we also evaluated colonic dilatation by body size. In addition, changes in colonic dilatation due to differences in the gas infusion pressure of an automated carbon dioxide delivery system were also

investigated.

2. MATERIALS AND METHODS

The subjects (96 males and 61 females) were randomly selected from 294 examinees that underwent CTC for screening between April and October 2009 by using a random number table.

Comparison of colonic dilatation with and without the use of antispasmodics

The subjects were divided into 43 treated with intramuscular injection of an antispasmodic (timepidium bromide: SESDEN® injection 7.5 mg, Tanabemitsubishi, Osaka, Japan) (treated group) and others who could not be treated with antispasmodics due to glaucoma and heart disease (untreated group). The treated group consisted of 34 males and 9 females aged 50.3±11.9 (mean±SD) years, and the untreated group comprised 30 males and 10 females aged 61.3±10.7 years. The gas infusion pressure was set at 20 mmHg in both groups.

Evaluation of colonic dilatation by body size

The body mass index (BMI) was used as an index of a subject's body size. For uniform test conditions, only 117 subjects with antispasmodic treatment were included, and 43 subjects without treatment were excluded. The subjects were divided into 3 groups based on the BMI: those with a BMI lower than 20, between 20 and 25, and 25 or higher. The subjects were further divided into 2 groups based on the gas infusion pressure: 20 and 23 mmHg. The 20 mmHg group consisted of 11 subjects with a BMI lower than 20, 17 with a BMI between 20 and 25, and 15 with a BMI of 25 or higher, and the 23 mm Hg group consisted of 15, 32, and 27 subjects, respectively (Table 1). The influence of body size on colonic dilatation was investigated according to the gas infusion pressure.

Acquisition method and conditions

For pretreatment before CTC, intestinal lavage solution (PEG, 2 L) was applied referring to that in endoscopy in all subjects. The system used was 64-row MDCT (Aquilion 64, Toshiba, Tokyo, Japan), and a workstation, ZIO station system N610 (Version 1.21b) (Amin, Tokyo, Japan) was used for analysis. The tube voltage was 120 kV, the tube current was 100 mA, and the gantry rotation speed was 0.5 sec. The collimation used was 0.5 mm x 64 in all subjects, the helical pitch was 0.83, and the table speed was 27 mm per rotation. The subject lay on the table in a left lateral position and received intramuscular antispasmodic administration 10 minutes before examination to inhibit intestinal peristalsis. After checking for the presence or absence of an anal lesion by rectal examination, a 12-EG nelaton catheter for gas delivery was inserted into the anus. The subject lay in a left lateral or supine position during gas delivery, and carbon dioxide was delivered at 20 or 23 mmHg using an automated delivery system equipped with a pressure measurement function (Nemoto Kyorindo, Tokyo, Japan). After confirming sufficient colonic dilatation in a scout view, images were acquired while breath-holding (expiration) in prone and supine positions. The acquisition area was the subdiaphragmatic region over the inferior margin of the pubes in both positions, and cephalocaudal images were acquired during breath-holding for 7-10 seconds. The obtained helical data were subjected to image reconstruction at a 0.5-mm slice thickness and 0.5-mm intervals (900-1000 images), and transmitted to the workstation.

Visual evaluation of colonic dilatation

The acquired image data were transmitted to the workstation and selected for examination, followed by the preparation of 3D air images employing VR. The large intestine was divided into 5 segments (ascending colon: A, transverse colon: T,

descending colon: D, sigmoid colon: S, and rectum: R). Five radiotechnologists and one radiologist assessed the degree of colonic dilatation in the segments and subjects in prone and supine positions using the 3D air images. The degree of colonic dilatation was given a score of 1-5: Score 1: the whole or nearly whole region was obstructed, score 2: partially interrupted, score 3: dilatation was insufficient, score 4: dilatation was not problematic, and score 5: dilatation was sufficient (Fig. 2).

For statistical analysis, the Mann Whitney-U and Kruskal-Wallis tests were employed, and a p-value of less than 0.05 was regarded as significant.

3. RESULTS

Comparison of colonic dilatation with and without antispasmodic treatment

The visual evaluation of colonic dilatation with and without antispasmodic treatment is shown in Table 2.

On visual evaluation by segment in the prone position, the score was 4.09 in the ascending colon, 4.28 in the transverse colon, 4.00 in the descending colon, 3.88 in the sigmoid colon, and 4.30 in the rectum in the treated group, and 3.48, 3.55, 3.18, 3.68, and 3.93 in the untreated group, respectively. The scores of the sigmoid colon and rectum were not significantly different, but those in the other segments and the mean for all segments indicated significantly greater dilation in the antispasmodic-treated group. In the supine position, the scores were 4.49, 4.56, 4.16, 4.02, and 3.98 in the treated group, and 3.70, 3.65, 3.15, 3.75, and 3.48 in the untreated group, respectively. No significant differences were noted in the sigmoid colon or rectum, as in the prone position, but dilatation of the other segments and mean for all segments were significantly greater in the treated group ($P<0.05$).

Evaluation of colon dilatation by body size

The results of visual evaluation by BMI at a gas infusion pressure of 20 and 23 mmHg are shown in Fig.2. Colonic dilatation significantly worsened as the BMI increased. Elevation of the gas delivery pressure to 23 mmHg improved colonic dilatation.

4. DISCUSSION

The potential for widespread use of CTC as a screening method for the detection of colorectal neoplasia is currently a topic of intense discussion and investigation [15].

Optimal colonic distention is a fundamental prerequisite for CTC data evaluation that allows intraluminal evaluation of the large bowel. The prevalence of synchronous cancer in patients with colorectal cancer is reported to range from 2% to 7.1% [36-38]. Under-distended or collapsed segments may hide intraluminal lesions. Distention of the colon at CT is achieved by rectal insufflation of ambient air or carbon dioxide, with maximal patient tolerance setting the limit for maximal distention. Timepidium bromide is an anticholinergic compound that acts predominantly by blocking parasympathetic ganglia, causing relaxation of visceral smooth muscle. Administration of timepidium bromide has been used as effective spasmolytic agents for conventional diagnostic assessments of the bowel for many years.

In this study, the scores of the sigmoid colon and rectum were not significantly different, but those in the other segments and the mean for all segments indicated significantly greater dilation in the antispasmodic-treated group. In the supine position, No significant differences were noted in the sigmoid colon or rectum, as in the prone position, but dilatation of the other segments and mean for all segments were significantly greater in the treated group ($P<0.05$). The volume and radial

distensibility of the colon were significantly higher after premedication with timepidium bromide than without premedication. Assessment of colonic distention at CTC is subjective and may change with reviewer experience and also among different reviewers.

Our study has some limitations. First, we did not evaluate the patients' acceptance or discomfort regarding the CTC procedure. Second, although 20 mm Hg and 23mmHg of maximum rectal pressure shutdown was consistently used throughout the study, the actual maximum rectal pressure that was achieved during CTC was not recorded. Although rectal pressure is an imperfect indicator of the varying intraluminal pressure of each colonic segment, the measurement of the maximum rectal pressure may have provided more precise information regarding the acceptable degree of intraluminal pressure. Third, we also did not assess the amount of gas that refluxed into the small bowel. One might assume, however, that after administration of muscle relaxants, a larger amount of gas could pass the ileocecal valve. Given that the premedicated groups had a larger colon volume, reflux of gas into the small bowel is not likely to have influenced our results.

5. CONCLUSION

Favorable colonic dilatation was achieved through the use of antispasmodics on CTC, compared to that without antispasmodic treatment. CTC with antispasmodics and CO2 insufflation is well tolerated by patients and was successful in imaging the entire colon in most patients, despite the presence of advanced colonic redundancy.

Colonic dilatation worsened as the BMI of the subjects increased, but favorable dilatation could be achieved by elevating the gas infusion pressure.
MDCT technology improves further and automatic cleansing software becomes available, CTC should become even more feasible and be readily tolerated by patients.

Table 1. Number of subjects in BMI and gas infusion pressure categories

	BMI value Less than 20	**BMI value Between 20 and 25**	**BMI value 25 or greater**
Gas infusion pressure 20 mmHg group	11 (6 males , 5 females) (47.8±15.6 ys)	17 (15 males , 2 females) (52.6±12.3 ys)	15 (13 males , 2 females) (49.3±8.1 ys)
Gas infusion pressure 23 mmHg group	15 (2 males , 3 females) (49.6±9.6 ys)	32 (12 males , 20 females) (54.9±11.8 ys)	27 (18 males , 9 females) (51.0±8.5 ys)

Table 2. Evaluation of colonic dilatation with and without antispasmodic treatment

	A	**T**	**D**	**S**	**R**	**Overall**
Prone						
Antispasmodic-treated group	4.09±0.68	4.28±0.73	4.00±0.82	3.88±0.73	4.30±0.64	4.09±0.76
Antispasmodic-untreated group	3.48±0.96	3.55±1.01	3.18±1.01	3.68±0.92	3.93±1.14	3.65±1.10
P-Value	<0.05	<0.05	<0.05	0.2876	0.186	<0.05
Supine						
Antispasmodic-treated group	4.49±0.59	4.56±0.55	4.16±0.84	4.02±0.77	3.98±0.80	4.29±0.74
Antispasmodic-untreated group	3.70±1.11	3.65±1.14	3.15±1.00	3.75±0.81	3.48±1.24	3.63±1.13
P-Value	<0.05	<0.05	<0.05	0.1182	0.092	<0.05

A:Ascending, T:Transverse, D:Descending, S:Sigmoid, R:Rectum

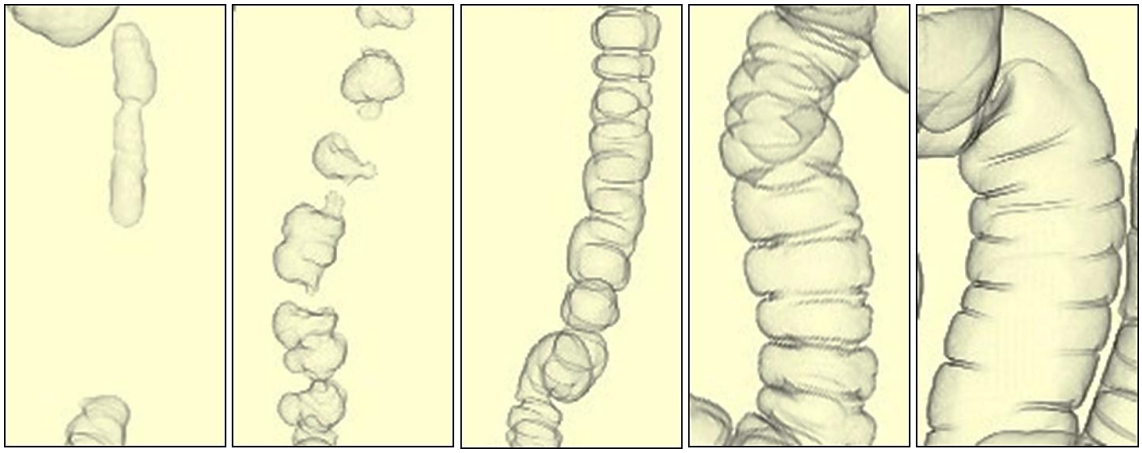


Fig. 1 Visual evaluation of colonic dilatation

Five segments from the ascending colon to the rectum were measured by VE imaging

The large intestine was divided into 5 segments (ascending colon: A, transverse colon: T, descending colon: D, sigmoid colon: S, and rectum: R), and the degree of colonic dilatation in the segments in prone and supine positions was given a score of 1-5 based on VE images.

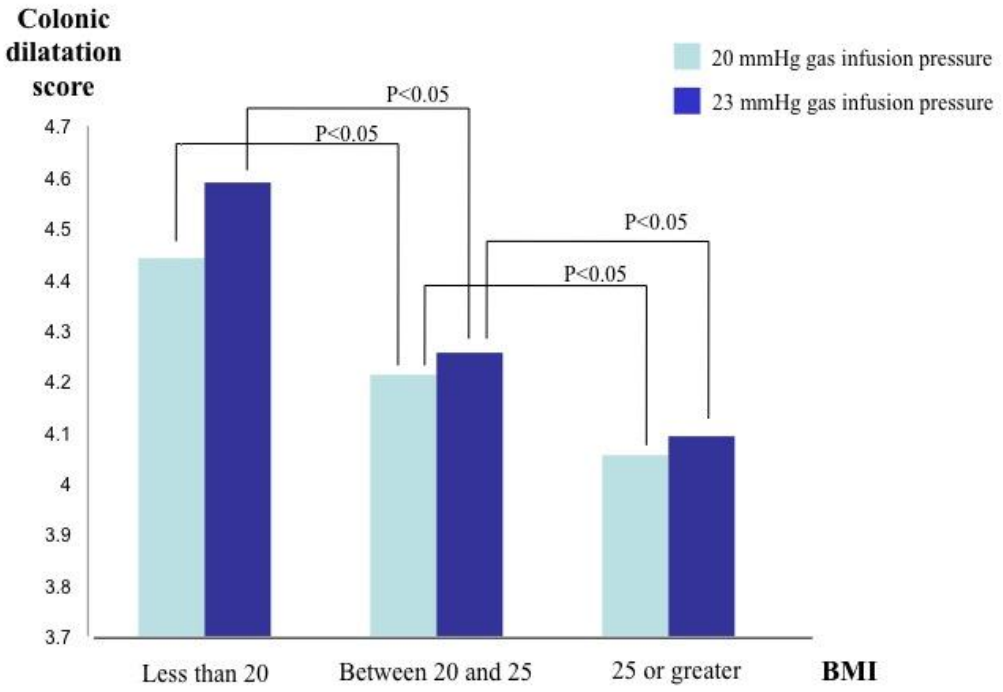


Fig. 2 Comparison of colonic dilatation by BMI and gas infusion pressure

- Chapter IV -

Detection of flat colorectal polyps at screening CT colonography in comparison with conventional polypoid lesions

1. Introduction
2. Materials and Methods
3. Results
4. Discussion
5. Conclusion

1. INTRODUCTION

Colorectal cancer is the second most common malignancy in United States and Europe, but it is preventable if detected early and meets for the population screening [39, 40]. Five-year survival rate is 92 % for the patients with stage I colorectal cancer; but if there is a distant metastasis, it decreases to less than 10% [41]. While OC is the preferred test for colorectal cancer screening, its invasiveness and inconvenience impaired the compliance of the form of screening.

There has been tremendous growth in the use of CTC for the noninvasive detection and evaluation of colorectal polyps in the last decade [15, 16, 35] as well as positive health outcomes [31]. CTC is now recognized as a preferred option in the joint colorectal cancer screening guidelines [42]. A meta-analysis by Halligan et al. [43] included 24 studies demonstrated a high per-patient average sensitivity of 93% and specificity of 97% for large polyps (>10mm).

Recently, flat elevated neoplasias along with laterally spreading tumors (LSTs) have been reported in colorectal neoplasias [44]. The previous studies [44, 45] reported that the incidence of the flat lesions was approximately 10% of advanced

neoplasia. The detection of such small flat elevated polyps is clinically important and challenging for colorectal cancer screening. However, the role of CTC screening for detection of such small- and flat lesions has not been thoroughly investigated. Thus, the purpose of our study was to evaluate the diagnostic accuracy and usefulness of CTC in the screening of flat lesions as well as polypoid lesions by comparing CTC- and optic colonoscopic findings.

2. MATERIALS AND METHODS

This retrospective study was approved by our institutional review board; patient informed consent was waived.

Patient population

Of 380 patients who underwent colorectal cancer screening at our institution between 2009 and 2010, for this study we enrolled 351 (236 men, 115 women) who underwent CTC and OC on the same day. Their age ranged from 25-79 years (average 51.4 ± 10.5 years). The target lesions were polyps of 2 mm or more in diameter that were detected by colonoscopy. Our Institutional Review Board approved the study and all patients gave written informed consent to undergo CTC study that exposed them to x-rays and required the injection of an antispasmodic agent immediately before CTC. All patients underwent bowel preparation on the day of the examinations. It involved the administration of a bowel-cleansing agent (1600 ml of PEG) followed by a 400-ml mixture of bowel-cleansing agent and water-soluble iodinated contrast medium (sodium- and meglumine amidotrizoate) (Gastrografin, Bayer, Tokyo, Japan). In addition, a water-soluble iodinated contrast medium was administered orally for fecal and fluid tagging. In our institution, the CT- and OC examination suites were located near to each other. First, the patient underwent OC after the bowel preparation.

Immediately after the completion of total OC the patient was transferred to the CT suite and underwent CTC examination. Therefore, the bowel preparation was performed once on the day of the OC- and CTC examinations.

OC protocol

After bowel preparation, we injected an antispasmodic agent (7.5 mg, Sesden, Mitsubishi Tanabe Pharma, Osaka, Japan) intramuscularly (i.m.) 10 min before colonoscopy and a sedative (7.5 mg, Horizon, Astellas Pharma, Tokyo, Japan) intravenously (i.v.) just before colonoscopy. A board-certified endoscopist who had performed more than 5,000 colonoscopies carried out OC. The colonoscope (EC-590MP, EC-450WM5, Fujinon Toshiba, Tokyo, Japan) was first advanced into the cecum and then withdrawn toward the anus while checking for polyps in each colorectal region. Findings on the region and the size and macroscopic morphology of polyps were recorded on a designated form. The size of the polyps was measured with biopsy forceps inserted via the forceps channel, with the forceps pressed against the polyps closed (2 mm in diameter) and open (5 mm in diameter). Biopsy specimens were obtained of polyps measuring 6 mm or more in diameter and of polyps characterized as depressed plaques measuring 5 mm or less in diameter.

CTC protocol

The patient was placed on the imaging table in the left lateral decubitus position to suppress intestinal peristalsis we injected another dose of an antispasmodic agent (i.m.) prior to CTC data acquisition. Rectal examination was performed to check for anal lesions, and a 12-EG Nelaton catheter was introduced via the anus for insufflation. The insufflated bulb was not used with the Nelaton rectal catheter due to the cost. Carbon dioxide was administered with the patient in the left lateral decubitus

or prone position using an automatic insufflator with a pressure measurement function. Average volume of Carbon dioxide used for optimal bowel distension was 1958 ± 983 mL, and no complications were observed. After a scout radiograph was obtained to confirm sufficient dilation of the colon, CT images were obtained on a 64-row MDCT system (Aquilion 64, Toshiba, Tokyo, Japan) during 7-10 sec breath-holding under expiration in the prone and supine position. The scan range extended from the diaphragm to the inferior edge of the pubis in both positions. The data acquisition protocol was: tube voltage 120 kV, tube current 100 mA, gantry rotation speed 0.5 sec/rotation, slice thickness 0.5 mm, field-of-view 320 mm, beam pitch 0.83. The CT dose index was 5.7 mGy per position in our study, and our CTC protocol was considered a low-dose protocol according to the American College of Radiology guidelines [46]. The mean range of data acquisition was 455 ± 29 mm. CT images reconstructed at a 0.5-mm slice thickness with 0.5-mm intervals were transferred to an image workstation (ZIO Station System N610 version 1.21b, Amin, Tokyo, Japan), and the images including MPR, VR, dissected colon (VGP), and VE images were generated.

Image interpretation

Two experienced physicians (a board-certified radiologist and a gastroenterologist qualified as supervising physician), blinded to clinical data, interpreted the CTC images by consensus. The colon was divided into 5 regions, the ascending colon (including the cecum), the transverse-, descending-, and sigmoid colon, and the rectum. The VR images were evaluated to check for insufficient dilation, wall deformation, and mucosal irregularities (Fig. 1). The VGP images were then used to identify regions harboring suspected lesions (Fig. 2). Dissected colon images were checked for polypoid lesions and morphological abnormalities by inspecting the image of each semilunar fold. All regions with suspected lesions were re-checked and then

evaluated in the diagnosis-confirmation mode where regions with suspected lesions were inspected on VE and MPR images. In addition, the VE images were observed from two directions (from the oral- and from the anal end of the colon) to check for lesions. When a suspected lesion was found, the region including the suspected lesion was checked again on the VGP image. The final diagnosis was based on findings identified on VE-, VGP-, and MPR images obtained in the prone- and supine position. The region, size, and macroscopic morphological characteristics of each lesion were recorded. Findings on CTC images for lesions measuring 2 mm or more in diameter were compared with findings made by total OC as the gold standard. The sensitivity, specificity, and positive- and negative predictive value (PPV and NPV, respectively) per patient for polyps (>2 mm) were calculated in each region of colon (ascending-, transverse-, descending-, sigmoid colon, and rectum). The reasons for missed lesions at CTC were assessed and classified as follows: invisible due to limitations of CTC (lack of spatial resolusion); inadequate bowel preparation; inadequate bowel distention; or misinterpretation of the observer. Furthermore, we visually evaluated which of the 4 reconstruction modes (MPR, VR, VGP, or VE) was appropriate for detection of flat- and polypoid lesions on a 3-point scale: 3 = valuable, the lesion was easily and correctly detected; 2 = acceptable, the lesion was detected, but the detection was not easy; 1 = non-valuable, the lesion was difficult to detect.

The lesions were classified into 3 groups based on size, i.e. 2-3 mm, 4-5 mm, and 6 mm or more. The maximum diameter of the lesion was measured on MPR images. Based on their macroscopic morphological characteristics, the lesions were first classified as flat or polypoid. The definition of flat lesions included mucosal elevation with a flat surface and a height not exceeding 3mm [47, 48]. Polypoid lesions were further classified as sessile, sessile-pedunculated (semipedunculated), and pedunculated. The detection sensitivity per lesion was evaluated based on its size and macroscopic

morphological characteristics.

Statistical analysis

Statistical analysis was with the chi-square test to compare the detection capability rates among colon regions and the detection rates on CTC of flat- and polypoid lesions. A p value of less than 0.05 was considered statistically significant. The results of visual evaluation of 4 reconstruction modes were compared with the Steel-Dwass test. We used software for statistical analysis (SPSS version 15.0, SPSS Inc., Chicago, IL, USA; and JMP 9.0.2, SAS Institute Inc., Cary, NC, USA).

3. RESULTS

A total of 460 polyps measuring 2 mm or more in diameter were found in 209 of the 351 patients on OC, cancers were detected in 8 patients. Of the 460 lesions: 243 (52.8%) measured 2-3 mm, 137 (29.8%) were 4-5 mm, and 80 (17.4%) measured 6 mm or more. Histopathologic study of biopsy- or surgical specimens from 105 patients (135 lesions) returned a final diagnosis of hyperplastic polyps (9 lesions, 9 patients), tubular adenoma (118 lesions, 90 patients), and adenocarcinoma (8 lesions, 6 patients).

Capability of CTC for detecting colorectal polyps per patient

Overall sensitivity and specificity in all 5 colon regions was 66.5% (230/346) and 85.3% (1,202/1,409), respectively. The overall PPV and NPV was 52.6% (230 /437) and 91.2% (1,202/1,318). The detection capability rates for the detection of colorectal polyps in each region of the colon are shown in Table 1. While PPV was significantly different among colon regions, other capability rates were not.

Detection rates per lesion based on morphological characteristics

The detection rate for the polypoid lesions was 64.1% (268/418); it was 59.7% (212/355) for sessile-, 89.7% (35/39) for semipedunculated-, and 87.5% (21/24) for pedunculated polyps; for flat polyps it was 47.6% (20/42). The detection rate was significantly higher for polypoid- than flat lesions ($p < 0.01$). The comparison of detection rates between flat- and polypoid lesions for different size ranges is shown in Table 2. The representative cases with polypoid- and flat polyp are presented in Figs. 3 and 4.

A total of 172 polyps including 22 flat lesions and 150 polypoid lesions were missed at CTC. The results of assessment of the missed flat- and polypoid lesions are summarized in Tables 3 and 4, respectively.

Visual evaluation of 4 different reconstructions

Mean visualization scores for flat lesions were 1.7 ± 0.6, 1.7 ± 0.8, 2.3 ± 0.8, and 2.7 ± 0.5, respectively, for MPR-, VR-, VGP- and VE images. The corresponding scores for polypoid lesions were 2.5 ± 0.7, 2.6 ± 0.6, 2.8 ± 0.4, and 3.0 ± 0.2, respectively. The distribution of visualization scores of the 288 polyps (20 flat lesions and 268 polypoid lesions) detected by CTC are summarized in Table 5. The results of analyses are shown in Table 6. The VE imaging showed highest visualization score for detection of both flat- and polypoid colorectal polyps.

4. DISCUSSION

As most colorectal cancers are thought to develop from adenomatous polyps [49], screening for early-stage cancer and pre-neoplastic lesions can significantly improve disease outcomes. Automated colonic insufflation and fecal tagging are advances in CTC and in average-risk populations, CTC performed every 5 years may be

a reasonable alternative for the screening suggested by the joint guidelines issued by 3 medical societies of the United States [42]. As the reported sensitivity and specificity of CTC for the detection of adenomas or cancers measuring more than 10 mm were 90% and 86%, respectively, its diagnostic capability is sufficiently high for screening an average-risk population [16]. However, the detection of flat polyps is important at colorectal cancer screening because small flat lesions are more likely to be stage T3/T4 than polypoid lesions that tend to be stage T1 [50]. In our study the detection sensitivity for flat polyps (>2 mm) was 47.6 %, for polypoid lesions it was 64.1 %. Although the detection of flat polyps by CTC is compromised by the lack of direct mucosal visualization, this disadvantage may be overcome by techniques such as bowel preparation and colonic distension. According to Ignjatovic et al. [49] routine fecal tagging lowered the examination failure rate from 4% to <1%.

In different colon regions, both the sensitivity and specificity of CTC were relatively high and we observed no significant regional differences. Ours were comparable to findings reported previously [43, 51, 52] and the quality of our CTC images was excellent although OC and CTC were performed on the same day. We carried out total OC before CTC and suctioned residual liquid in the colon during colonoscopy, the conditions for CTC were therefore optimal as the effects of residual liquid were markedly reduced.

In most previous studies on the detection of polyps at CTC [15, 31, 53-56], the polyps were classified into 3 categories based on their size: 5 mm or less, 6-9 mm, and 10 mm or more. Johnson *et al.* [16] excluded polyps smaller than 5 mm from their assessment. Lieberman *et al.* [55] reported that 1.7%, 6.6%, and 30.6% of polyps measuring 1-5 mm, 6-9 mm, and 10 mm or more, respectively, were associated with advanced neoplasia. Our search of the literature found no studies in which polyps measuring 5 mm or less were stratified based on their size for evaluation. These lesions may be very small

screening targets and their natural history remains to be elucidated [55]. We sub-classified small polyps to determine whether lesions 5 mm or smaller can be detected by CTC. We found that sensitivity was 46.5 % and 74.5 % for polyps measuring 2-3 mm and 4-5 mm, respectively. Due to the thin-slice collimation of 64-row MDCT systems and the establishment of optimal conditions by careful bowel preparation, 56.6 % of all lesions 5 mm or less were detected. Consequently, we consider the sensitivity of CTC for such small lesions acceptable. Our results document that 91.3 % of polyps measuring 6 mm or more, the targets for treatment and detailed examination, can be detected at CTC screening.

The adenoma-carcinoma pathway is thought to be involved in approximately 2/3 of all colorectal cancers [49, 57, 58]. Another growth pattern of de novo cancers, in which superficial flat tumors progress to infiltrating cancers, is encountered in clinical practice [59, 60]. Among superficial flat tumors, depressed tumors account for approximately 15.5% of all infiltrating cancers. As polyps measuring 5 mm or less tend to infiltrate the submucosal layer and most polyps measuring 10 mm or more infiltrate this layer massively, depressed tumors have drawn interest [49]. We found that by CTC it may be possible to detect small and flat lesions although their identification continues to present challenges. To improve their detection rate, the spatial resolution and the performance of fecal tagging and electric cleansing must be improved. In addition, the development of high-precision computer-aided detection methods that facilitate the detection of small height differences and of tylosis of the intestinal wall is desirable.

Our study has some limitations. First, not all polyps were examined histopathologically. Second, we did not record the time needed for image interpretation. The interpretation of CTC images are usually time-consuming, and it should be clarified which mode of CTC image reconstruction is most time-effective in the future studies. Third, since CTC was performed immediately after colonoscopy,

the conditions were optimal as there was almost no residual liquid or solid matter in the colon. When only CTC images are acquired, their interpretation will be performed under less favorable conditions due to the presence of larger amounts of residual liquid and solid matter in the colon. This may lower the detection rate. Nonetheless, lesions measuring at least 6 mm, the targets for treatment and detailed examination, can be detected by CTC, rendering this method useful for colon cancer screening. Improvements in the spatial resolution of CTC images and detailed evaluation will facilitate the detection of smaller lesions. Efforts are underway in our laboratory to improve the detection of superficial flat tumors with small height differences.

5. CONCLUSION

CTC using 64-row MDCT is useful for colon cancer screening to detect lesions measuring 6 mm or more although small, flat lesions are still difficult to detect. The optimization of imaging conditions at CTC may make it possible to detect small, flat lesions.

Table 1. Detection capability rates of CTC in each region of the colon

	Detection capability rates (%)			
Region of colon	Sensitivity	Specificity	PPV	NPV
Ascending*	65.3	83.2	50.0	90.3
	(47/72)	(232/279)	(47/94)	(232/257)
Transverse	71.2	79.6	44.8	92.3
	(47/66)	(227/285)	(47/105)	(227/246)
Descending	71.1	86.9	39.7	96.1
	(27/38)	(272/313)	(27/68)	(272/283)
Sigmoid	67.0	87.8	70.3	86.0
	(71/106)	(215/245)	(71/101)	(215/250)
Rectum	59.4	89.2	55.1	90.8
	(38/64)	(256/287)	(38/69)	(256/282)

*The cecum is included in the ascending colon.

PPV: positive predictive value, NPV: negative predictive value

Table 2. Comparison of detection rates between flat- and polypoid lesions for different size ranges

	Detection capability rates (%)	
Polyp diameter	Flat lesions	Polypoid lesions
2-3mm	31.3	47.6
	(5/16)	(108/227)
4-5mm	44.4	79.0
	(8/18)	(94/119)
6mm-	87.5	91.7
	(7/8)	(66/72)
Total	47.6	64.1
	(20/42)	(268/418)

Table 3. Evaluation of the 22 flat lesions missed at CTC

	Polyp diameter		
	2-3mm	4-5mm	>6mm
lack of spatial resolution	6	6	0
inadequate preparation	3	0	1
inadequate distention	2	2	0
misinterpretation	0	2	0

Table 4. Evaluation of the 150 polypoid lesions missed at CTC

	Polyp diameter		
	2-3mm	4-5mm	>6mm
lack of spatial resolution	53	10	0
inadequate preparation	26	5	2
inadequate distention	9	4	1
misinterpretation	31	6	3

Table 5. Degree of polyp visualization with 4 reconstruction modes at CTC

	Image reconstruction mode							
	Flat lesions (n=20)				Polypoid lesions (n=268)			
Score	MPR	VR	VGP	VE	MPR	VR	VGP	VE
3	2	3	9	14	165	176	224	260
2	10	8	8	6	78	71	40	8
1	8	9	3	0	25	21	4	0

Note: Score 3 = valuable; 2 = acceptable; 1 = non-valuable

MPR = multiplanar reconstruction; VR = volume rendering; VGP = virtual gross pathology; VE = virtual endoscopy

Table 6. Multiple comparisons of polyp visualization among 4 reconstruction methods

Comparison	Visualization score	
	Flat lesions	Polypoid lesions
MPR vs VR	NS	NS
MPR vs VGP	NS	S
MPR vs VE	S	S
VR vs VGP	NS	S
VR vs VE	S	S
VGP vs VE	NS	S

Note: S = significant; NS = not significant

MPR = multiplanar reconstruction; VR = volume rendering, VGP = virtual gross pathology; VE = virtual endoscopy

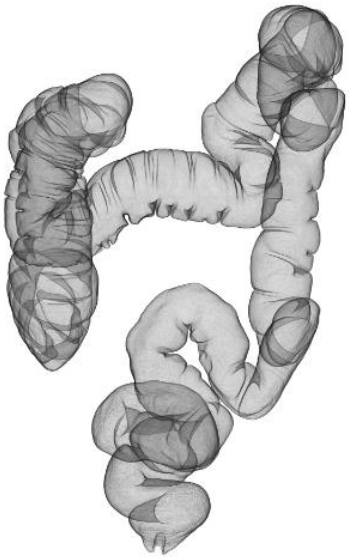


Fig. 1

Volume rendering method to check for insufficient dilatation, deformation of the walls, and mucosal irregularities.

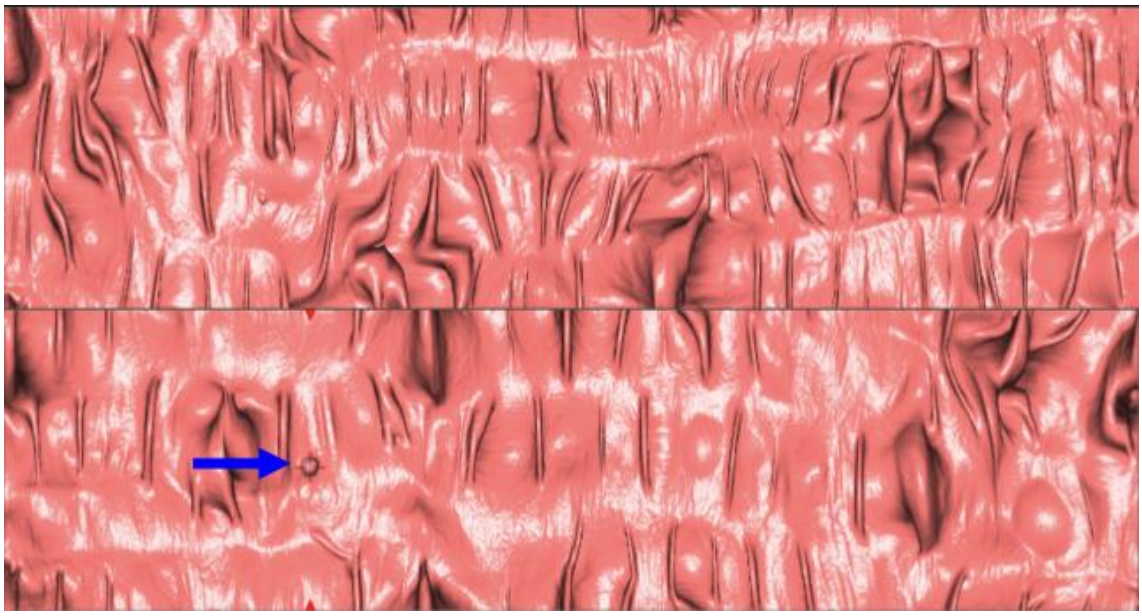
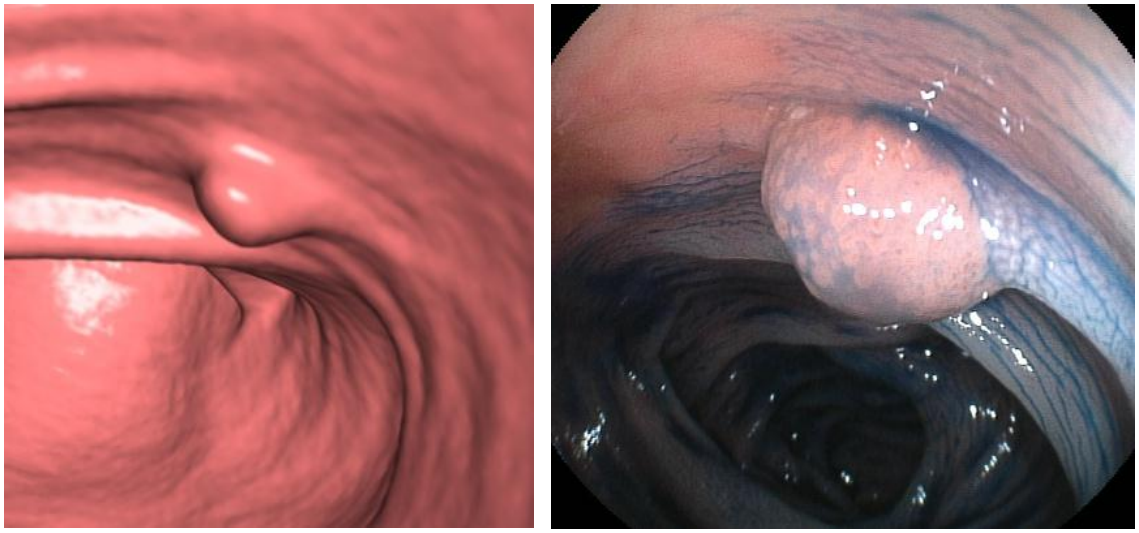


Fig. 2

A virtual gross pathology image was used to identify regions containing suspected lesions (arrow).

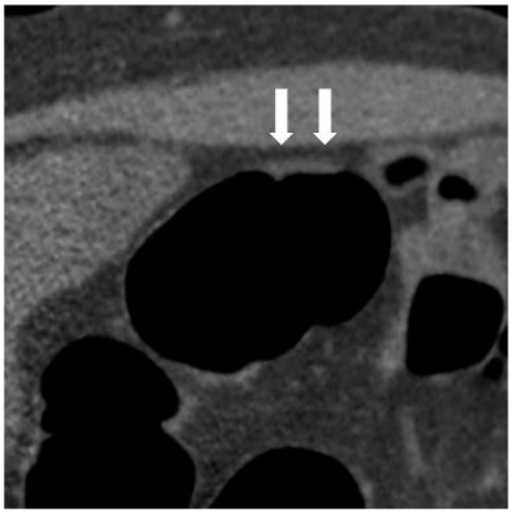


(A) **(B)**

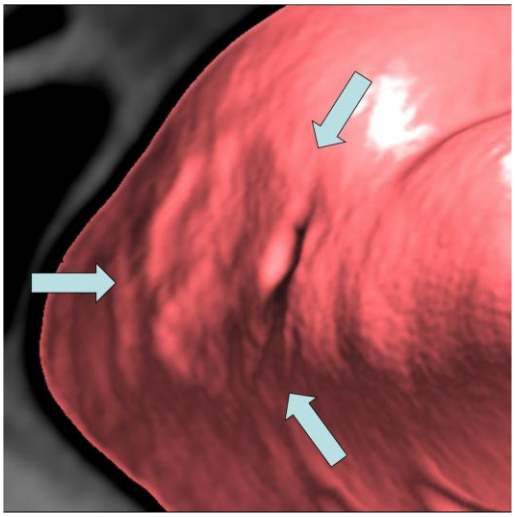
Fig. 3

41-year-old woman with sessile polyp measuring 5 mm in the sigmoid colon.

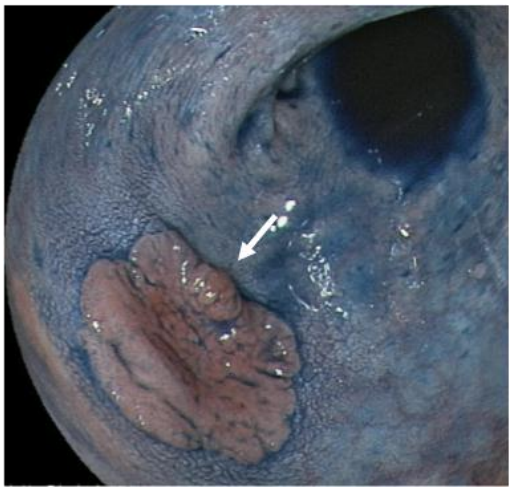
Virtual endoscopy image (A) shows polypoid lesion measuring 5 mm. This coincides with optic colonoscopy finding (B).



(A)



(B)



(C)

Fig. 4

54-year-old woman with flat polyp in descending colon. MPR image (A) shows flat lesion of uniform soft tissue density (arrows). Virtual endoscopy image (B) shows flat lesion (arrows). This coincides with optic endoscopy (arrow) (C). Histopathological examination confirmed that lesion was carcinoma in adenoma.

General conclusions

CTC is a minimally invasive technique for imaging the entire colon, and rapidly emerging as a more recent option for colon cancer screening. CTC is based on a helical, thin-section CT of the cleansed and distended colon. The examination consists of three major steps: patient preparation, including cathartic cleansing and distention of the bowel; and post-processing of CT data sets.

Our bowel preparation study, visual assessment scores were also significantly different between the three methods ($p<0.05$). The lumen was visualized more clearly when the volume of residual colonic contents was less. Performing PEG on the previous day allows blind areas to be reduced with high precision. In the bowel distention study, the use of antispasmodics was found to be very effective for achieving appropriate colonic dilatation. In the third clinical study, Detection sensitivity for flat polyps was 31.3%, 44.4%, 87.5% for lesions measuring 2-3 mm, 4-5 mm, and ≥6 mm, respectively; the corresponding sensitivity for polypoid lesions was 47.6%, 79.0%, and 91.7%. Due to the thin-slice collimation of 64-row MDCT systems and the establishment of optimal conditions by careful bowel preparation, 56.6 % of all lesions 5 mm or less were detected. Consequently, we consider the sensitivity of CTC for such small lesions acceptable. Our results document that 91.3 % of polyps measuring 6 mm or more, the targets for treatment and detailed examination, can be detected at CTC screening. VE imaging showed best visualization among the reconstructions.

CTC using 64-row MDCT is useful for colon cancer screening to detect the lesions measuring 6 mm or more. The VE imaging showed highest visualization score for detection of both flat- and polypoid colorectal polyps.

CTC may also have the potential to detect small, flat lesions, although the further techniques should be optimized to improve the detection sensitivity.

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