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TOPIC HIGHLIGHT

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Computed tomography colonography in 2014: An update on technique and indications

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Abstract

Twenty years after its introduction, computed tomographic colonography (CTC) has reached its maturity, and it can reasonably be considered the best radiological diagnostic test for imaging colorectal cancer (CRC) and polyps. This examination technique is less invasive than colonoscopy (CS), easy to perform, and standardized. Reduced bowel preparation and colonic distention using carbon dioxide favor patient compliance. Widespread implementation of a new image reconstruction algorithm has minimized radiation exposure, and the use of dedicated software with enhanced views has enabled easier image interpretation. Integration in the routine workflow of a computer-aided detection algorithm reduces perceptual errors, particularly for small polyps. Consolidated evidence from the literature shows that the diagnostic performances for the detection of CRC and large polyps in symptomatic and asymptomatic individuals are similar to CS and are largely superior to barium enema, the latter of which should be strongly discouraged. Favorable data regarding CTC performance open the possibility for many different indications, some of which are already supported by evidence-based data: incomplete, failed, or unfeasible CS; symptomatic, elderly, and frail patients; and investigation of diverticular disease. Other indications are still being debated and, thus, are recommended only if CS is unfeasible: the use of CTC in CRC screening and in surveillance after surgery for CRC or polypectomy. In order for CTC to be used appropriately, contraindications such as acute abdominal conditions (diverticulitis or the acute phase of inflammatory bowel diseases) and surveillance in patients with a long-standing history of ulcerative colitis or Crohn's disease and in those with hereditary colonic syndromes should not be overlooked. This will maximize the benefits of the technique and minimize potential sources of frustration or disappointment for both referring clinicians and patients.

Key words: Computed tomographic colonography; Virtual colonoscopy; Computed tomographic colonography, technique; Computed tomographic colonography, neoplasm; Computed tomographic colonography, polyp; Computed tomographic colonography, indications; Computed tomographic colonography, colorectal cancer screening; Computed tomographic colonography, diverticular disease; Computed tomographic colonography, surveillance

Core tip: Computed tomographic colonography (CTC) is easy to perform, standardized, and patient-friendly. Radiation exposure is minimized and image interpretation is facilitated by the use of a computer-aided detection algorithm. The diagnostic accuracies for colorectal cancer (CRC) and large polyps are similar to that of colonoscopy (CS) and are largely superior to that of barium enema. Incomplete, failed, or unfeasible CS and investigation of symptomatic, elderly, and frail patients and diverticular disease are clear indications. CTC is recommended for CRC screening and in surveillance after surgery or polypectomy if CS is unfeasible. Acute abdominal conditions and surveillance in patients with ulcerative colitis, Crohn's disease, and hereditary colonic syndromes are known contraindications.

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INTRODUCTION

Twenty years after the introduction of computed tomographic colonography (CTC)[1], this technique has reached its maturity, and it can reasonably be considered the best radiological diagnostic test for imaging CRC and polyps.

Recent evidence in the literature shows that the diagnostic performance for the detection of CRC both in symptomatic[2,3] and asymptomatic subjects[4,5] is similar to that of colonoscopy (CS) and is largely superior to that of barium enema (BE), thus leading the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the European Society of Gastrointestinal Endoscopy (ESGE) "… to recommend CT colonography as the radiological examination of choice in the context of colorectal neoplasia"[6], and to discourage the use of BE if CTC is available.

In this paper, this technique will be reviewed and the performance and current indications and contraindications to CTC will be discussed.

TECHNIQUE

The technique is easy, standardized[7], and much less labor-intensive and invasive than BE and CS. The process consists of four consecutive steps: bowel cleansing, colon distention, CT protocol, and image analysis.

Bowel cleansing

Similar to CS, in which an optimal examination requires a clean colon, bowel cleansing is critical for CTC. Residual stools may mimic cancer or a polyp or, alternatively, may hide a real colonic lesion; the same is true for fluid residues. Bowel preparation is an evolving area of research since the ultimate goal is to reduce or abolish the use of laxative agents in order to improve patient compliance compared with CS, but not at the expense of diagnostic quality. The ideal colonic preparation is still being debated, but general agreement exists regarding the need for dietary restriction, fecal tagging, and bowel purgation[7]. Dietary restriction (*e.g.*, a low fiber diet) for one to three days before CTC examination is aimed at reducing fecal volume and stool inhomogeneity, thus favoring optimal tagging[8]. Bowel purgation should normally be included in CTC preparation; however, in order to improve patient compliance, aggressive catharsis should be restricted to 24 h or less and a reduced volume of laxative agent should be preferred[9-12]. The choice of the agent reflects local experiences, with no clear preference for any agent.

In order to improve polyp detection and to reduce the number of false-positive examinations, "labelling" or "tagging" of residual stools and fluids is strongly recommended and is considered mandatory unless contraindicated. Fecal tagging consists of oral administration of either water-soluble iodinated contrast medium or, alternatively, a diluted barium sulfate suspension. Because such oral contrast agents are hyperattenuating to X-rays, the tagged residual bowel content appears hyperdense and can be readily distinguished from true colonic lesions. The use of electronic stool subtraction software allows the colon to be cleansed of tagged residues and virtual navigation to be performed[13] (Figure 1). Although robust data are not available in the literature comparing the two tagging agents[14-16], iodinated contrasts offer more homogeneous tagging and the possibility for same-day CS; the risk of allergic reactions, due to iodine absorption through the gastrointestinal tract, is extremely rare, or even anecdotal[17].

A further step to improve patient compliance is the utilization of reduced bowel preparations[18] using only high doses of hyperosmolar contrast agents, without the need for any additional laxative agent[19,20]. This approach, which is associated with better patient compliance and with reduced cathartic effects compared with a conventional colon cleansing for CS, can now be considered routine practice, particularly in screening[5] and in elderly and frail patients[21,22].

Colon distention

The colon is inflated with air or carbon dioxide by using a thin and flexible rectal catheter by a radiologist, resident, technician, or nurse specifically trained in the technique[23]. Although automatic insufflation with carbon dioxide is the method of choice to optimize colonic distention and to maximize patient comfort, a higher cost is a drawback of this technique[24]. No sedation is required. The use of a spasmolytic agent, and in particular hyoscine butylbromide (Buscopan®)[25], may provide better distension, especially of the sigmoid colon in the case of diverticular disease or severely stenosing cancer, although a clear improvement in the accuracy of polyp detection has not been demonstrated[26,27]. The intravenous injection of iodinated contrast medium is reserved for the following situations: in patients with known CRC, to improve staging, and in symptomatic patients based on the clinical indication, and for the need to investigate the extracolonic organs fully[28].

CT protocol

The use of multidetector row CT (MDCT) scanners ($\geq$ 16 rows) is considered an essential prerequisite to achieve high-quality (max collimation $\leq$ 2.5 mm; single breath-hold) and low-dose examinations. The use of dose modulation devices[29], which reduce does exposure by 30%-35% (except in obese patients) is strongly recommended; if available, adaptive statistical iterative reconstruction and model-based iterative reconstructions[30], which reduce dose exposure up to 50%, are preferred.

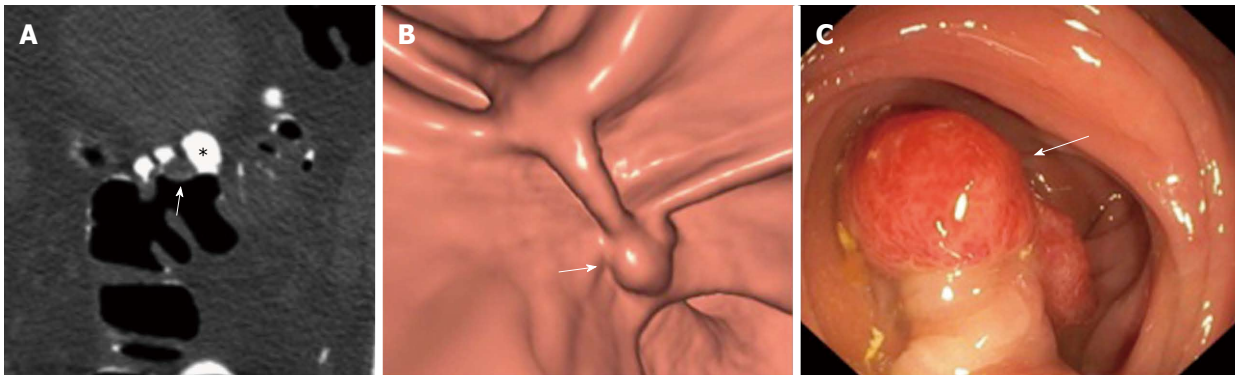

Figure 1 Pedunculated polyp submerged by fluid residues. A: Polyp displaying soft-tissue density (arrow) is partially submerged by tagged fluid (asterisk) on an axial prone computed tomography image; B: On electronically cleansed endoluminal view, a polyp with a pedunculated morphology (arrow) is clearly observed; C: On colonoscopy, a pedunculated polyp is detected before resection.

Table 1 All of the relevant data

Ref.	Year	Design	Polyp > 6 mm		Polyp > 6 mm, < 10 mm		Polyp > 10 mm		Cancer
			Se	Sp	Se	Sp	Se	Sp	Se
Pickhardt *et al*[33]	2011	Meta-analysis							96.1%
de Haan *et al*[4]	2011	Meta-analysis	75.9%	94.6%	68.1%	96.5%	83.3%	98.7%	
Sosna *et al*[43]	2003	Meta-analysis			84%		88%	95%	
Chaparro *et al*[41]	2009	Meta-analysis			63%	90%	83%	92%	
Mulhall *et al*[44]	2005	Meta-analysis			70%	93%	85%	97%	
Halligan *et al*[42]	2005	Meta-analysis	86%	86%			93%	97%	
Rosman *et al*[45]	2007	Meta-analysis			63%		82%		
Sosna *et al*[69]	2008	Meta-analysis			70.7%		82.3%	95.4%	
Plumb *et al*[46]	2014	Meta-analysis	89.7%	74%			92%	95%	95.8%
Atkin *et al*[2]	2013	RCT							96.5%
Halligan *et al*[3]	2013	RCT							93.3%
Stoop *et al*[5]	2012	RCT							
Johnson *et al*[37]	2008	Obs Multic	78%	88%			90%	86%	
Regge *et al*[38]	2009	Obs Multic	85.3%	87.8%			90.8%	84.5%	95.1%
Neri *et al*[7]	2013	Obs Single	95.6%	93.9%			100%	98%	
Graser *et al*[40]	2009	Obs Single	91.3%	93.1%			92%	97.9%	
Pickhardt *et al*[39]	2003	Obs Single	88.7%	79.6%			93.8%	96%	
Mean			86.3%	87.1%	69.8%	93.1%	88.8%	94.3%	95.4%

RCT: Randomized controlled trial.

Image analysis

Image post-processing is performed on dedicated off-line workstations suitable for 3D data management and reconstruction. CTC interpretation should be based on both 2D and 3D images, and the use of either a primary 3D or 2D approach depends on personal preference and availability[31]. Computer-aided detection (CAD) software is useful to reduce perceptual errors during CTC interpretation, if employed in a second-reader paradigm. Particularly, CAD improves sensitivity for small (6-9 mm) polyps, even in expert readers[32]. However, the use of CAD should not preclude adequate reader training, since the interpretation of CAD markings is under the control of the radiologist.

PERFORMANCES

All of the relevant data are provided in Table 1.

Cancer

Recent meta-analyses[4,33] and randomized clinical trials have reported that the diagnostic performance of CTC for the detection of CRC and clinically significant adenomatous polyps (≥ 10 mm) both in symptomatic[2,3] and asymptomatic subjects[5] is similar to CS and is largely superior to BE. In fact, the sensitivity of CTC and CS for CRC were shown to be 96% and 95%, respectively, in a recent meta-analysis[33]. The importance of this study is that it showed that sensitivity is maintained, despite a wide variation in technique, demonstrating potential generalizability and widespread implementation of CTC. In the first randomized trial[2], which compared CTC and CS in symptomatic patients, the overall performances were not statistically significant different for either CRC or large (≥ 10 mm) polyps. Given the relatively low prevalence of CRC, even among symptomatic cohorts, primary CTC may be more suitable than CS for the initial investigation of suspected CRC. In fact, the cancer miss rate of CTC is low. In a study on 3800 patients who were followed-up by using the National Cancer Registry database after CTC[34], seven cancers were missed (five because of tech-

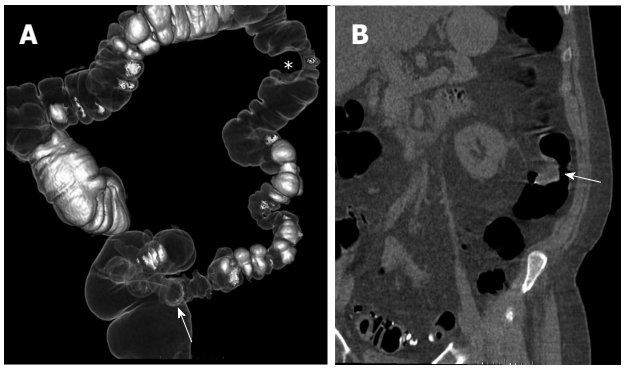

Figure 2 Patient with incomplete colonoscopy due to severe angulation and stricture secondary to diverticular disease of the sigmoid colon. A: On a volume-rendered colon map, a stricture of the sigmoid colon (arrow) and a large filling defect (asterisk) on the medial wall of the descending colon are evident; B: On a coronal image, a large polyp (arrow) of the descending colon is observed.

nical limitations and two because of perceptive errors; systems errors and severe patient co-morbidity contributed to three of the cases), with an overall missed rate of around 5.3%. These data are similar to those collected for CS (miss rate, 5.9%)[35] and were better than those collected for BE (missed rate, 6.7%)[36].

Adenomatous polyps

Several studies have demonstrated the accuracy of CTC in identifying and characterizing colonic polyps (Figure 2). Two randomized clinical trials[2,3,5], two multicenter trials[37,38], two single-center trials[39,40], and eight different meta-analyses[4,33,41-46] came to similar conclusions: CTC sensitivity for clinically significant polyps (larger than 10 mm) is high and is similar to that of CS; the sensitivity for small (6-9 mm) polyps is slightly lower than that of CS; the specificity and negative predictive value, even for small polyps, are good, especially if fecal/fluid tagging techniques are used; and the variability of the results among different series is mostly due to perceptual errors and consequently to reader inexperience[47]. The importance of reader experience was also confirmed by a multicenter study[48] designed to assess the accuracy of CTC in detecting polyps or cancers after a preliminary training and qualifying program for radiologists. The most relevant finding of the study was that radiologist's polyp detection rate during training was the only significant factor in predicting the accuracy of CTC for detecting polyps.

This result leads to the issue of training and the learning curve. Although the debate is on-going, one study[49] attempted to determine how many CTC training datasets had to be evaluated by a novice reader to reach an adequate level of diagnostic confidence, which was defined as a sensitivity of 95% for lesions 10 mm or larger, a sensitivity of 90% for lesions 6 mm or larger, and a per-patient specificity of 80% for lesions 6 mm or larger. This study showed that at least 175 CTC studies with colonoscopic verification are necessary for most trainees, although a sub-group may require additional training because of the inability to reach the predefined threshold levels. However, once adequately trained, radiologists can obtain consistent performance for adenoma and advanced neoplasia detection, as well as other clinically relevant endpoints, in a CTC screening program[50].

Non-polypoid ("flat") lesions

Non-polypoid lesions represent a sub-group of colonic neoplasms, which are classified into the following types: slightly elevated (type 0-Ⅱa), completely flat (type 0-Ⅱb), and depressed (type 0-Ⅱc)[51]. Type 0-Ⅱa lesions are sometimes misclassified as sessile polyps because they are slightly elevated from the mucosal surface. In order to avoid this confusion, the height of a flat lesion should not exceed ½ of its diameter[52]. In CTC, a lesion is defined as flat when the vertical elevation above the surrounding mucosa is less than 3 mm[53] (Figure 3). Another sub-type of non-polypoid tumors is the so-called "carpet" lesion, which is defined as a flat, laterally spreading colorectal mass measuring 3 cm or greater in size[54].

Although the epidemiology is not completely clear, recent data suggest that the prevalences of non-polypoid lesions in Europe[55] and the United States[56] are close to that of Japan[57]. The likelihood of malignancy is directly related to morphology rather than to size: types 0-Ⅱa and 0-Ⅱb have a risk of harboring high-grade dysplasia or cancer similar to polyps, whereas type 0-Ⅱc has a definitely higher likelihood of malignancy[57]. CTC can potentially detect flat and depressed adenomas, which result in focal thickening of the colonic wall, but it is probably not suitable for evaluating the presence of completely flat lesions[58]; however, the latter are exceedingly rare[56,57]. At the time of this paper, data regarding CTC sensitivity for flat lesions are sparse, and the patient series are small for the available studies. The largest studies report sensitivity in the range of 80%-90% for flat adenocarcinomas[59,60], and excellent results were also described for lateral spreading tumors[61].

Extracolonic findings

A possible advocated advantage of CTC is the detection of extracolonic findings (ECF). ECF are common in symptomatic patients as well as in screening patients referred for CTC, with a prevalence ranging between 25% to more than 50%[62]. They increase with age and are not clinically significant in most cases; however, they are reported as important in 10% of patients, requiring further work-up[63]. Important ECF include extracolonic cancers (with the most common being renal and lung cancers and lymphoma), abdominal aortic aneurysms, and adrenal lesions. The work-up for ECF produces additional costs that should be considered when calculating the cost-effectiveness of CTC, particularly for screening. In a mathematic model, the detection of an ECF such as abdominal aortic aneurysm and extracolonic cancers in addition to CRC makes CTC a dominant screening strategy over both CS and CS with one-time ultrasonography[64].

INDICATIONS AND CONTRAINDICATIONS

The availability of robust and evidence-based data in the

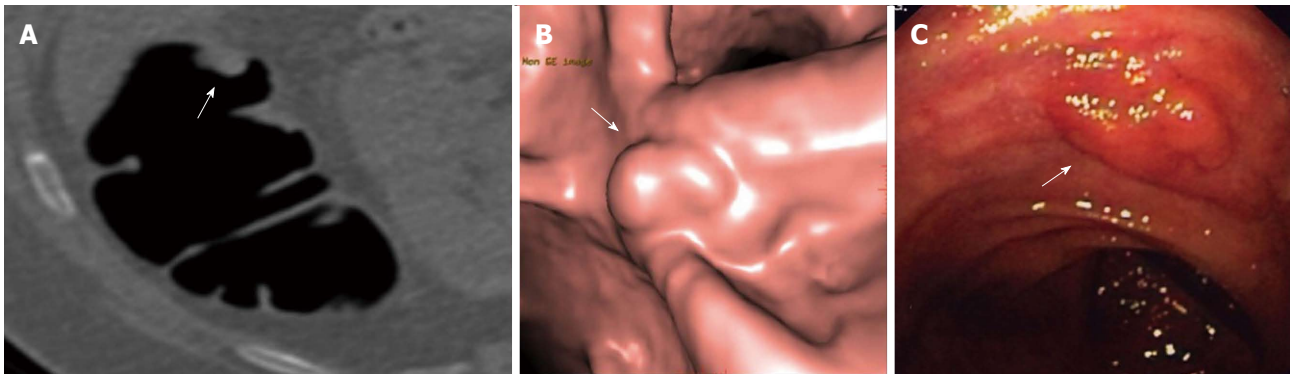

Figure 3 Non-polypoid lesion (type Ⅱ-A). A: Non-polypoid lesion (arrow) is observed on an axial image; B: Lesion (arrow) is confirmed on an endoluminal computed tomographic colonography image; C: Colonoscopy confirming the presence of the non-polypoid lesion (arrow).

literature has increased the indications for CTC. Today, incomplete or failed CS, the evaluation of elderly, frail, and symptomatic patients, and the investigation of diverticular disease are clear clinical situations where CTC can be safely proposed. However, CTC can also be recommended in CRC screening and surveillance despite the lack of robust evidence, if CS is unfeasible. Further, potential contraindications should not be overlooked in order to ensure the appropriate use of CTC.

Absolute indications

Incomplete or failed CS: Incomplete or failed CS is not an uncommon event. The caecal intubation rate, a quality metric recorded by the endoscopists, is extremely variable in daily practice and it can be far from high-quality standards[65].

CS can be incomplete for a variety of reasons other than poor bowel preparation: obstructing masses, neoplastic or inflammatory strictures, redundant colon, patient discomfort, colonic spasm, severe diverticulosis, and adherences from previous surgery. Further, incomplete CS is more common in elderly patients and in women[66]. The experience of the endoscopist is another extremely important variable because up to 10% of CS procedures are considered technically challenging, even for experts[67].

In the case of incomplete/failed CS, examination of the entire colon is recommended in order to avoid missing an advanced lesion[68]. Because the performance of CTC is superior to BE[3,46,69], CTC is the examination of choice[70]. In the case of neoplastic obstruction, CTC can be used for excluding synchronous lesions in the remaining colon and for whole body staging of primary colonic neoplasm, if contrast-enhanced CTC is performed[71,72]. Moreover, CTC can define predictive factors for a potentially difficult CS, such as colonic looping, acute angle flexures, and tortuosity, because it reveals colonic anatomy[73].

Elderly and frail patients: CS, apart from being incomplete or failed, can be unfeasible because of the patient's condition, including advanced age, poor compliance to bowel preparation, or associated severe co-morbidities. CS has an increased risk of perforation and bleeding in elderly patients[74] and in those undergoing anti-coagulant therapy[75], respectively. Because of the progressive aging of the population, this sub-group of patients is likely to increase in the future, with consequently higher frequencies of colonic cancer and diverticular disease[76,77]. CTC has the advantage of being technically feasible, well tolerated, and safe. Only patients with a positive finding will be referred for more invasive and risky examinations because of the high positive and negative predictive values for cancer and large polyps[78,79].

Investigation of diverticular disease: Diverticular disease is the most common colonic disorder in the Western world, with a prevalence of over 60% at 80 years[77]. The clinical diagnosis is challenging because patient symptoms and laboratory findings are unspecific and overlap with other gastroenterological entities (*e.g.*, irritable bowel syndrome) and in young women (< 40 years of age) with gynecological disorders[80]. Thus, imaging tests are necessary for the diagnosis. The choice of either CTC or CS as the first-line imaging examination depends mostly on the patient's age, risk factors, clinical status, and preference, as well as on imaging availability and local expertise[81]. In elderly individuals, especially those who are frail and have potential contraindications to CS and sedation, CTC is preferred because it is minimally invasive. On the other hand, CS should be the first choice in younger patients in whom symptoms might be related to colic inflammatory changes because the diagnosis would be challenging with CTC. The use of BE should be discouraged because of poorer patient compliance[82], longer examination time, higher risk of complications[83,84], and radiation exposure[85].

In patients with established diverticular disease, CTC can provide a balanced view of the disease by incorporating visual analysis with quantitative analysis by using a CTC-based diverticular disease severity score; this score appears to correlate with relevant coexisting lesions and can potentially influence therapeutic decision-making[86].

Symptomatic patients: Gastrointestinal alarm symptoms potentially suggestive of CRC such as abdominal pain or discomfort, rectal bleeding, iron-deficiency anemia, and unintended weight loss are highly non-specific;

further, these symptoms are, unfortunately, common in the general population, particularly in the elderly[87]. The accuracy for identifying patients with underlying structural disease is disappointing, and many of these patients who are referred for CS will ultimately prove to be normal[88]. Elderly patients are often frail and more likely to have an incomplete or difficult CS, with a greater risk of adverse events[65,66] and an increased workload for endoscopy centers. For these reasons, CTC might be used as a triage technique, with only patients with positive findings being referred for CS. Practically, proposing CS as the best indication for symptomatic patients presenting with bleeding and diarrhea and proposing CTC for those with pain or weight loss may be reasonable.

Other indications: New and emerging indications have been explored, with some of them being entered *de facto* in clinical use: CTC for tumor localization before laparoscopic surgery because of the inaccuracy of CS in determining the precise localization and extent of the lesion[89]; investigation of patients with colonic stoma[90]; and assessment of colonic involvement in patients affected by deep pelvic endometriosis[91].

Relative indications

CRC screening: CRC screening is complex, and this is particularly true in Europe, where population-based programs using fecal occult blood tests are already organized. Within the framework of an established screening program, the role of CTC is to replace BE in the case of incomplete CS[92] and to evaluate patients with a positive fecal occult blood test who refuse CS[93].

Despite the current situation, research is committed to exploring the potential use of CTC as a screening modality alternative to the available tests. Before implementing CTC, data on patient adherence to CTC-based screening programs and cost-effectiveness are necessary. The recent results of a Dutch trial[5] showed that the participation rate for the screening program was increased with CTC compared with CS (34% *vs* 22%; $P < 0.0001$). Although these results are extremely interesting, they must be confirmed by other on-going trials[94,95].

The available data on the cost-effectiveness of CTC for screening based on mathematical models are discordant: in the majority of the models, CTC is dominated by either CS or a combination of flexible sigmoidoscopy and fecal occult blood test[96]. However, the costs of CT-screening in the Dutch trial[97] were substantially lower than the cost assumptions used in published cost-effectiveness analyses, indicating the need for re-evaluation of those data.

Apart from population screening, on an individual basis, CTC can be suggested as a CRC screening test provided the individual is adequately informed about the test characteristics, benefits, and possible risks[98].

Surveillance: In patients who have undergone previous surgery for CRC, colonic and extracolonic surveillance are needed because more than 50% of recurrent tumors will present as extracolonic metastatic disease (particularly in the liver parenchyma), and many local recurrences lack an intraluminal colonic component[99]. The current surveillance guidelines include a combination of clinical assessment, serum carcinoembryonic antigen (CEA) testing, CS, and contrast-enhanced CT[100]. CTC, if performed by using a different technical strategy (*i.e.*, during the intravenous administration of iodinated contrast medium), combines the ability of detecting polyps and cancer with an accuracy similar to CS, while simultaneously offering an evaluation of extracolonic findings[101]. However, this approach is presently recommended only if a patient is unable or unwilling to undergo CS because of the lack of robust and evidence-based data.

Patients who have previously undergone endoscopic resection of colonic adenoma are likely to develop a metachronous lesion; therefore, these patients must be included in a surveillance program using CS. The frequency intervals for follow-up remain controversial[102]; these are based on the findings at index CS (size, number, and histology of the removed polyp/s). Unfortunately, despite the official recommendations, patient adherence to follow-up is extremely variable and is generally poor in clinical practice[103]. For those patients unwilling to undergo CS, follow-up CTC can be suggested as an alternative option.

Contraindications

Acute abdominal conditions, like diverticulitis or the acute phase of IBDs, are contraindications to CTC because of the high risk of complications (*i.e.*, perforations)[84].

Further, precautions should be taken when performing CTC after endoscopic resection. A two-week delay is suggested[6], although clear scientific evidence is lacking to confirm this. In fact, a study on patients who underwent CTC within 24 h following CS with either polypectomy or biopsy sampling did not find colonic perforation[27]. On the other hand, endoscopic biopsy is not considered a contraindication and same-day CTC can be safely performed.

CTC should be also avoided as a surveillance test in patients with a long-standing history of ulcerative colitis or Crohn's disease and in those with hereditary non-polypoid colorectal cancer (HNPCC), Lynch syndrome, and APC-associated polyposis conditions. In all of these cases, CS is the preferred diagnostic option at a timing and interval different from screening in average- or higher-than-average risk individuals because of the highly increased risk of developing CRC[104,105].

CONCLUSION

In conclusion, CTC is a mature and robust imaging modality, with an accuracy very close to CS. CTC has completely replaced BE because of its superior performance, higher patient compliance, and lower dose exposure. CTC can be considered the leading modality for colonic imaging in many clinical situations, although CS is still

preferred for several indications. A clear understanding of the exact role of CTC will be beneficial to maximize the benefits and minimize the potential sources of frustration or disappointment for both referring clinicians and patients.

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