

REVIEWS

THE ROLE OF OPTICAL AND VIRTUAL COLONOSCOPY IN COLORECTAL NEOPLASMS

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ABSTRACT

PURPOSE: High prevalence of colon carcinoma explains the continued high mortality rate of this disease. Utilizing a strategy of virtual colonoscopy (VC) in patients aged over 50 years with optical colonoscopy (OC) following-up for removal of detected adenomatous polyps may result in lowering the colon cancer death rate. However, VC diagnostic potential has not been widely recognized yet.

MATERIAL AND METHODS: This article reviews the currently available in diagnostic options in colorectal neoplasms and discusses their advantages and drawbacks.

RESULTS: VC has many advantages over the existing options and its several drawbacks can be mitigated so that it would become a valuable diagnostic modality. A strategy that utilizes VC for screening of patients over the age of 50 years and OC for screening high-risk individuals and those with positive VC findings would result in a significantly reduced colon cancer mortality rate.

CONCLUSION: Both OC and VC (i.e., CTC and MRC) progress toward the clinical needs as new technologies are developed and applied to overcome the drawbacks of these diagnostic methods. Each of them plays a unique role for colon cancer prevention.

Key words: optical colonoscopy, virtual colonoscopy, computed-tomography colonography, colon cancer, diagnosis

INTRODUCTION

Colorectal carcinoma (CRC) is the third most commonly diagnosed cancer and the second leading cause of death from cancer in the world (1,2). Similar to other cancers, it is often diagnosed at advanced stage, after the patient has developed symptoms. Different from many cancers, colon cancer can be prevented by detection and removal of its precursor lesion, the adenomatous polyp. Colon cancer is amenable to screening because of the long-time interval (approximately 10 years) of adenoma-carcinoma sequence. For example, it takes more than two years for an adenomatous polyp to grow up to 5 mm

in size with far less than 1% cancer risk, additional three or more years to 10 mm in size with cancer risk approaching to 1%, and other five or more years to 20 mm in size and 10% cancer risk (3). Therefore, screening of an asymptomatic patient at an adequate time interval and removal of detected adenomatous polyps of less than 10 mm in size can effectively reduce the likelihood of cancer development (12,13). Small colorectal adenomas measuring between 6 and 9 mm should not be ignored, in order to decrease CRC prevalence rate (19).

Fecal occult blood testing (FOBT) is, probably, the easiest method for screening the fatal disease. It can be performed at home by collecting stool samples without bowel preparation and complication and delivering the samples to a service laboratory. Conceptually, FOBT is highly sensitive. However, it detects only 30-40% of CRC and 10% of adenomas at late stage of the malignant transformation with specificity ranging from 88% to 98% (20). This

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screening option is currently recommended annually for asymptomatic patients. This test can reduce cancer mortality rate by 15-33% (3). Recently, stool DNA testing shows a wide sensitivity range from 52% to 91% and specificity ranging from 93% to 97% at a late stage of the malignant transformation, too (3). It costs more than FIT. While their sensitivities can be improved by adequately taking the stool samples as detailed elsewhere (3), these three screening methods share the same limitation of detection at advanced stage of the malignant transformation. In addition, their detection does not provide the location information where the malignant transformation occurs. Complete bowel preparation involves significant invasiveness and is essential for an optimal examination. The risk of bowel perforation is rare, about 1 in 25000 cases. It can have therapeutic capability of resecting the diagnosed polyps and removing the rest abnormalities, but it fails to detect polyps in the proximal colon, where 40% of all the cancers occur, and misses up to 10-15% of sigmoid colon carcinomas (4). The risk of bowel perforation is rare, less than 1 in 20000 cases.

OPTICAL COLONOSCOPY

Since the first reported complete examination of the colon using a flexible fiberoptic endoscope by Wolff and Shinya in 1971 (cited after 2), OC has evolved to be the current gold standard for evaluation of the entire colonic mucosal surface with therapeutic capability of resecting the detected lesions. Prior to OC, the patient must undergo bowel preparation usually consisting of (i) taking clear liquid diet and (ii) ingesting purgative solutions for colon cleansing the day before examination. Sedation is commonly used to relieve the discomfort during the procedure and, therefore, an escort is needed to accompany the patient to home. The modern colonoscope is equipped with a charge-coupled device or camera and four-way tip controls (3). The camera can produce images of high-definition television quality with zoom or magnification capability. The four-way tip controls include (i) interrogating a found patch to confirm an abnormal growth if it cannot be pushed away, (ii) insufflating air to extend the lumen for mucosal inspection and relieving air after inspection, (iii) irrigating a concerned region, (iv) sucking to avoid missing lesions under fluid, and (v) inserting biopsy

or polypectomy snare devices. Currently, OC is the definitive test in following-up the positive findings of the above screening options, i.e., FOBT, FIT, stool DNA testing, DCBE, FS, and other imaging modalities. In addition, it is also the most common choice of evaluating a variety of signs and symptoms such as (i) unexplained gastrointestinal bleeding or iron deficiency anemia, (ii) chronic inflammatory bowel disease, (iii) significant diarrhea of unexplained origin, (iv) abdominal pain, etc. It is also the most common modality of performing interventions such as hemostasis, polypectomy, foreign body removal, balloon dilation, palliative treatment of neoplasms, etc. (4). The current practice of OC is to attempt removal of any detected polyps, regardless of histology (adenomatous or hyperplastic).

A reduced incidence rate of colon cancer from 76% to 90% would be expected by the use of OC procedures every 10 years if no findings and shorter time intervals of abnormalities are found and therapeutic actions are performed (4). While it is accurate, OC has several drawbacks as a screening option: (i) it is an invasive procedure and sedation may be needed. Sedation use requires an escort, increases the costs and may induce complications such as cardiac arrhythmias, hypotension, oxygen desaturation, etc. (4,5); (ii) bowel preparation prior to the procedure is stressful, requiring a full oral laxative colon cleansing, and may cause abdominal discomfort, cramps, nausea, and other symptoms (3); (iii) OC is time-consuming (especially for elderly patients), ranging from 30 minutes to an hour; (iv) it carries a small risk of perforation and death - colonic perforation in one of about 1000 cases and death in one of about 5000 cases (1). It may fail to demonstrate the entire colon in 10-15% of cases and may miss up to 10-20% of polyps <1 cm (11). Overall, the missing rate of OC for large adenomas and cancer is about 12% and 5%, respectively (3). For the asymptomatic patient population aged over 50 years, where the prevalence of polyps ranging from 6 to 9 mm would be 8-9% and polyps of 10 mm and larger would be 5-7% (4), screening OC would be expected to be normal in more than 80% of cases. The risk and cost on these normal cases would be unnecessary. Furthermore, it would be expected that of the 16-20% of cases in which a polyp is found out, only one third would be

true adenomas and the other two-thirds would be hyperplastic lesions (6). The resection of these other hyperplastic polyps by current OC practice may not be necessary.

For patients with non-specific gastrointestinal symptoms, such as anemia and change in stool habits, OC may find polyps of size 10 mm or greater in about 7% (slightly higher than the findings in the asymptomatic patient population aged over 50 years) as compared to 17% in patients with a positive FOBT (2). Therefore, the safe and least expensive screening options of FOBT, FIT and stool DNA testing may be of benefit for the patients with non-specific gastrointestinal symptoms prior to OC procedure application. With further technology development, OC can improve its performance as a screening tool, but it could not be an optimal option to screen the entire targeted population due to: (i) the drawbacks associated with OC (e.g., more than 80% of the screened subjects would be negative because the prevalence of polyps is less than 20% in the population (10), (ii) the risk of sedation and perforation, (iii) the cost including an escort, (iv) the costs associated with unnecessarily removing the hyperplastic polyps (14), and (v) the lack of resources as it could take many years and great efforts to train a sufficient number of OC operators to perform the screening task (12,13). Because of the high prevalence of the disease and the low compliance rate to the currently available screening options, CRC mortality rate remains high. A more effective screening method as compared to the above mentioned options for evaluation of the entire colon and detection of polyps as small as 5 mm is desired. To that end, a great research effort has been seen in the past decades in searching for such an alternative. Developing virtual colonoscopy (VC) to supplement the screening role of OC is one example of these research efforts.

VIRTUAL COLONOSCOPY

Since 1994 onwards, several pilot studies (12) evaluating the feasibility of an alternative means using computed tomography (CT) imaging technology for the purpose of screening the entire colon motivate a substantial research interests ranging from image formation and segmentation to visualization (13), although there is already an earlier report (12). This alternative means, i.e., CT-based virtual colonoscopy

or CT colonography (CTC), utilizes computer virtual-reality techniques to navigate inside a three-dimensional (3D) patient-specific colon model reconstructed from abdominal CT images looking for polyps. It starts by inflating the cleansed colon by room air or CO₂ introduced through rectal insert tube (11). Then abdominal CT slice images are taken in seconds (during a single breath holding) with sub-millimetre resolution in both axial and transverse directions and good image contrast between the colon wall and the lumen filled by air/CO₂. The slice images are stacked together as a volume image, from which the colon model is constructed. Image segmentation is necessary for the construction of an accurate colon model (7). Computer graphics are heavily involved to navigate or fly through inside the 3D colon model (9). For the purpose of validating the detection in the 3D colon model, interpretation of the 2D image slices at the three orthogonal (i.e., transverse, sagittal and coronal) directions is often included in the VC procedure.

Initial clinical trials on the concept of CTC using laboratory prototypes show satisfactory sensitivity and specificity compared to the clinical OC (7). Significant improvement is later on demonstrated by large clinical trials using commercially available CTC systems. One example is the DoD clinical trial on 1233 asymptomatic patients using the commercial V3D Colon Module system (7). A sensitivity of 93,9% and specificity of 92,2% is achieved versus OC sensitivity of 91,5% for polyps of 8 mm and larger by the same bowel preparation and same day operation of CTC and OC. Other examples are the more recent ACRIN trial (7) and IMPACT trial (9), which include a wider range of subjects, radiologist's experience and CT/CTC systems and generate similar results for polyps of 10 mm and larger. The results of these studies indicate that by a similar full oral bowel cleansing, both CTC and OC have a comparable performance for detecting the polyps of 10 mm and larger and thus CTC can be a potential screening tool to supplement OC for CRC prevention. Current CT scanning for VC procedure is usually operated at a mAs level over 100 and delivers a significant amount of x-ray radiation exposure (two to four rads of dosage) to patient's abdomen (9). In comparison, a routine x-ray chest radiograph (or x-ray film) delivers approximately 0,5 rads of radiation exposures. For

screening purpose, the radiation to the population would be excessively high and could increase the risk of getting cancer and other diseases (12). Despite the hardware optimization and software improvement for CT advancement in the past decades, the concern on the CT-associated radiation risk remains. Given the current CT technologies, a simple and effective strategy to further reduce the radiation would be to lower the mAs level (i.e., delivering less x-ray photons to the body) during data acquisition (3). Despite the great effort on this solution in the past decade (11), CTC still faces challenges at a mAs level lower than 50. Given the clinical task of detecting the polyps as small as 5 mm, the goal of further research is to achieve the lowest mAs level on the most recent CT systems. An alternative solution to minimize the radiation is to use magnetic resonance imaging (MRI) instead of CT for the VC procedure, i.e., MR colonography (MRC). However, this MRC alternative solution has several limitations compared to CTC. It is more costly, more sensitive to motion and other artifacts, and has lower spatial resolution (8). Compared to other imaging modalities, low-dose CT and high performance MRI are the two most attractive imaging modalities for VC.

Great research efforts are devoted to advance CTC and MRC, especially CTC, toward a viable screening option. Regarding the issue of detection of small polyps, current modern CT can reach sub-millimetre spatial resolution and acquire a volumetric image of the abdomen in a single breath-holding time period. By theory, the achieved sub-millimetre spatial resolution could resolve polyps protruding to the colon lumen by a size as small as a couple of millimetres. In practice, the missing of polyps greater than 5 mm is common in the hands of experts with current CTC system (6). A major reason for the cause may be due to the imperfect colon cleansing and air/CO₂ inflation. They will not generate a perfect interface between the colon wall and the air/CO₂-filled lumen for detection of polyps at the CT spatial resolution. The complexity of colon anatomical structure may add more difficulties for the detection. For example, a small polyp could be highly likely missing the detection when it is located at the sharp turn of the colon or at the root of a colon folder. Another major reason for missing

polyp detection can be the loss of image information by the post-image processing algorithms in current CTC systems (e.g., segmentation for the colon lumen, construction of the colon model, incomplete coverage of the entire colon mucosa surface in endoscopic views, etc.). There are recent improvements in these aspects and more details are given below. Because of the similarity in x-ray attenuation among colonic fluid, stool and colon wall, it is almost impossible in the CT images to find a polyp submerged inside the residue fluid (after a routine full oral bowel cleansing). To avoid this problem, the patient is scanned at both supine and prone positions. It is hoped that the residue colonic materials will fall to another side when the patient is turned from one position to another while the polyp remains at the same location. Unfortunately, this is frequently not the case due to many reasons (11). Clear fluid may move, but some sticky residual stool/fluid may not. The use of two CT scans doubles the radiation. An alternative solution is to tag the colonic materials for enhanced image contrast between the colonic materials and the colon wall and to use computer algorithms to virtually cleanse the colon, called virtual or electronic colon cleansing (ECC) (18). It includes three major components of (i) image intensity alteration by oral fecal tagging, (ii) image segmentation for classifying the tagged image voxels, and (iii) postsegmentation operation for cleansing the colon lumen or extracting the colon wall. This alternative solution is a major contribution to the high CTC performance (12), where the scans at supine and prone positions are taken and the routine cathartic bowel preparation of OC is adapted and so, the ECC works on the residual colonic materials. Since it works for virtual cleansing of the residues after the routine cathartic bowel preparation, ECC shall also work on virtual cleansing of any fecal materials without the routine cathartic bowel cleansing, leading to cathartic-free CTC - a substantial relief of the bowel preparation stress of the current CTC practice. In addition, if ECC works on one of the two scans, the other scan may not be needed and, therefore, the radiation can be reduced by a half. If cathartic-free CTC is available, the patient may choose the less-stressful screening procedure first, and only those patients who present with clinically

significant polyps will undergo the OC intervention after the stressful cathartic bowel preparation.

Further development of ECC for single CT scan and cathartic-free CTC would depend on powerful image segmentation and feature extraction. Because of the enhanced image intensities, there are several challenges associated with the alternative ECC solution, e.g., the presence of partial volume (PV) effect at the interface between the colon wall and the fecal materials with non-uniformly enhanced image intensities. The PV effect blurs the interface over a variable range as wide as several image voxels depending on the surrounding image contrast, causes the loss of details about the interface and, therefore, results in the missed detection of small polyps. The PV effect and the non-uniformly altered image intensity distribution must be handled by the ECC algorithms (11). Differentiation of the colonic materials from the colon wall/polyps could also be made by the use of dual energy scans of a modern CT device (e.g., a dual x-ray source scanner). Despite the increased x-ray radiation to the patient by dual energy scans, this alternative approach for image contrast may be worthy for investigation. With accurate handling of the PV effect and the non-uniformly altered image intensity distribution via improved image segmentation, the innovative ECC strategy should further reduce the risk from x-ray radiation, mitigate the challenge in detecting the small polyps, and relieve the stress on the bowel preparation toward cathartic-free CTC. While constructing the accurate colon model from an ECC-cleansed colon lumen of an abdominal volume image for inspection of the entire colon inner surface possibly achieved by the commercial V3D Colon Module (8), searching for abnormalities and identifying the polyps along the long colon 'pipe' would be a challenge task because of the involved intensive user interaction during the fly-through navigation. In addition, the variation among readers with different experience is widely noticed. Conceptually computer-aided detection (CAD) can reduce the readers' interaction effort and minimize the variation among readers' assessments. However, a series of recent studies turns out that developing an effective CAD system is very challenging (13) because of many causes of false positives (FPs) such

as imperfect bowel cleansing, complicated colon fold structures, image noise, motion artifacts, etc.

Based on our experience in the field, surface-based CAD as reported in most previous CAD papers is not sufficient to reduce the FPs to an accepted level (e.g., <10 per patient). Morphological and texture features beyond the inner surface inside the mucosal layer and probably even inside the colon wall are needed (16). High sensitivity CAD with minimal number of FPs remains an active research topic. Recent development of various texture features of the image intensity distribution and virtual biopsy features of the image intensity projection from the colon wall shows promise for high performance CAD (17).

DISCUSSION

Because of the high colon carcinoma prevalence, screening of asymptomatic patients to detect and remove adenomatous polyps is an effective strategy to reduce the mortality rate. However, the screening options currently available have their limitations and offer a suboptimal solution. While effective for detecting polyps, OC would consume a great deal of resource if American Cancer Society (ACS) guidelines are applied to the target population. It is unlikely that OC will be able to single out asymptomatic patients with adenomatous polyps. Compared to other screening options, VC has the potential to identify patients with adenomatous polyps for colonoscopy. The combination of VC screening with OC follow-up could be a cost-effective means to prevent the fatal disease. However, there are several challenges in developing VC to accomplish this task. With CT-based VC or CTC, the associated radiation is a concern. Differentiation of the colonic materials from the colon wall remains a great challenge. While MRI-based VC or MRC alleviates the radiation concern and is more capable of differentiating the colonic materials from the colon wall with the potential to obtain more image contrast inside the colon wall, it possesses a lower spatial resolution and is prone to motion artifacts. Both CTC and MRC need sophisticated image processing operations to construct the colon model and perform real-time fly-through inside the model when looking for abnormalities. Sophisticated image processing operations would be more essential if differentiation

of adenomatous polyps from hyperplastic ones is desired. In other words, the extraction of the colon wall volume via the ECC innovation (9) and the analysis of texture features from image intensity of the wall (7) would be the key steps toward computer-aided detection and diagnosis. If the colon wall volume, rather than only the inner mucosa surface of the wall, can be accurately extracted by a sophisticated ECC pipeline, then almost the entire clinically desired information can be obtained. From the extracted wall volume, we can analyze both geometric and image-density textural information for early signs of abnormality (12). This will improve not only the current VC detection capability of small polyps protruding into the lumen space, but also the detection of flat polyps which cause the wall thickening, rather than protruding into the lumen, and render an extremely challenging detection task (11). Taking CTC as an example, the strategy of lowering the mAs level during data acquisition and utilizing the statistical methods for image reconstruction is an innovation to reduce the risk of radiation (13-15). Furthermore, application of a statistical restoration algorithm to estimate the line integrals or radon transform of the CT attenuation distribution and inverting the radon transform for the CT image is another innovation to overcome the challenge of reconstructing the low-mAs data of huge size. The image segmentation is the key component in ECC. The presence of PV effect and non-uniform fecal tagging render a very challenging task for image segmentation to preserve the details of the mucosa, where clinical information resides. While many segmentation algorithms are already reported, the MAP-EM (maximum a posteriori expectation-maximization) segmentation of tissue mixtures in each image voxel shows the potential to mitigate the challenge (17). Since the PV layers are accurately identified, extraction of the colon wall mucosa becomes feasible. The preserved details on the mucosa layer by the MAP-EM mixture segmentation improve noticeably the detection of small polyps (10). Given the extracted volume of mucosa layer, more useful texture information can be available for development of CAD methods. This benefit for CAD development is already identified (18). Further improvement of CAD for small polyps should be

expected when more useful texture information is extracted from the volumetric mucosa. In summary, low-dose CTC and/or high resolution MRC are likely to become a screening modality, supplement to OC to reduce colon cancer incidence rate. This is because of the following reasons: (i) both imaging modalities can generate high-quality abdominal volume image, including the entire colon, (ii) given the abdominal image from either imaging modality, extraction of the colon wall is a key operation to achieve high sensitivity and specificity by both the human and computer observers. The under-developing MAP-EM segmentation of tissue mixtures has the potential to accurately identify the colon mucosa, from which an ECC pipeline can be built-up to cleanse the lumen and extract the wall.

CONCLUSION

Both OC and VC (i.e., CTC and MRC) advance toward the clinical needs as new technologies are developed and applied to overcome their drawbacks. Each of these two methods plays a unique role for the goal of colon cancer prevention. OC will remain the choice for follow-up intervention and therapeutic operation in the patients with symptoms and positive findings from other easy screening options. By its inherent invasive nature, OC will encounter competition from other less invasive modalities for the purpose of mass screening because of the high prevalence but preventive nature of the colon cancer. For screening purpose, VC has many advantages over other options such as FOBT, FIT, stool DNA testing, and DCBE. Nowadays it is the most competitive alternative method to OC for colon screening. The competition could lead to a good combination of VC screening with OC follow-up of the positive findings to reduce the incidence rate of this fatal disease (20). There are a few medical imaging modalities currently available for VC, such as CT and MRI. As time goes on, other medical imaging modalities may become available for VC.

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