REVIEW

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Review of Computed Tomographic Colonography from a Surgeon's Perspective

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ABSTRACT

New research has addressed many of the early concerns of Computed Tomographic colonography (CTC) and these studies are now beginning to shape clinical practices. A review of the literature demonstrates that the sensitivity of CTC in screening for large polyps (≥ 1cm) or cancers in the large intestine is as high as that of conventional optical colonoscopy, however, the sensitivity decreases with the diameter of the polyp. Despite this, CTC is well tolerated, more acceptable to patients than optical colonoscopy and therefore may improve colorectal cancer screening compliance. This review not only describes the diagnostic accuracy and sensitivity of CTC, and the evolving role of CTC as a primary colon cancer screening option, but also the recent studies that have demonstrated the additional value of CTC utilization for practicing clinicians.

Key words: computed tomographic colonography – colonic cancer – colorectal adenoma – rectal cancer – surgery – colonoscopy – virtual colonoscopy.

Abbreviations: CAD: computer aided detection; CTC: computed tomographic colonography; CT: computed tomography; CRC: colorectal cancer; FOBT: fecal occult blood test; NPV: negative predictive value; OC: optical colonoscopy; PPV: positive predictive value.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer diagnosed and the third leading cause of cancer-related deaths in both men and women in the United States. A combination of early detection and the removal of adenomas remains the best method to decrease both the incidence and mortality related to this disease. Essential to this goal is the identification of the most cost effective population-screening test. Currently, optical colonoscopy (OC) is the most widely accepted method for this screening, but it is expensive, resource intensive, technically difficult, and has a small but well-recognized morbidity and even mortality [1].

Computed tomographic colonography (CTC), first developed in 1994, did not gain much recognition until the diagnostic validity of CTC was published in the *New England Journal of Medicine* five years later [2]. Subsequently, CTC has been the subject of over 20 prospective performance studies evaluating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the detection of CRC and polyps. New research has demonstrated the additional value of CTC utilization for the practicing clinician such as its value in the preoperative evaluation after incomplete colonoscopy and preoperative planning and staging for CRC, surveillance after colorectal resection and follow-up after a diverticulitis attack. This review will examine the most recent literature and discuss the evolution, indications and usefulness of CTC through a surgeon's perspective.

INDICATIONS: SURGEON'S VIEWPOINT

The most widely accepted clinical indication for CTC is incomplete or unsuccessful colonoscopy [3]. Incomplete colonoscopy occurs on average in 10% of the patients [4] and is commonly due to sharp angulations, fixed points, intolerance to the procedure, incomplete visualization secondary to poor bowel preparation or to an obstructing lesion [5]. In the two largest retrospective series of more than 100 patients undergoing CTC after incomplete colonoscopy, additional clinically relevant colonic findings, including large polyps and cancers, were found in more than 10% of the patients [3, 6]. In both these series, the majority of the patients with positive CTC findings underwent repeat colonoscopy, which may be performed the same day without additional bowel preparation. However, this is not possible in the case of an obstructing cancer or a high-grade stenosis. In these cases, the colon can be examined successfully with CTC using low-pressure carbon dioxide, obviating the need for intra-operative colonoscopy [7, 8]. Moreover, in one of the large series of obstructed cancers, Kim et al. showed that CTC can reliably exclude proximal pathology and that OC can be safely postponed until 12 months after resection [9].

Another clinical scenario where CTC could provide an alternative tool to colonoscopy for proximal colonic evaluation is after metallic stent placement. In these cases, clinicians are usually reluctant to perform a colonoscopy to find synchronous colonic lesions. In a study of 50 consecutive patients who underwent CTC after metallic stent placement for acute severe cancer obstruction, CTC was performed adequately in 94% of the patients and no procedure-related adverse events were reported [10]. However, if a metallic stent is placed across the stenotic segment, air insufflation should be performed only after CT images have ruled out a stent-related perforation.

Several series of CTC performed after incomplete OC in patients with CRC show that, by providing surgeons with accurate preoperative information about additional colonic disease, tumor localization and distant metastasis, CTC can alter the surgical plan in up to 20% of the patients [11, 12]. CTC can easily be extended to the lungs and, when intravenous iodinated contrast media is used, the liver can also be evaluated for distant metastasis. Correct localization of CRC is mandatory prior to laparoscopic surgery because of the lack of tactile feedback. While neither OC nor abdominal CT is considered a reliable method for tumor localization prior to surgery, CTC is 95-100% accurate [13, 14]. Moreover, CTC is also the most accurate test to stage both extramural (≥T3) and nodal invasion with a NPV of 87 and 86%, respectively [12]. In presence of T4 colonic disease or extensive nodal involvement the surgeon may opt for an open instead of laparoscopic approach or a complete mesenteric excision [15, 16]. Accurate preoperative T and N staging for intraperitoneal colon cancer will become more clinically relevant if the benefit of neoadjuvant chemotherapy for stage II and III cancer, namely a higher rate of R0 resection, shown by the interim analysis of the FOXTROT trial is confirmed [17].

Current surveillance strategy after surgical resection of CRC includes periodic abdominal CT scans with intravenous contrast media and colonoscopies; therefore, contrast enhanced CTC may be able to replace both of these tests [18]. Moreover, CTC has additional value to evaluate the anastomosis for local tumor recurrence in patients with previous colorectal surgery [18]. In 742 consecutive patients after CRC surgery, most of whom underwent confirmatory colonoscopy, CTC identified 80% of patients with adenomas and 100% of those with carcinomas including one anastomotic recurrence (NPV for advanced adenomas and carcinomas were 99% and 100%, respectively). Importantly, CTC findings indicated the need for colonoscopy in only 19% of the patients.

Another indication for CTC is in the elderly or frail patient in whom colonoscopy poses a higher risk [19]. The elderly is at a higher risk of dehydration and of poor bowel preparation resulting in incomplete colonoscopy. Minimal preparation CTC using fecal tagging and no cathartics has been used successfully in this patient population with a sensitivity of 90% and a NPV of 99% [20]. Optical colonoscopy can be then reserved for patients with positive and/or doubtful findings at CT and patients requiring biopsy and/or other procedures. In the future, we can expect that the role of CT for the diagnosis of colon disease in the elderly patient will expand.

CTC also has value in the follow-up of acute diverticulitis [21-24]. Although debatable, some guidelines still recommend that the entire length of the colon should be evaluated after an episode of complicated colonic diverticulitis resolves, to rule out the presence of abnormal lesions such as polyps or cancer [25]. Recent studies have shown that CTC with intravenous contrast media appears to have a better diagnostic potential for imaging of diverticular disease-specific findings when compared with colonoscopy and is a reasonable alternative in follow-up of patients with symptomatic diverticular disease (Figs.1, 2). In a prospective comparative study, 50 patients diagnosed with diverticulitis underwent CTC immediately followed by conventional colonoscopy. Diverticular disease was found in 48 of the 50 (96%) patients utilizing CTC and in 45 of 50 (90%) patients with conventional colonoscopy [21]. In addition, two prospective studies reported that patients found CTC less painful and unpleasant than colonoscopy and thus CTC was preferred by a majority of patients [21, 22]. Where available, water enema CT with intravenous contrast (Fig. 1) may be a good alternative to CTC and is preferred by some authors because of improved distension of the diverticular segments and improved definition of bowel wall thickening, overcoming some of the known pitfalls of CTC such as non-distensible segments, inverted and impacted diverticula [26, 27].

DIAGNOSTIC PERFORMANCE OF CTC FOR THE DETECTION OF CRC

A meta-analysis of the 49 performance studies (i.e. where CTC was compared to OC as gold standard), published until December 2009 and including data on 11,151 patients concluded that "high quality" CTC has a sensitivity in diagnosing CRC similar to that of OC (96% vs. 95%) [28]. Similarly, a recent population study on 1,177 symptomatic patients referred for CTC showed a sensitivity of 95% and a negative predictive value of 99% [29].

The most recent compelling evidence on the ability of CTC to detect CRC comes from SIGGAR studies, two randomized trials that compared CTC with barium enema (n=3,804) or colonoscopy (n=1,580) for the investigation of patients with symptoms suggestive of CRC [30, 31]. The aim of the SIGGAR study was to compare the detection rate of CTC, using different examination techniques, versus barium enema and versus OC for the diagnosis of CRC and of colonic polyps measuring ≥1 cm.

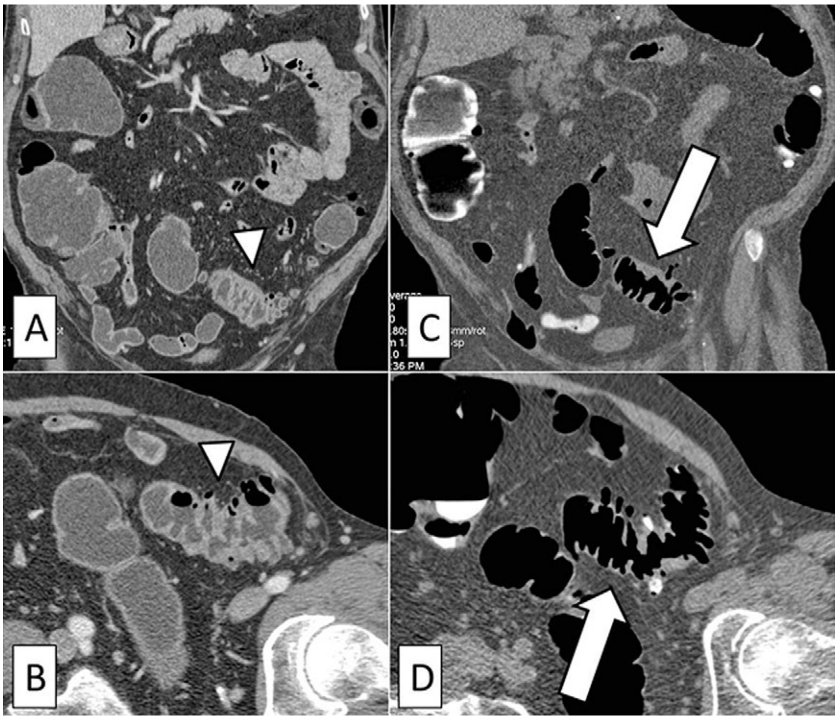

Fig. 1. A water enema CT with intravenous contrast in a patient with a recent episode of diverticulitis. CT nicely depicts the thickened sigmoid wall and diverticula (arrowhead in A and B). The same patient underwent CTC 5 years later because of anemia (C and D). This time, CTC was performed after fecal tagging and without intravenous contrast media and shows thickened sigmoid wall and diverticula (arrows in C and D). OC was subsequently done because of persistent anemia, confirming the absence of pathologic findings.

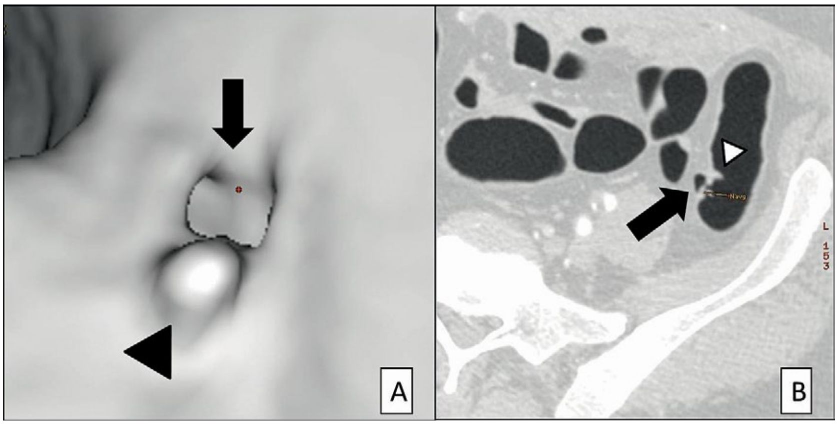

Fig. 2. Three-dimensional endoluminal CTC image reconstruction showing a sigmoid polyp (arrowhead) adjacent to colonic diverticula (arrow) (A), and the corresponding two-dimensional image (B).

The findings of the CTC vs. barium enema trial [30] showed that the detection rate of CRC or large polyps was significantly higher in the CTC group (7.3% vs. 5.6%, $p = 0.039$), while there was no significant difference in the detection of cancer alone (3.7% vs. 3.4%, $p = 0.66$). As shown in Fig. 3, a semitransparent 3D global view map of the entire colon at CTC looks similar to the appearance of a double-contrast barium enema.

The findings of the second trial (CTC vs. colonoscopy) [31] showed that there was no difference in the rates of detection of CRC or large polyps between the two groups (10.7% vs. 11.4%, $p = 0.69$). However, patients in the CTC group were more than three times as likely to have additional colonic investigations (30.0% vs. 8.2%, RR = 3.65, $p < 0.0001$) mostly due to small polyps or clinical uncertainty. Cancer or large polyps were found in 34% of the CTC patients referred for colonoscopy and in 17% of patients initially studied with colonoscopy. During 3-year follow-up, 1 (3.4%) additional cancer was found in the CTC group and no cancers were missed in the colonoscopy group. In conclusion, while barium enema should be abandoned in favor of CTC, OC remains the test of choice in patients in whom CRC is suspected. Also, it has to be reminded that the radiation dose of a double contrast barium enema is much higher than that of a CTC.

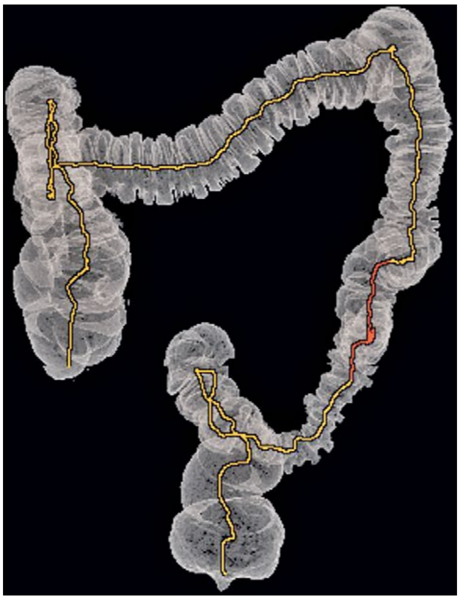

Fig. 3. Schematic map of the colon generated by CT colonography software. The software automatically isolates the air-filled colon and rectum and generates an endoluminal centerline (yellow line).

CTC is not the only CT technique used in the diagnosis and staging of suspected CRC (Figs. 4, 5). Colonic and extra-colonic disease may also be correctly staged with water enema CT, minimal preparation CT and CT opaque enema [19]. All four different CT examinations make it possible to obtain three-dimensional images of the colon and offer, at the same time, an evaluation of the abdomen that can be further improved using intravenous iodinated contrast media.

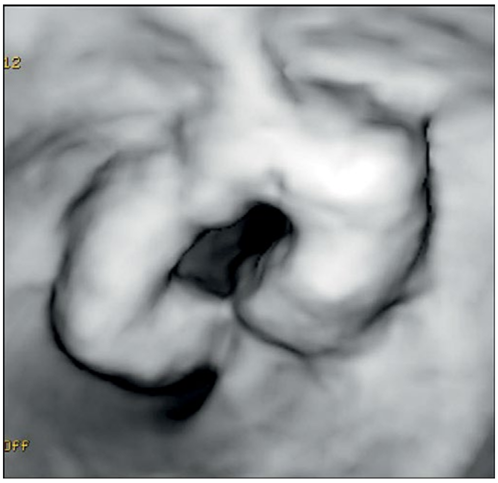

Fig. 4. Antegrade three-dimensional endoluminal evaluation of an annular constricting sigmoid carcinoma with corresponding 2D oblique positioned image.

CTC FOR CRC SCREENING

Screening of asymptomatic, average risk patients

To date there have been only five studies comparing CTC with OC in whom the majority of the study population was composed of asymptomatic, average risk patients (i.e. ≥50 years old without predisposing conditions). Two of these studies enrolled more than 1,000 screenees and account for more than 80% of the data [32, 33]. A meta-analysis of the five studies showed a per patient sensitivity of 78% for adenomas 6-9 mm, 83% for adenomas ≥6 mm and 88% for adenomas ≥1cm with marked heterogeneity between studies, especially for adenomas 6-9 mm. Corresponding per patient specificities were 95% for adenomas 6-9 mm, 91% for adenomas ≥6 mm and 98% for adenomas ≥1 cm [34].

Interestingly, CTC can identify lesions missed at OC [28]. A review of all CTC studies with un-blinding of CTC results at the time of colonoscopy revealed that 20 of 188 advanced lesions detected by CTC were initially missed by colonoscopy. Polyps may hide behind folds, be obscured by inadequate preparation or simply be missed by the endoscopist [35]. Many of these limitations may not apply to CTC. On the other hand, depressed and flat neoplasms may be missed at CTC screening [36]. However, of 734-screened individuals with lesions on CTC who subsequently underwent OC, only 9 flat lesions were missed, and only 2 of them were adenomas [37]. Similar results are reported for laterally spreading tumors, a subset of flat lesions with increased malignant potential [38]. However, in a recent prospective study of lateral spreading tumors first identified at colonoscopy, 80% of carcinomas and only 30% of adenomas were seen on CTC by an expert radiologist blinded to the colonoscopic results [39].

A definite advantage of CTC over colonoscopy for screening of asymptomatic individuals is in the more uniform adenoma and cancer detection rate among radiologists as opposed to colonoscopists [40]. Extra-colonic findings when handled appropriately can also enhance the value of CTC screening. In fact, as outlined in a recent review by Pickhardt et al. more unsuspected extracolonic cancers than CRC are detected at CTC screening [41]. It is therefore surprising that the possible variability of radiologist performance and potential harm from additional diagnostic testing generated by extra-colonic findings are among the reasons why CTC is not considered a valid screening choice by the U.S. Preventive Services Task Force.

Recently, a Dutch prospective randomized trial compared CTC with colonoscopy in a screening population [42]. Of 5,924 individuals invited for colonoscopy, 1,276 (22%) participated, compared with 982 (34%) of 2,920 CTC invitees (relative risk [RR] 1.56, 95% CI 1.46–1.68; p<0.0001). The diagnostic yield for all advanced neoplasia was 9% for colonoscopy versus 6% for CTC (RR 1.46, 95% CI 1.06–2.03; p=0.02). However, since the rate of participation for CTC was higher, the diagnostic yield among invited patients was higher for CTC. A higher patient preference is likely also in the US where, out of 441

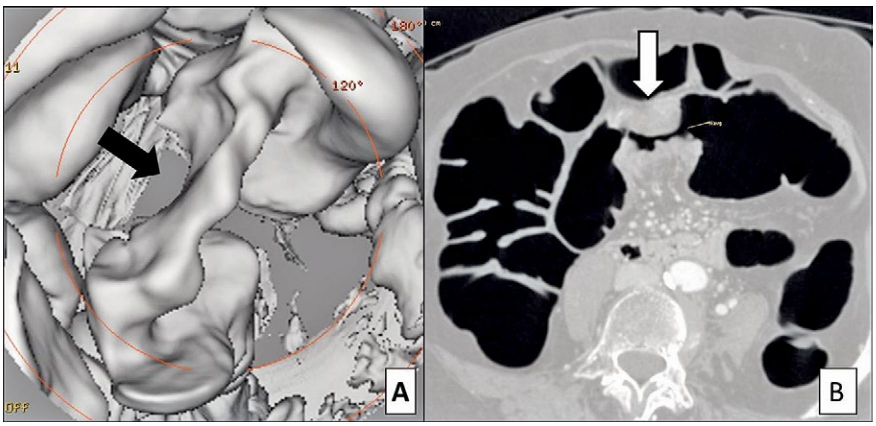

Fig. 5. 3D cast representation of the sigmoid colon looks similar to the appearance of a single-contrast barium enema. The "apple core" lesion (arrow) on 3D (A) imaging represents an annular constricting carcinoma confirmed on the 2D (B) supine image.

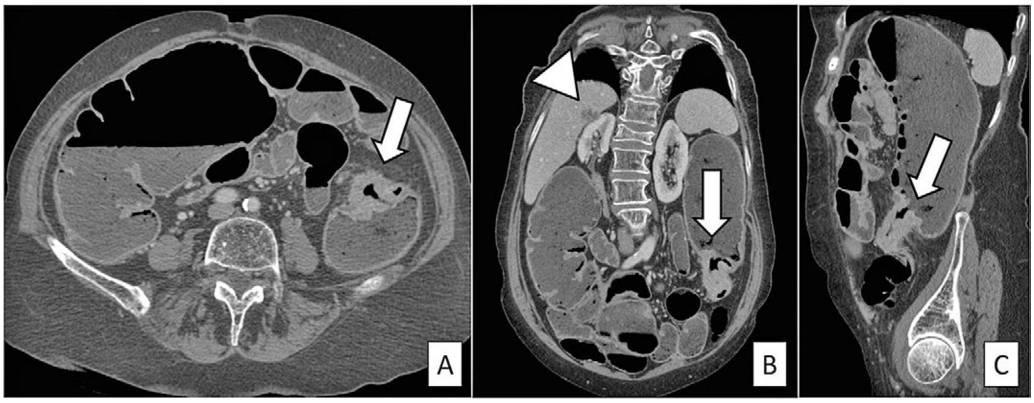

Fig. 6. Stenosing CRC (arrow) of the descending colon, CT performed briefly after the emergency admission for bowel occlusion. In this case the assessment of the proximal colon is possible because of the distention caused by the occlusion causing a contrast similar to CTC and colon water enema CT. Arrowhead indicates a liver metastasis.

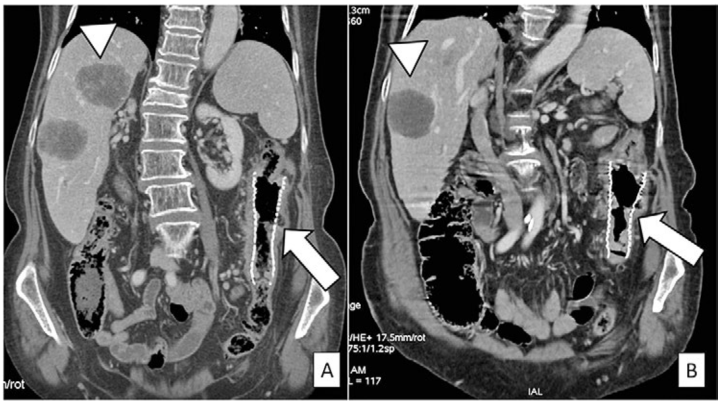

Fig. 7. Same case of Fig. 6: after placement of colonic stent (arrow) the colonic distention is resolved (A). In the subsequent control following chemotherapy (B) the vascularization of the liver metastasis (arrowhead) is reduced and also the primary tumor thickness is reduced comparing the mass around the stent in A and B (arrow).

patients who had experienced both CTC and OC, 77.1% preferred CTC and 13.8% preferred OC [43].

Long term results of this screening trial (i.e. how many cancers were missed and how many were prevented) are still unknown. However, after an average follow-up of 4.7 years, in a cohort of 1,050 asymptomatic individuals with negative CTC only one adenocarcinoma was found [44]. In another retrospective study of 1,833 patients who had undergone screening CTC, of 53 diagnosed cancers only 2 (3.8%) were missed [45]. Despite these encouraging results, most patients and physicians remain unaware of the possibility to use CTC for screening. In a 2011 US preference survey of 100 average risk individuals and 170 practitioners, CTC ranked very low [46].

Screening of asymptomatic, high-risk patients

Fecal occult blood test (FOBT) screening is a very cost-effective way to reduce CRC mortality and is the main screening tool in the UK, Australia, Canada and many other countries with a public health care system that cannot afford the cost of colonoscopic screening. Among its drawbacks there is a low specificity with a 55-65% rate of negative colonoscopy in patients with positive FOBT [47]. The use of CTC in patients with positive FOBT has been investigated as a way to triage patients and reduce the number of colonoscopic examinations [48, 49]. A meta-analysis of the five studies where CTC was followed by OC in patients with a positive FOBT showed a sensitivity of 89% for ≥6 mm polyps and a specificity of 75%, and concluded that CTC may be useful in reducing the burden of colonoscopic examinations after positive FOBT [50].

Several investigators have assessed the diagnostic accuracy of CTC in patients with a personal or family history of CRC, and in surveillance after polypectomy or CRC resection. Recent studies in 373 and 303 first degree relatives of CRC patients showed a per patient sensitivity of 82% and 89% and a NPV of 98.5% and 99% in detecting advanced lesions defined as ≥1cm or with high risk histological features [49, 51]. Similarly, high sensitivity (85%) and NPV (98%) have been reported in patients undergoing post-polypectomy surveillance [47]. These results suggest a role for CTC in patients with a family history of CRC and in post-polypectomy surveillance but further data is needed. Other authors suggested that patients at increased risk who have previously undergone colonoscopy tend to have lesions that are hard to detect with CTC because larger lesions are detected and removed at colonoscopy [52, 53]. A significant proportion (24-33%) of large polyps in this patient population are flat lesions and more than 50% of large flat polyps may be missed by CTC [52, 54].

Cost-effectiveness

In all of the screening trials cost was never calculated prospectively, therefore all cost analysis studies are based on theoretical assumptions and simulation models. The results of these cost studies differ: while the Pickhardt group [55] showed that CTC every 5 years followed by OC for ≥6 mm polyps is more cost effective than colonoscopy every 10 years and reduces the number of polypectomies by 77%, in other studies CTC is dominated (i.e. less beneficial and more expensive) by all other screening strategies [56, 57]. The differences between these studies are due to the use of different simulation models with different baseline assumption. In the model used by the Pickhardt group, the assumption for a diminutive polyp is that 4% will grow to a size of 1 cm or more in 10 years, while the MISCAN model, used by all other investigators, assumes that 10–64% of the diminutive adenomas will become cancer within 10 years. Moreover, CTC cost, which is assumed to be the same as a CT of the abdomen and pelvis, is largely unknown and cost-effectiveness is very likely to change with improvements in performance and efficiency afforded by the new computer aided technology [58]. A recent assessment of the actual cost of CTC screening within a nationwide screening program was much lower (€170) than the ones used in cost analysis studies that are based on CTC reimbursements in clinical settings (€346–€594) [59]. Another variable that adds uncertainty to the cost-effectiveness studies is the number of important extracolonic findings and of additional studies required.

COMPLICATIONS OF CTC

Although the complications of CTC are very small, they are not insignificant. Potential hazards associated with the technique are radiation exposure (however, lower than needed for a barium enema radiographic examination), risks of insufflation of air, bowel preparation (clear liquid diet, laxatives, large quantities of bad-tasting oral solutions), and need for OC (about 8% of patients will end up getting both procedures) [60].

Recently, a retrospective study reported on the frequency and magnitude of complications associated with CTC in clinical practice. A questionnaire sent to Italian public radiology departments, identified as practicing CTC with a reasonable level of training, showed that no death occurred in over 40,000 examinations [61]. However, bowel perforations occurred in 0.02% (7 examinations). All perforations were asymptomatic and occurred in patients undergoing manual insufflations. Five of the perforations (71%) occurred in procedures performed following a recent colonoscopy. Complications related to vasovagal reaction (either with or without spasmolytic) occurred in 0.16% (63 examinations). All vasovagal reactions resolved in less than 3 hours, without any sequelae. Perforation rate at CTC is negligible when compared with the risk of diagnostic colonoscopy.

The exposure to ionizing radiation and the potential harm of radiation-related cancer risk have received much attention. Newer generation CT scanners utilize radiation dose reduction software such as iterative reconstruction, automatic exposure control and BMI-based dose reduction. Implementing low kV and low mA scanning protocol parameters and reducing the number of scanning series through the abdomen and pelvis will minimize dose when possible. Benefit-risk analyses models have concluded that the benefit of CRC prevention by early detection far outweighs the potential harm of radiation-related cancer risk ranging from benefit to risk ratios of 24:1 to 35:1. It should be stressed that in elderly patients, the risk of radiation from CT is totally negligible, instead the risk of perforation during optical colonoscopy and of incomplete OC may carry a much higher morbidity. The main risk of CT for elderly patients is contrast-induced nephropathy; therefore, intravenous iodinated contrast media have to be limited to patients with an adequate creatinine clearance and multiple contrast-enhanced CT scans should be avoided.

RECENT TECHNOLOGICAL ADVANCES IN CTC

From a radiological point of view, CTC has always been and will probably always be linked to technology developments and improvements regarding CT scanners ("hardware") and/or CTC "software".

A new generation of CT scanners that has been recently applied to CTC is the dual energy CT. Dual energy CT represents a substantial improvement in CT technique. The term "dual energy" refers to the possibility of using different energies (kV) of x-rays. In virtual colonoscopy these systems offer mainly the advantage of a better automatic removal of the fecal tagging [62].

Recent developments in CT scanners include also different systems aimed to reduce the radiation dose [63, 64]. Today the accepted dose for CTC of a normal size patient is 3.6mSv (with a dose conversion factor of 0.017) [64]. Computer aided detection (CAD) has reached good results in CTC and is continuously being improved. New CAD tools are being developed that may make easier the automatic depiction of colon polyps and cancer within the complex anatomy of the colon haustra, turns, physiological strictures [65-67]. In the future CAD will most likely perform the first reading of the CTC, with the radiologist reviewing only the CAD findings. This approach can significantly decrease reading times of virtual colonoscopy, down to 3.1 minutes per patient as demonstrated by Mang et al. [68].

An interesting field to develop is prep-less virtual colonoscopy replacing air with water plus hidrosoluble iodated contrast media. The objective of prep-less virtual colonoscopy water plus hidrosoluble iodated contrast media is to study the interface between the high-density enema and the low-density mucosa. This technique requires the acquisiton of only a single decubitus of the patient (only the supine) compared to the two (prone and supine) usually needed for standard CTC [60].

CONCLUSIONS

The high sensitivity of CTC for large polyps and cancer and its ability to detect extra-colonic lesions make it an appealing procedure to offer. CTC is also a less invasive alternative to colonoscopy, and is preferred by patients. From the surgeon's perspective, CTC should be offered to patients when colonoscopy is attempted but incomplete because the full length of the colon is not visualized. More widespread implementation of CTC, especially in the surgical planning of CRC and the surveillance after colorectal resections should be accompanied by protocols to optimize the sensitivity and specificity of the procedure, guidelines on reporting and patient referral for both radiologists and referring clinicians, adequate training, and a system of continuous audit.

Conflicts of interest: None to declare.

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