COMMENTARY

CT Colonography - Towards Applications for Colorectal Cancer Screening

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Abstract

Three-dimensional (3D) imaging of the large intestine is globally called computed tomography colonography (CTC). CTC has been intensively investigated for application in colorectal cancer screening in Western countries and with the advent of multi-slice CT (MSCT), which provides effective high resolution in 3D CT images, the diagnostic use of CT for colorectal lesions has become a concept widely accepted throughout the world. Computer-aided detection (CAD) for colorectal polyps using digital CT image data and digital pre-processing are also advancing in the West. Compared with colonoscopy, which depends largely on the skill of the performer, CTC produces objective and reproducible diagnostic images and presents a high probability of standardizing examination protocols. Development of effective systems for screening colorectal lesions is expected, leveraging the excellent processing capability of MSCT to enhance 3D visualization and allow efficient detection.

Key Words: CT colonography - large intestine - screening - virtual gross pathology

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Introduction

Recent proliferation of multi-slice computed tomography (MSCT) has brought revolution to efficiency of CT scanning and image enhancement (Fujita, 1997; Taguchi et al., 1997; Nakamura et al., 1999). Multiple slice data are acquired with MSCT, enabling wide-ranging rapid scrutiny. Research on the diagnostic application of three dimensional (3D) CT images to different organs is also ongoing, using volume data (digitalized density data of the patient) with high spatial resolution obtained by helical scanning with MSCT (Niinuma, 2006). Even the visualization of the digestive tract, a challenge with conventional CT, has become relatively easier when air-filled and inflated (Shiragami, 2000). Three dimensional visualization of the intestine is globally called CT colonography (CTC) (Hara et al., 1997), the usefulness of which for colorectal cancer screening is evidenced by numerous studies in the West (Halligan et al., 2005; Pickhardt et al., 2006). CTC produces objective and reproducible diagnostic images, and can be more useful in standardizing the examination process than other modalities. CTC presents another study focus, which is the variety of volume expressions made possible by combining different image processing methods depending on different diagnostic objectives (Vos et al., 2003; Iinuma et al., 2005). Particularly for screening, 3D views with minimum blind spots are being developed in addition to the virtual endoscopic view to avoid overlooking important features. Computer-aided detection (CAD) using digital CT image data (Summers et al., 2001; Yoshida et al., 2002) and digital pre-processing (Lefere et al., 2002) are also being developed, along with the construction of practical diagnostic systems. Unlike an invasive colonoscopic examination, CTC involves a brief and safe examination, and MSCT offers a high processing capability that allows a larger number of patients to be examined. The patient's burden is particularly lightened by digital pre-processing. CTC is likely to be the principal method for screening colorectal cancer in the near future when the volume display is optimized and CAD technology is applied.

This report describes the history, present status, and perspective of the development of CTC as an application for colorectal cancer at the National Cancer Center in Tokyo, Japan.

CT Colonography at the NCC, Tokyo

The National Cancer Center has a long history involving CTC, which dates back to the era of single-slice helical CT. The first report on CTC was published in the US in 1994 as virtual endoscopy for the large intestine (Vining et al., 1994). At the same time, the East Hospital of the Center began research on CTC (Moriyama and Sekiguchi, 1998). However, the helical CT of that era with a minimal slice width of approximately 5 mm and a relatively long scanning time produced CTC images

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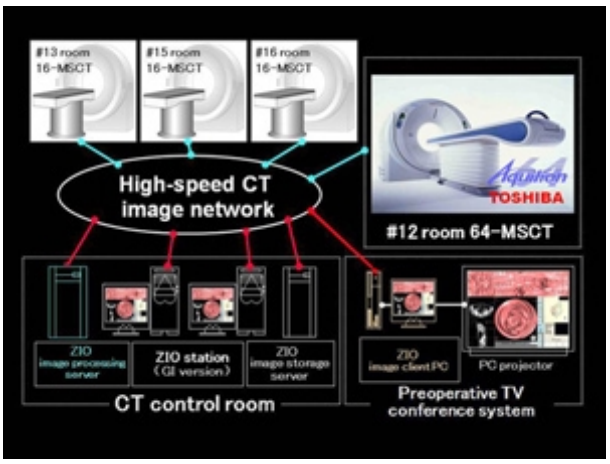

Figure 1. High-speed CT Network (Central Hospital, National Cancer Center). 3 units of 16-detector MSCT and 1 unit of 64-detector MSCT are connected to an image storage server and an image processing server via a high-speed network, enabling 3D diagnosis on referring terminal PCs

with quality insufficient for clinical application. In Japan, where colonoscopic diagnosis is well-developed, the helical CT was not evaluated for use in clinical diagnosis in practice. However, the advent of MSCT, which enables high-speed acquisition of large quantities of high-resolution volume data (thin slice) along the vertical axis, completely changed the evaluation of CTC in colorectal diagnosis. The Central Hospital of the Center introduced a 4-detector MSCT in 2001, and verified the effectiveness of CTC in pre-surgery staging of colorectal cancer and studied its fundamental capability of visualizing early-stage invasive carcinoma (Iinuma et al., 2004). In 2003, the Hospital introduced a 16-detector MSCT and started investigation on 3D visualization with the purpose of screening colorectal lesions in addition to that of pre-surgery diagnosis. The Center advanced a joint research effort with the Yamashita Hospital and the Otaru Ekisaikai Hospital, where colorectal screening had already begun using the common image workstation (WS) produced by Ziosoft, Inc. [city, country?] to develop an effective diagnostic protocol for the detection of colorectal lesions. In 2005, the Center introduced a 64-detector MSCT, laid a high-speed CT network to respond to the need to process a great volume of CT image data with high resolution, and completed a system practically applicable to the clinical pre-surgery diagnosis of colorectal cancer (Figure 1) (Iinuma et al., 2006). This preoperative CTC examination was highly evaluated among colorectal surgeons of the Center, which completely eliminated the preoperative enema study in the Central Hospital (Morimoto et al., 2008). Presently, we are preparing for CTC screening practice for colorectal cancer to be inaugurated in the Research Center for Cancer Prevention and Screening in fiscal year 2008.

CT colonography using 64-detector MSCT

One of great features of the 64-detector MSCT is the high-speed scanning by isotropic imaging (Jaffe et al., 2006). The CT axial image has 512 x 512 pixels along the x- and y-axes and a resolution of approximately 0.5 x 0.5 mm. Therefore, the spatial resolution of the volume data is determined by the slice width along the body axis (z-axis) and the resolutions along the x-, y-, and z-axes are equal when the slice width is 0.5 mm. The whole body can be scanned in a little more than 10 seconds using this 0.5 mm slice thickness or isotropic voxel by 64-detector MSCT (Katada, 2005; Iinuma et al., 2007).

In the preoperative diagnosis for colorectal cancer, the CTC scan is performed immediately after preoperative colonoscopy. First, a non-contrast CT scan is performed in the supine position followed by contrast-enhanced acquisition in the prone position for rectal lesions and in the supine lesion for colon lesions to facilitate clear depiction of the lesions. The vein is secured using a 20G elaster needle for the intravenous injection of the contrast agent, and Buscopan 1A is injected intravenously for preparation. Next, a probe is inserted from the anus, and the large intestine is expanded using the automatic CO2 gas inflation device manufactured by E-Z-EM Inc. (USA) [city, state?](Burling et al., 2006). This device is equipped with various safety measures, and inflates the gas with the pressure managed at a certain level and is capable of expanding the large intestine with CO2 safely without causing any pain to the patient. Adequate gas inflation of the intestinal tract is indispensable for a quality CTC examination. Inflation using the automatic CO2 inflation device enables constant acquisition of good 3D images. No complications, including abdominal distension or pain, are reported because CO2 is absorbed rapidly through the intestinal tract (Sumanac et al., 2002). After the scan site and gas volume in the intestinal tract are confirmed by the positioning image, the artery phase image of the entire large intestine is captured using a contrast agent. When multi-organ metastases are suspected, the liver and lung images are captured in the late phase. A 0.5 mm-width image is reconstructed on the CT console and transferred to the image WS via a high-speed CT network. The newly developed image WS can offer effective diagnostic images created by various combinations of different 3D views in accordance with the objectives (Figure 2).

The large intestine keeps subtle peristalsis, even after administering a spasmolytic agent and the effect cannot

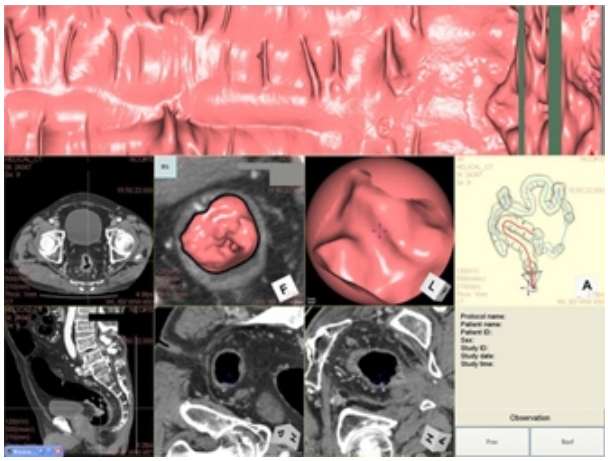

Figure 2. CTC 3D Views in Colorectal Preoperative Diagnosis. Various combinations of different CTC views allow detailed observation of primary lesions and metastases for enhanced effectiveness of preoperative diagnosis

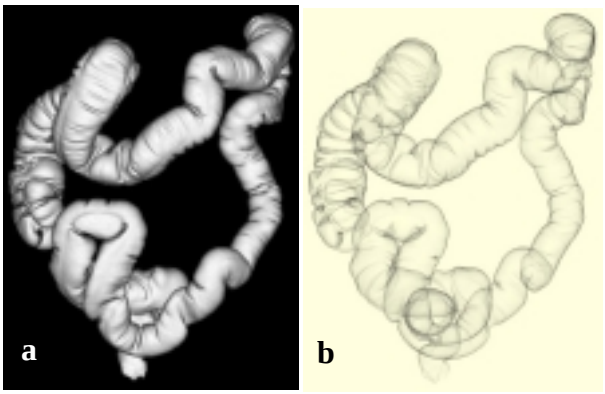

Figure 3. Volume Rendered 3D Views of the Entire Large Intestine. The reconstructed image is volume-rendered in the CTC to show the VR view of the entire large intestine with the boundary depicted between the intestinal gas and mucosal surface. By modifying the opacity of the boundary, a solid image view (a) and air-image view (b) can be obtained

be totally avoided in capturing images. With CTC using a 64-detector MSCT, compared with a 4-16 detector MSCT, not only the resolution is improved, but the image distortion or artifacts caused by intestinal peristalsis are minimized, and even a slight elevation or depression within the intestine mucosa can be depicted more clearly (Iinuma et al., 2006). More than 1,000 preoperative cases of colorectal cancer have already been evaluated with CTC using a 64-detector MSCT. This extensive experience resulted in the development of our own CTC system, which is used in routine preoperative diagnoses for colorectal cancer. MSCT itself constitutes a required examination for the preoperative evaluation of lesion localization and metastasis. Performing CTC immediately after colonoscopy unquestionably contributes to improved efficiency of preoperative procedures.

3-D views in CT colonography

The multi-planar reconstruction (MPR) feature at the imaging WS for extremely thin-slice reconstructed images obtained with the isotropic imaging of a 64-detector MSCT allows for high resolution slice images in any orientation in addition to the conventional coronal and axial images. Further, colorectal 3D images can be reconstructed by the volume rendering (VR) feature (Suto, 1996) that digitally depicts the boundary between the intestinal gas and mucosal surface. The density contrast between the intestinal gas and the mucosa is distinct, which allows relatively easy VR reconstruction of the entire large intestine to display and observe. In addition to the solid image display, VR reconstruction can display air images similar to enema x-ray images by changing the opacity of the extracted boundary plane (Figure 3a, b). A virtual endoscopy (VE) view is also obtained when the viewing point is moved to the interior space of the intestinal tract inflated with CO2. In VE, the viewing point can be placed at any point and orientation. Combining the VE and MPR (VE+MPR view), the simultaneous display of images of both the lumen and wall of the large intestine is possible (Fig ure 4). The large intestine can be viewed either from the oral or anal side freely, with virtually no limitation.

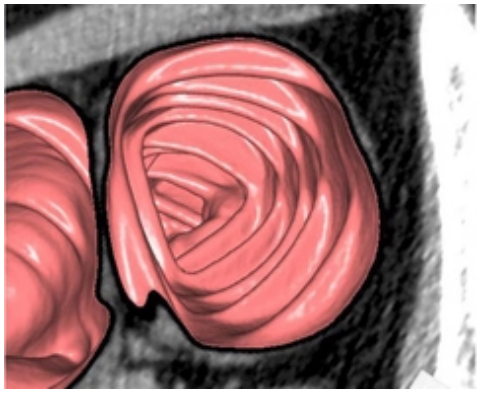

Figure 4. Virtual Endoscopy (VE) Vew of the Large Intestine. The VE view is obtained when setting a viewing point inside the intestinal tract in the VR view. Combining the VE and MPR views, simultaneous display of both images of the lumen and wall of the large intestine is possible.

While the field of vision is typically set at 90 degrees in VE as well as in colonoscopy, image processing also allows a VE view at 210 degrees that is comparable to a fish-eye view, which is useful to minimize the blind spots. The VE+MPR view along the tract axis provides a splitting image which is useful in observing both the inside and outside of the lumen to diagnose the extension of local lesions and metastasis to the lymph nodes. The isotropic imaging provided by the 64-detector MSCT is excellent in spatial resolution, enabling simultaneous observation of both the inside and outside of the lumen with higher details in all CTC views.

Virtual Gross Pathology in CT colonography

In Western countries, researches on colorectal screening using CTC have been advanced mainly by radiologists. In most cases, 2D MPR views were primarily used for detection and 3D images were used to confirm the suspected sites detected in 2D (Johnson et al., 2000). However, the recent studies comparing diagnostic capabilities between 2D and 3D images for colorectal polyps proved the effectiveness of the 3D images, and a diagnostic protocol suitable for screening is now being

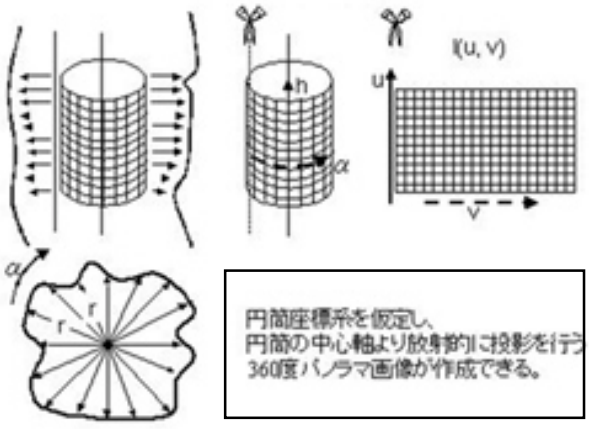

Figure 5. Image Analysis Algorithm for Virtual Gross Pathology. VGP assumes a cylindrical coordinate system in the colon lumen with CTC, finds the virtual centerline of the lumen, and obtains a stretched view of the inner colonic surface using a cylindrical projection

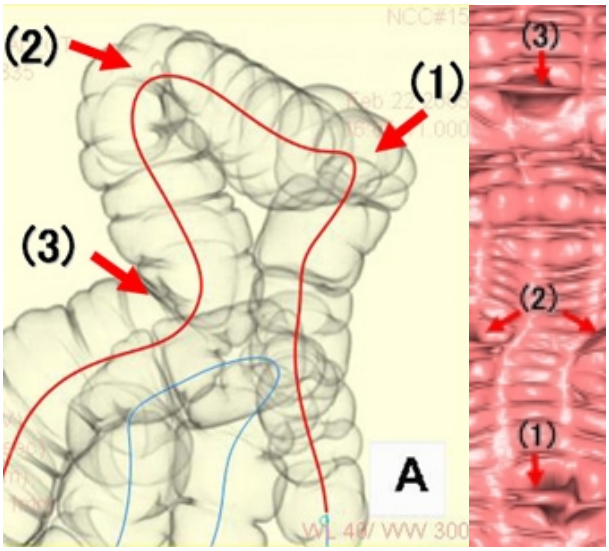

Figure 6. Image distortion in VGP view. At present, the semilunar folds and the colic taenia are correctly displayed in 3D, but considerable distortions persist in the tract curves and narrowing sites

developed (Vos et al., 2003; Kim et al., 2007; Pickhardt et al., 2007). Since the introduction of a 16-detector MSCT, we have noted the virtual gross pathology (VGP) to be an effective 3D view in colorectal screening and have been engaged in research and development (Figure 5). VGP assumes a cylindrical coordinate system in the colon lumen with CTC, finds the virtual centerline (path) of the lumen, and obtains a stretched view of the inner colonic surface using a cylindrical projection.

Though VGP in CTC has already been studied in the West as a view free from blind spots for observation, it is not yet used in practice due to the imperfect analytic algorithm. With semilunar folds existing on the inner surface of the colonic lumen, the irregularity of the cylindrical form of the lumen caused by peristalsis, and the curved track of the lumen itself, our VGP images were also distorted significantly and observation of the colonic mucosal surface was difficult in the early stage of development. The imaging algorithms improved since the image quality was increased by minimizing the distortion to provide images sufficiently clear for observing the findings on the mucosal surface. At the present time, some distortion persists in the tract curves and narrowing sites, but the semilunar folds and the colic taenia are correctly displayed in 3D. VGP images are now sufficiently useful in indicating lesions when the nature of the image distortion in the normal sites is correctly understood (Figure 6). In VGP, the entire colonic mucosal surface can be observed in still images with no blind spots caused by semilunar folds or curved tract, as found in the VE view. Thus, VGP is considered to be the most appropriate CTC view for screening lesions (Tomimatsu et al., 2005). Compared with the VE view, the VGP view allows an observation of the entire mucosal surface in an extremely short time, and is expected to contribute to increased efficiency in diagnostic screening systems. There still remain challenges in diagnosing flat lesions of colonic tumors, but the VGP view is continuously being improved.

New examination technologies in CT colonography

1) Computer-aided detection (CAD)

Research involving CAD in CTC is advancing in the West for colorectal polyp detection and the system has already been completed. In CAD in CTC, the shapes of the colonic lumen surface is recognized from the digital image data and colon polyps are auto-detected (Summers et al., 2001). Presently, the National Cancer Center is engaged in a joint research venture with London University through a British corporation, Medicsight, Inc., [city?] to develop a CAD system in CTC for colon lesions using an algorithm called "Sphericity," which was developed by the corporation (Taylor et al., 2007). Medicsight's CAD is the only system approved by the U.S. Food and Drug Administration (FDA) and is rapidly gaining acceptance in Western countries. "Sphericity" is an algorithm that detects quasi-spherical colorectal polyps by separating them from normally protruding structures, such as semilunar folds, within the colon lumen. Our joint research focus on CAD is applicable to the detection of flat lesions whose significance is recently drawing particular attention from researchers in the West as well . CAD has a great potential in screening because most colorectal cancers develop locally from its early stage. However, in the initial CAD evaluation regarding 33 cases of early-stage colorectal cancer examined with our 64-detector MSCT (Table 1), the detection rates for protruding lesions (Ip, Isp, and Is) and superficial elevated lesions (see Figure 7) were 100% and 70%, respectively. Development of detecting algorithms for flat lesions was considered to be required (Taylor et al., 2009). Further enhancement of CT image details realized by the technological progress of MSCT and improvement of the

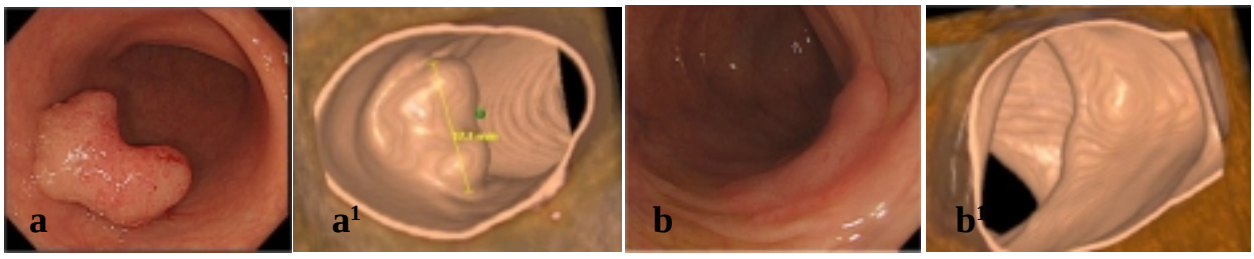

Figure 7. Example of CAD Analysis Results for Protruding and Superficial Elevated Types of Early-stage Cancer. a) Isp in the upper rectum successfully detected with a green point placed correctly; b) low-raised type IIa in the descending colon not detected; a/b) colonoscopic images; a^1/b^1) CAD analysis result in a VE viewtype

Table 1. CTC Detection of Protruding and Superficial Elevated Lesions

Tumour type	Number	Detection rate
Protruding		
Ip + IIc	1/1	(100%)
Isp	3/3	(100%)
Is	6/6	(100%)
Is + IIa	6/6	(100%)
Is +IIc	1/1	(100%)
Superficial		
IIa	8/10	(80.0%)
IIa +IIc	1/3	(33.3%)
Total	26/30	(86.7%)

CAD algorithm with accumulated flat lesion case data will certainly increase CAD accuracy in the future. We are also studying the method of diagnosis in which CAD analysis results are super-imposed on the VGP view or air image, expecting to construct more effective CTC-ACD diagnosing systems.

2) Digital pre-processing

Bowel preparation is required equally for CTC to remove fecal matter, except for the case where CTC is performed following preoperative colonoscopy. Bowel preparation for CTC has been performed in the same way as for colonoscopy and enema studies. When the bowel is inadequately prepared, polyps cannot be differentiated from fecal remains and lesions may also be missed due to remaining liquids. To avoid interference from fecal and liquid remains, images must be captured both in the prone and supine positions in CTC for screening. In a recently developed digital pre-processing method, the combined administration of cathartic and oral contrast agents (i.e., barium and Gastrografin) labels the fecal and liquid remains as high dense areas which can be deleted from the CO2-inflated lumen by image processing.

For digital pre-processing, also known as “tagging” or “electronic cleansing” in the West (Lefere et al., 2002; Pickhardt et al., 2003), the FDA-approved barium products specially developed for CTC are available from E-Z-EM, Inc. (USA) [city, state?]. We have initiated a trial implementation of an E-Z-EM system including an automatic CO2 inflating device under the approval of the Ethics Review Committee of the National Cancer Center. Our joint research with Ziosoft, Inc., is also proceeding with image processing, and starting fundamental evaluation on digital pre-processing with a small number of cases. The artifacts observed along the boundary of the high- and low-dense areas on the mucosa may in fact pose some problems, but diagnostic images with no fecal or liquid remains were obtained even in the VGP view, suggesting the great potential of digital pre-processing in CTC.

Future Perspectives of CT Colonography in Colorectal Cancer Screening

Compared with colonoscopy or barium enema studies, CTC is an easier and less invasive modality which enables evaluation of the entire organ, as well as local lesions. With enhanced acquisition speed and quality of 3D images, CTC has virtually proved its clinical effectiveness in preoperative diagnosis when performed following colonography. In diagnosing early-stage lesions, CTC using a 64-detector MSCT can depict subtle elevations or depressions within the mucosa, which was difficult with a 4-16 detector MSCT. CTC is more useful than other colorectal study modalities for harmonizing study qualities among different institutions by standardizing the protocol. Enhanced accuracy of CAD and digital pre-processing will also help create a more standardized environment for diagnosis that minimizes overlooked lesions. The infrastructure required for CTC proliferation is expected to be set on place steadily, along with further improvement in performance and a wider use of MCST in radiologic diagnosis (Tomimatsu et al., 2005). In fact, the ratio of MSCT in the total CT sales in unit is steadily increasing. In 2006, a 16-64 detector MSCT with CTC features attained a ratio > 40% (Anonymous, 2007). Further improvement in image quality, development of 3D views, CAD, and digital pre-processing, and optimization of study dose (Muramatsu et al., 2003; Iannaccone et al., 2005) will certainly increase the value of CTC in colorectal diagnosis.

There certainly exist some flat lesions that are difficult to diagnose with the present CTC, which should be a target of improvement in screening. These flat lesions are challenges for accurate diagnosis, even by colonoscopy. An efficient CTC study with fewer blind spots might become more effective than colonoscopy in screening, depending on the lesion criteria setting for screening. At present, a fecal occult blood test (FOBT) is used for colorectal screening in Japan. However, its sensitivity for early-stage lesions is low and a more accurate method is desired. Colonoscopy presents a certain limitation in processing and the subjects express significant repulsion to the study burden, including the preparation.

The low rate of undergoing a close examination, even after a positive result of FOBT, is presenting a serious situation (Matsuda and Watanabe, 2003). Leveraging advantages of CTC digital image diagnosis will hopefully provide effective solutions to this critical situation of colorectal cancer screening. Construction of a truly effective system for colorectal screening is expected by integrating CTC successfully in the colorectal screening process, highlighting its unique features in colorectal studies.

Summary

Compared with invasive colonoscopy, which depends largely on the skill of the performer, CTC is a safer and easier study modality with significant potential for study processing. Further, the objective and reproducible diagnostic images present a high probability to be standardized. CTC is also capable of presenting 3D views in accordance with different diagnostic purposes. Used together with new diagnostic technologies, including CAD, CTC is expected to contribute to standardizing diagnostic capabilities among different institutions. When the considerable burden to the subject in the colorectal

study is lightened by application of digital pre-processing, CTC will revolutionarily reform the examination flow for routine colorectal examination. It is very likely that CTC will play a major role, not only in preoperative diagnosis, but also in colorectal cancer screening in the not too distant future.

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