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CT colonography: What radiologists need to know☆

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Abstract In 2008, CT colonography was approved by the American Cancer Society as a technique for screening for colorectal cancer. This approval should be considered an important step in the recognition of the technique, which although still relatively new is already changing some diagnostic algorithms. This update about CT colonography reports the quality parameters necessary for a CT colonographic study to be diagnostic and reviews the technical innovations and colonic preparation for the study. We provide a brief review of the signs and close with a discussion of the current indications for and controversies about the technique.

PALABRAS CLAVE
Pólipo;
Colonografía TC;
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TC;
Colon

Colonografía por TC. Lo que el radiólogo debe conocer

Resumen La colonografía por TC fue aceptada por la *American Cancer Society* en el 2008 como técnica de cribado para el cáncer colorrectal. Este hecho debe considerarse un gran paso en el reconocimiento de la técnica, que aun siendo relativamente nueva está cambiando ya algunos algoritmos diagnósticos. En esta actualización sobre colonografía por TC se describen los parámetros de calidad que hacen a una colonografía por TC diagnóstica y se revisan las innovaciones técnicas y de preparación colónica. Se apunta, aunque brevemente, un recordatorio de la semiología, y se discute, para finalizar, el estado actual de sus indicaciones, incidiendo en las controversias actuales.

Introduction

CT colonography, virtual colonoscopy, or simply CTC are different terms used to describe the same technique. Although this technique, which we will call CTC, was developed in 1994,[1] it has undergone a rapid technical development since then, together with the improvement of CT scanners. Its classic definition is straightforward: ''*A CT study of the colonic wall after the insufflation of air via the rectum, intended for the detection of lesions, basically polyps or cancer*''. However, we consider more appropriate the definition with conditionals provided by Pickhardt in one of his reviews: ''*When a properly prepared and distended colon is imaged with CT, clinically relevant polyps can be*

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readily detected with dedicated CTC software''.[2] Based on this description, we will provide a point-by-point analysis of the technique:

Properly distended colon

Adequate distention is critical to analyze the colonic wall. Because uniform and simultaneous segmental distention is difficult to achieve, both supine and prone acquisitions have been routinely obtained since CTC was first implemeted.[3–5] In this way, two complementary series are obtained that allow, in most occasions, the distention required for a full analysis. For elderly patients or difficult-to-position patients, the lateral decubitus position represents an alternative to the prone position.[6]

The insufflation process should be performed carefully, and anesthesia or sedation is not required. With the patient in lateral decubitus, a thin flexible catheter is placed in the ampulla of the rectum through the anal channel. In general, gaseous distention can be achieved with either room air or CO_2. Room air has, logically, a lower cost and it is insufflated manually until the patient feels discomfort. Conversely, CO_2 requires continuous automated insufflation as it is rapidly resorbed through the colonic wall, and this property accounts for improved comfort after the procedure in comparison with room air. Although both procedures are accepted for CTC by the different consensus guidelines, automated CO_2 delivery is the preferred technique.[4,5] Systematic use of spasmolytic agents is controversial and their administration is thus selective and limited to particular cases.[5]

After insufflation and prior to image acquisition, a topogram gives a general indication of distention adequacy (Fig. 1). If the patient feels discomfort early than expected, before continuing with forced insufflation, a topogram will help rule out the presence of severe stenosis with risk of perforation. The risk of perforation ranges between 0.03% and 0.009%.[7,8] The risk using automated CO_2 delivery is practically nonexistent.[9] Signing an informed consent is recommended given the potential, albeit minimal, risk of perforation.

If after the acquisition, some of the segments (more frequently the sigmoid colon) have not been distended properly on both supine and prone scans, a third complementary series in lateral decubitus is obtained since the spasm normally subsides afterwards.[2] The degree of distention should be specified in the report since a segment that is not distended is a segment that is not examined.

Properly prepared colon

At present, there is no general consensus on the best colonic preparation for CTC. Initially, the preparations were similar to those used in optical colonoscopy, i.e. based on cathartic agents. However, even if the patients followed the instructions correctly, many of the colonic segments showed a certain amount of residual fluid or solid material, which complicated CTC examination hiding lesions or producing false positives. In addition to these difficulties, the reading process itself was cumbersome, 3D navigation was difficult and the diagnosis was mainly based on the

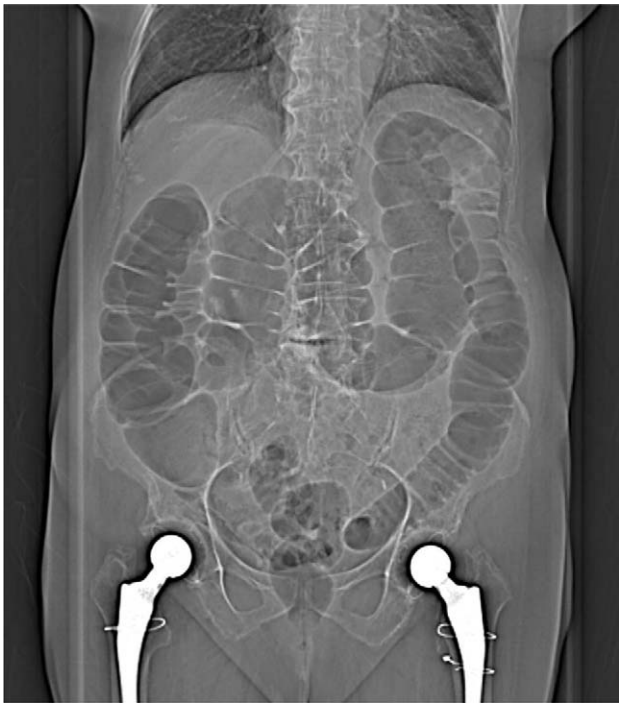

Figure 1 Topogram in prone shows proper colonic distention so that acquisition of CTC images can be initiated.

mobility or lack of mobility of the suspicious findings, which was not very reliable.[10] As a result of these limitations, the concept of fecal tagging or labelling was developed, adapted from MR colonography.[11] The process involves high-intensity fecal tagging detectable by CT using a contrast agent orally administered during the colonic preparation (Fig. 2). Tagging can be achieved using different oral contrast agents, usually iodine, barium or a combination of the two. This has resulted in the emergence of multiple modalities of fecal tagging that vary between countries or even within the same institution. For instance, Pickhardt's group advocates the necessity of reduced cathartic preparations together with fecal tagging that combines low density barium with meglumine and sodium amidotrizoate (Gastrografin®).[12] A multicenter study conducted by the ACRIN used full doses of cathartic agent and high density barium tagging and Gastrografin®.[13] Lefere et al. use barium alone with reduced doses of cathartic agent.[14] New preparations exclude completely the cathartic agents in order to improve CTC tolerance. These preparations involve the administration of several doses of Gastrografin® several days prior to the examination and a low-residue diet.[15–18] In addition to improving tolerance, these regimens prevent electrolyte disturbances caused by some types of cathartics, particularly in elderly patients.[19] The Spanish research group IVIRCO (virtual colonic imaging) advocates this preparation, the most widely used in Spain. Although this approach has yet to be validated by population-based studies, current results are very promising.

Clinically significant polyps and their detection by CTC

Not all types of polyps are targets for CTC screening. The primary target is the advanced adenoma, which is defined

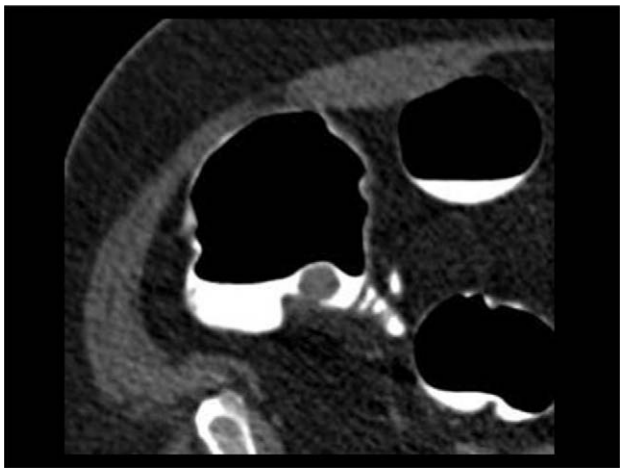

Figure 2 Fecal tagging allows easy identification of polyps based on density differences.

as an adenoma with high risk of progression to cancer in the adenoma–carcinoma sequence.[20] Advanced adenoma is defined as an adenoma $\geq$1 cm in size with either a prominent villous component or high-grade dysplasia.[21] Although 35–50% of the screening population older than 50 years has the risk of having at least one polyp, the term polyp is unspecific and refers to any protruding lesion of the colorectal mucosa, including adenomas, hyperplastic or inflammatory polyps. According to recent studies, the prevalence of advanced adenomas is much lower, ranging from 3.3% to 6.9%.[21] One of the studies published by Pickhardt and his research team, which reviewed all the advanced adenomas detected in a screening population, concluded that 90–95% of these lesions qualified as advanced adenomas on the basis of the size criterion alone; in other words, advanced adenomas were large lesions, $\geq$1 cm in size. Conversely, only a small percentage (4%) of lesions measuring 6–9 mm were advanced adenomas (confirmation based, of course, on histologic features, not on the size).[22] These findings thus support the clear correlation between size of the lesion and risk of degeneration. The sensitivity of CTC in the detection of polyps is clearly dependent on polyp size. It is no longer a matter of controversy that the sensitivity of CTC for the detection of large lesions is similar to that obtained with optical colonoscopy (close to 100%), and that the sensitivity for medium-sized lesions (6–9 mm) is high, even in screening population.[12,13] In view of these findings, we, radiologists specialized in CTC, believe that this technique helps us to detect the vast majority of advanced adenomas, in other words, the clinically significant lesions.[12,13] In the light of these considerations, there appears to be a consensus that lesions $\leq$5 mm could be ignored on CTC, based on the cost–benefit criterion.[4,5] These polyps are a source of false positive on CTC and therefore a source of unnecessary optical colonoscopic examinations and the risk of potential complications, being the risk of a diminutive polyp progressing to cancer minimal. A source of controversy, though, is the fact that while most gastroenterologits share the opinion that the majority of isolated diminutive polyps do not require immediate polypectomy, others disagree.[23] A second controversial issue, also based on previous considerations, is that medium-sized polyps (6–9 mm) could undergo surveillance and not being sent for immediate polypectomy, as supported by some groups including Pickhardt's[20] These polyps will undergo polypectomy if their size grow. The debate behind surveillance or immediate resection of medium-sized polyps actually comes from the lack of knowledge of the natural history of polyps. There are practically no studies on the progression of polyps over time since, so far, any polyp detected was systematically resected. Nonetheless, Hofstad et al. reported that only one of 189 subcentimeter lesions grew beyond 1 cm at one-year endoscopic follow-up. After three years, most lesions remained stable or had shrunk in size.[24] In the Pickhardt et al. series,[25] 128 polyps of 6–9 mm (9.4%) had grown at follow-up and underwent resection; only 4% of them were advanced adenomas and none showed findings of carcinoma.

Acquisition and dedicated software

The use of multidetector CT scanners is recommended for CTC acquisitions. Although the first CTC studies were performed on 4-row detectors obtaining excellent results, the use of more advanced equipments is now recommended, especially due their shorter acquisition times.[12] Slice thickness should be < 3 mm and reconstruction interval $\leq$2 mm.[4] A key aspect is the implementation of protocols that use low radiation doses, since CTC is on many occasions performed in asymptomatic patients. For prone and supine acquisition a tube current <50 mAs and <100 mAs, respectively should be used.[4] With 64-slice scanners and 120 kV, the radiation dose per complete CTC study using 50 mAs was 3.8/4.2 mSv (men/women) for a 1.2 mm collimation, and 4.2/4.5 mSv for 0.6 mm.[26] Neri et al. reported a radiation dose <2.17 mSv using automatic tube current modulation, with values between 20 and 80 mAs, which can be graphically compared to the dose delivered by a double-contrast barium enema (4.12 mSv).[27] Tube current should be increased when using IV contrast in order to achieve the adequate resolution to evaluate the solid abdominal organs. However, IV contrast is seldom used in CTC examinations, for instance to evaluate the extension of a previously diagnosed colorectal carcinoma.

Both 2D and 3D visualization modes can be used for the analysis of CTC images. 2D evaluation uses axial images and their MPR reconstructions; in contrast, 3D visualization offers endoluminal view, which simulates traditional optical colonoscopy (Fig. 3). Thanks to the development of CTC software systems, navigation through the lumen of the colon is rapid and easy; nonetheless, if some segments are not properly distended or residual material persists 3D visualization will be limited. 3D visualization magnifies lesions making their detection easier, but 2D evaluation is always needed for characterization. 2D polyp search is more onerous since it has been associated with eye fatigue, but in return, it allows transmural evaluation. It is therefore important to stress that 2D and 3D are complementary modalities and that the CTC study should be a combination of both.

Nonetheless, several studies have compared primary 2D CTC evaluation with primary 3D evaluation and although some of them have shown that primary 3D is more sensitive for polyp detection than 2D, others show similar results with both methods.[28–30] For this reason, no consensus exits

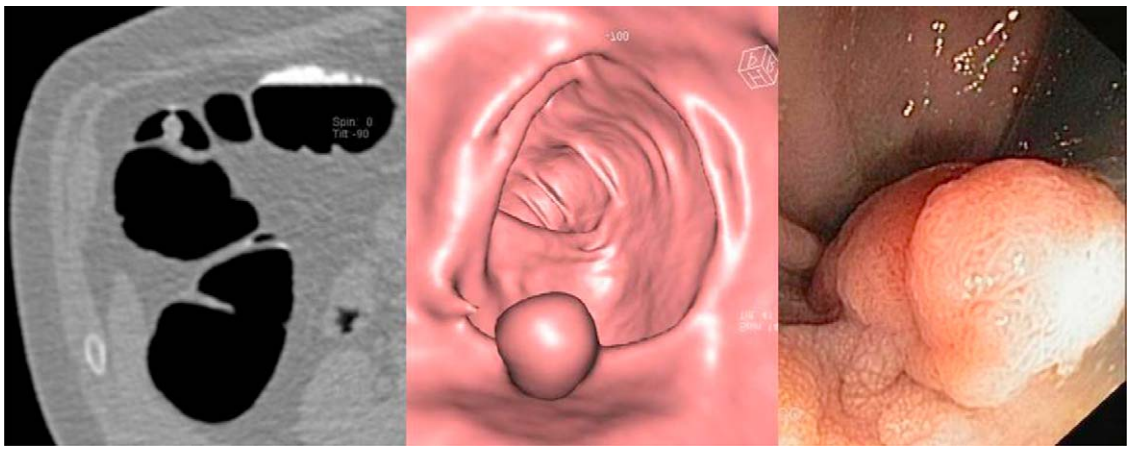

Figure 3 From left to right: 2D, 3D and endoscopic views of the same polypoid lesion.

on the choice of primary analysis method, and both 2D and 3D modalities are considered valid.[4]

Recent advances in CTC software have given rise to a number of new features aimed to facilitate analysis and improve diagnostic accuracy. In this respect, endoluminal data can be analyzed by virtual colon dissection, which virtually dissects and unfolds the colon to obtain a quick view of the entire colonic surface without requiring antegrade or retrograde fly-through.[31] However, this display of the colon similar to a surgical specimen results in considerable distortion of the colon anatomy, particularly at bend level, thus hindering the detection of lesions. In addition, virtual dissection requires training. Translucency rendering is a postprocessing tool that assigns colors to

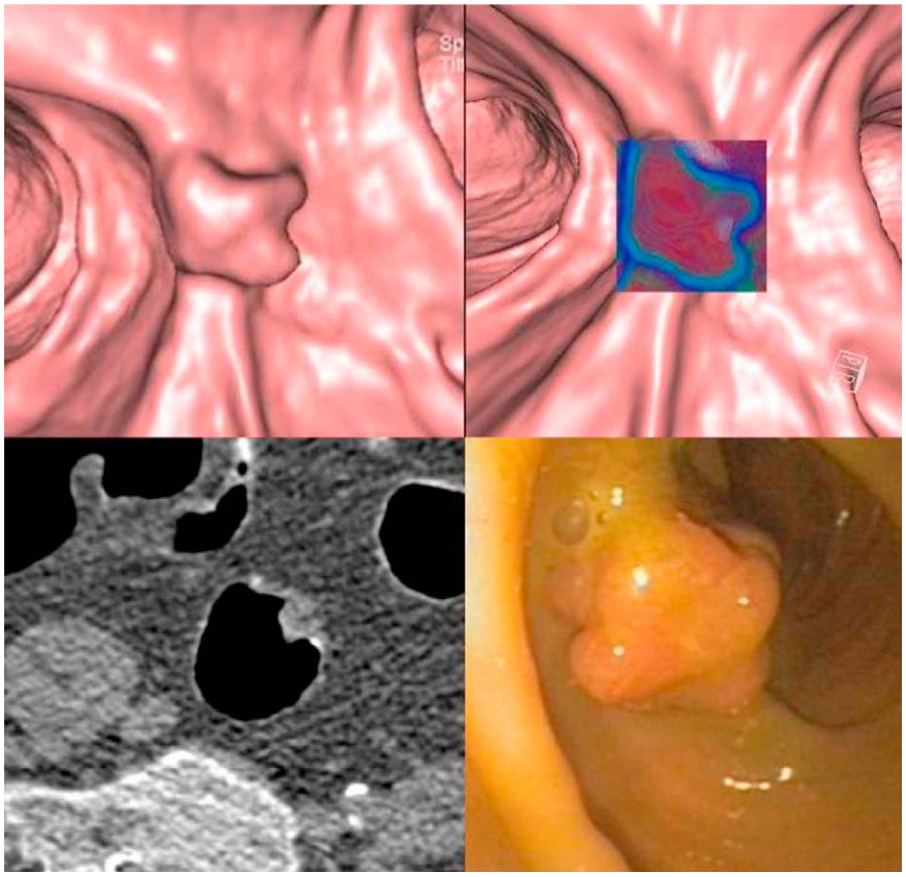

Figure 4 Translucency is a diagnostic tool that helps in the characterization of 3D findings assigning colors to Hounsfield unit values. The figure shows the use of translucency for imaging a polypoid lesion in red (in our software, red color is linked to soft-tissue density); therefore, this lesion is a true polyp. The bottom row shows the 2D and endoscopic visualization.

the mucosa according to Hounsfield unit values, and allows differentiation between fecal matter and true polyps[32] (Fig. 4). Electronic cleansing of stools removes tagged stools to expedite examination of the colonic mucosa, but this digital subtraction can also remove polyps. Other programs assign a color to the residual stool, instead of suppressing them, to make them easily visible on 3D views (Fig. 5). Many current studies focus on CAD or computer-aid detection. Some studies in high-risk patients have reported a 80–100% sensitivity of CAD in the detection of lesions $\geq$1 cm in size, with a false-positive rate of 1–8 per patient.[33,34] It should be noted that this is a detection system, not a characterization system, and it is common for CAD software to detect potential lesions that are in fact false positives. In addition, CAD systems have limited success in the detection of flat lesions. For these reasons, most experts recommend these systems as second reader. A study showed that CAD increased the sensitivity of CTC for the reader by 15% for polyps $\geq$6 mm, although at the expense of a 14% decrease in specificity.[35]

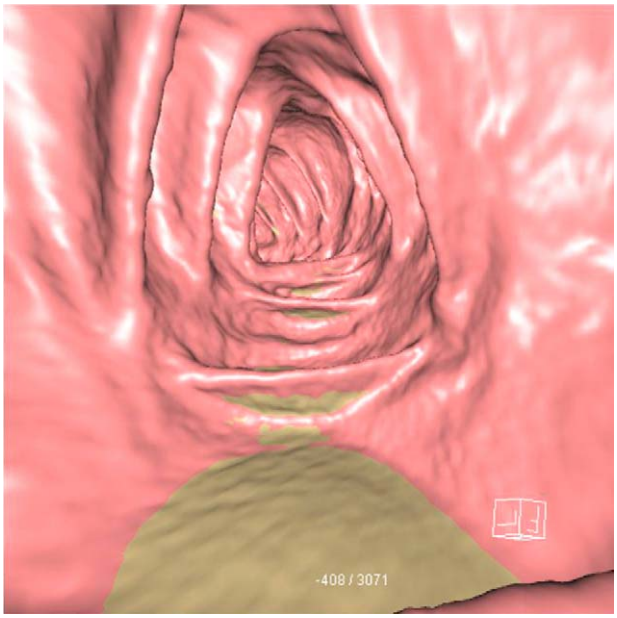

Figure 5 Some computer programs allow quick 3D visualization of residual fecal matter by assigning a color (green in the image depicted), facilitating the reading.

CTC semiology

Although the different guidelines for CTC recommend, but do not require, the use of fecal tagging, in our opinion, any CTC examination should always include fecal tagging.[4,5] With the use of tagging, the semiology has become much simpler. Years ago, the main diagnostic problem was the presence of residual fecal material and the differentiation from polyps was based on its mobility when moving the patient from one position to another. Interpretation of these changes was challenging since some colonic segments already change direction when the patient moves from the supine to the prone position.[10] Proper stool tagging allows for the labelling of the majority of the residual stool, allowing their quick identification and thus without representing a diagnostic problem. However, in cases of untagged stools or suboptimal tagging, the presence of stools may be confirmed by their heterogeneous density and the presence of internal gas bubbles. Conversely, a true polyp shows homogeneous soft-tissue density and no internal gas[36–41] (Fig. 6). Polyps usually appear as enhancing lesions on images obtained after contrast agent administration. No CTC findings allow us to distinguish adenomas from non-neoplastic polypoid lesions such as hyperplastic or inflammatory polyps, making the histological study necessary in all instances (Fig. 7). Based on morphological criteria, polyps are classified as pedunculated, sessile or flat (Fig. 8). Some types of polyps can be further characterized, such as the large villous adenomas in which the villi are recognizable and which sometimes contain trapped tagging material or gas, complicating the diagnosis (Fig. 9). Carpet lesions are usually found in the right colon involving a large surface area and showing flat morphology.[41] Lipomas are submucosal lesions that are easy to characterize thanks to their fat density.

Colorectal carcinoma also has a varying appearance.[42] The classic ''apple core'' appearance that determines stenosis is common in symptomatic patients. Small-sized

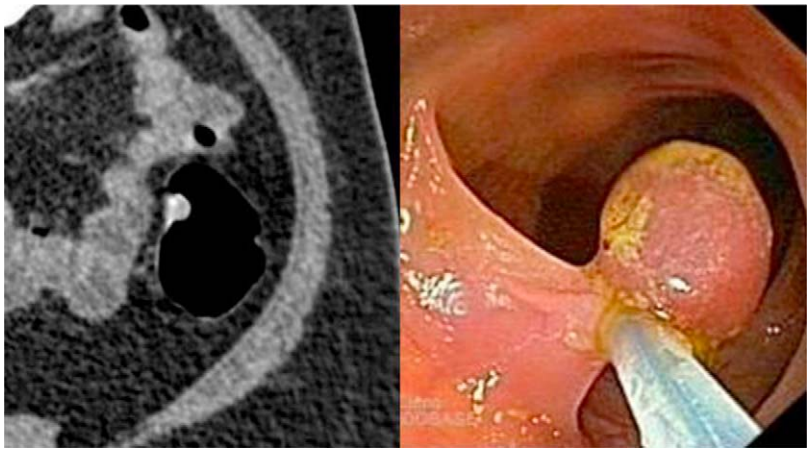

Figure 6 Polyps show soft-tissue density in the 2D image, usually appear as enhancing lesions after contrast agent administration, and may exhibit minute amount of tagging material adhered to their surface.

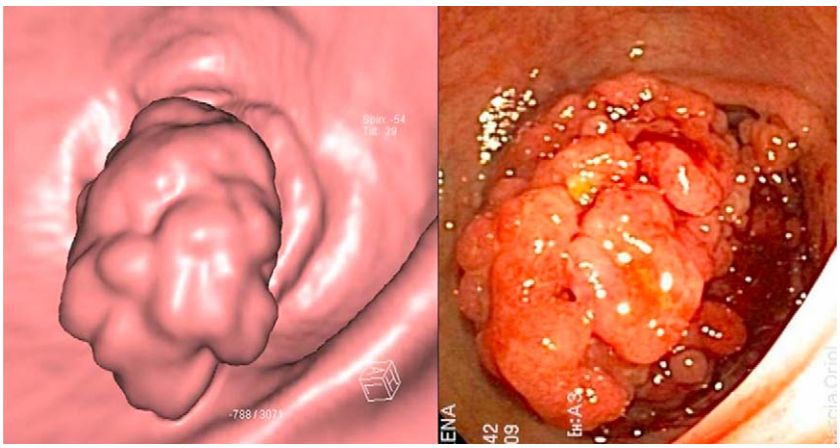

Figure 7 The histological study is required in all cases for characterization of the lesion. The biopsy of the large polyp depicted here revealed an inflammatory nature.

carcinomas, which generally are not yet concentric and may appear only as a focal thickening in the circumference of a haustrum, or as sessile or flat lesions, are the most difficult to detect (Fig. 10). Carcinomas in asymptomatic patients or the synchronous and metachronous lesions in patients who have already (or previously) been diagnosed with cancer usually show these more subtle morphologies.

Images that can be misinterpreted and can mimic polyps include untagged stool, partially distended haustra or focally thickened folds.

Regarding polyp size measurement, all consensus guidelines recommend to measure the maximum polyp diameter.[4,5] In pedunculated polyps, only the head and not the pedicle should be measured.[43] Some controversy exits regarding whether 2D reading is better than 3D, but 3D measurements seem to be closer to optical colonoscopy measurements.[43] A window setting of −500 UH is best for 2D polyp measurement. Although automated measurements seem to eliminate intra- and interobserver variabilities, they have not been sufficiently validated and they cannot as yet replace manual measurements.

CTC findings have been standardized in a classification known as C-RADS in order to establish a protocol on how to describe these findings in the reports (Table 1).[44]

Once CTC has been broadly defined, following we describe its current indications:

Indications of CTC

Incomplete colonoscopy

One of the unanimously accepted indications of CTC is to complete a colonic work-up after an incomplete colonoscopy. Some 10% of colonoscopies cannot be completed for different causes: neoplastic stenosis secondary to diverticulosis, adhesions, loops or redundant colon.[45–47] A study revealed that 4.3% of neoplasms were missed by incomplete colonoscopy and were found in additional imaging studies.[47] Moreover, the study of the proximal colon is particularly important in case of neoplastic stenosis, as the percentage of synchronous cancer is high (4–5%),[48] and its presence can frequently change the surgical approach.

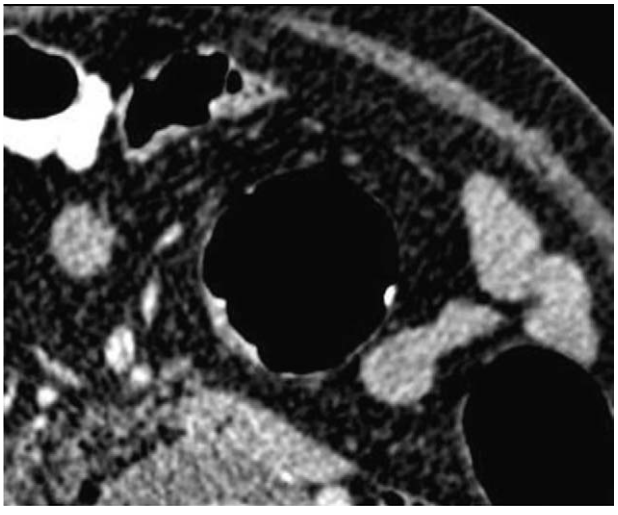

Figure 8 Flat polypoid lesion. According to the C-RADS classification, flat lesions are those lesions that measure 3 mm or less in height.

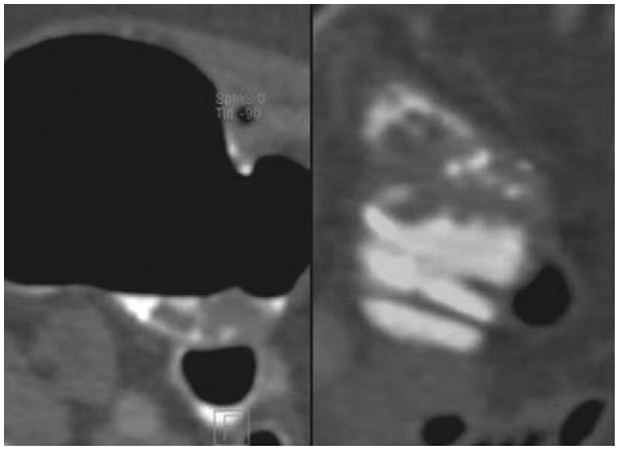

Figure 9 Villous adenoma in 2D visualization. Polyp's villi are observed.

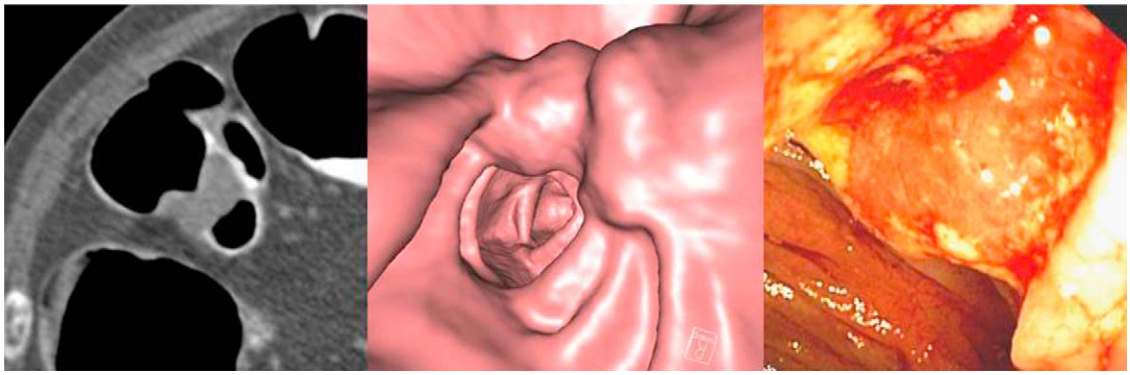

Figure 10 CTC 2D, 3D and endoscopic view of a semicircular adenocarcinoma.

CTC is proven to be clearly superior to barium enema examination, which has been used for this indication until recently.[49,50] Several studies have demonstrated the accuracy of CTC to complete the colonic evaluation after an incomplete optical colonoscopy.[49,51–53] Neri et al. found a sensitivity of 100% for CTC in the detection of colorectal cancer after an incomplete colonoscopy, and a sensitivity of 86% for polyps >6 mm. The study by McArthur et al. reported detection rates of 100% for synchronous cancer and of 83.3% for lesions $\geq$1 cm using CTC.[54] We should remember that in the case of obstructing tumors, in addition to information of the entire colon, CTC can also provide cancer staging information. Moreover, it has been reported that CTC determines the segmental location of the cancer, required for a proper surgical planning, more accurately than endoscopy.

In the light of these excellent results, the implementation of protocols of collaboration between endoscopists and radiologists aimed to complete unsuccessful optical colonoscopy examinations is highly recommended. CTC and optical colonoscopy may be performed on the same day avoiding the need for additional colonic preparation, although this means compromising the use of fecal tagging, whose relevance has already been discussed. For this reason, some authors recommend to postpone the examination, particularly when non-cathartic preparations have been used, which represents less discomfort for the second preparation.[55]

The recommended approach after the finding of a clinically significant lesion at CTC after an incomplete colonoscopy is repeating the optical colonoscopy. On many occasions, the colonoscopic study can be completed in the second optical colonoscopy and be directly aimed to the CTC finding.

Contraindications or refusal to undergo optical colonoscopy

CTC is indicated in patients with contraindications to optical colonoscopy; however, these contraindications are really quite limited (anticoagulation, risk of complications from sedation, history of incomplete colonoscopy). CTC is also the alternative for patients who refuse conventional colonoscopy.

Post-surgical follow-up of colorectal cancer

CTC is a useful option for the surveillance of patients with resected colorectal cancer. A single examination with intravenous contrast administration allows full endoluminal evaluation of the colon to rule out metachronous recurrences and exploration of the abdomen to rule out extraluminal recurrences and distant metastases.[56–60] Several months should elapse between the colonic resection and the CTC follow-up. CTC may be successfully performed in patients with a colostomy but the catheter should be inserted carefully, and the retention balloon should be inflated only after the catheter has passed the stoma and it should be filled to half capacity.[58]

CTC has, nonetheless, some limitations for endoluminal evaluation. Suboptimal distention can occur when air passes to the small intestine in patients with right hemicolectomy.[56,58] Moreover, the evaluation of the anastomosis can be difficult due to the presence of inflammatory polyps that mimic neoplastic recurrences.[56–58] Nonetheless, these granulomatous lesions are indistinguishable at optical colonoscopy from a recurrent carcinoma and thus biopsy is required for confirmation.[58]

The guidelines of the American Cancer Society and US Multisociety Task Force do not recommend CTC in the surveillance of patients with resected colorectal cancer and address only the use of endoscopy.[61] However, the threefold benefit of contrast enhanced CTC described here could make this technique to be accepted for surveillance in the future.

CTC in asymptomatic patients

Optical colonoscopy is the examination of choice in patients with symptoms of colorrectal cancer, but recent studies have questioned its adequacy in symptomatic elderly patients.[17,62,63] In this group of patients, the primary goal is to rule out colorectal cancer and CTC shows, in this respect, a diagnostic accuracy close to 100%, being the detection of small- or medium-sized polyps a secondary goal. Moreover, symptoms of colorectal cancer are usually unspecific or may be secondary to other conditions including non-colonic cancers, thus the CTC study of the entire abdominal cavity can be very useful. Elderly patients are also more prone

Table 1 Classification of CTC findings and management recommendations drawn up by the *Working Group on Virtual Colonoscopy* and known as C-RADS.

C0	Inadequate study/Awaiting prior CTC comparisons: Inadequate preparation: cannot exclude lesions ≥1 cm due to the presence of residual matter Inadequate insuflation: one or more segments collapsed on both series of images Awaiting prior studies for comparison
C1	*Normal colon or benign lesions* Recommended: continue routine screening (every 5–10 years): No visible abnormalities of the colon No polyps ≥6 mm Lipoma or inverted diverticulum Non-neoplastic lesions (e.g. diverticula)
C2	*Intermediate-sized polyps or indeterminate findings* Recommended: surveillance (can be postpone to 3 years but subject to individual circumstances) or colonoscopy: Medium-sized polyps 6–9 mm, <3 in number Indeterminate findings cannot exclude polyps ≥6 mm in technically adequate studies
C3	*Polyp, possibly advanced adenoma* Recommended: colonoscopy: Polyps ≥10 mm ≥3 polyps, each 6–9 mm in size
C4	*Colonic mass, likely malignant* Recommended: surgical consultation: Lesion compromises colonic lumen or shows extracolonic invasion

to colonoscopic complications. If in addition to this a non-cathartic preparation is used for CTC, all the more reason to consider the use of this technique.[17,62]

Characterization of lesions detected on optical colonoscopy

Sometimes CTC helps in the characterization of lesions detected on optical colonoscopy. For instance, some submucosal lesions, such as lipomas, can be easily detected at colonoscopy because of their fat density.

CTC for colorectal screening

Colorectal screening is the most controversial indication of CTC and the focus of most published studies. Preventive measures can be adopted against colorectal cancer, like resecting adenomatous polyps that are, in most cases, their precursors.

In 2008, CTC was approved by the American Cancer Society (ACS) as one of the potential techniques for colorectal screening.[64] The American College of Radiology (ACR) and US Multisociety Task Force also participated in the drafting of a joint guideline. In this document, screening tests are grouped into those that primarily detect cancer (fecal occult blood test) and those that can detect polyps and cancer (colonoscopy, sigmoidoscopy, double-contrast barium enema and CTC). CTC acceptance was predictable given the excellent results in screening populations obtained by Pickhardt's working group and the ACR.[12,13] The ACS considers that the accuracy of CTC in the detection of cancer and polyps is similar to that of optical colonoscopy. The ACS recommends CTC screening every 5 years, unlike colonoscopy that is recommended every 10 years, basically because CTC data on interval cancers—those cancers that develop in the interval between two CTC examinations—are not yet available. However, this acceptance of the technique is not shared by all the medical societies that take part in the diagnosis of colorectal cancer. In this respect, in the list of preferences of the American College of Gastroenterology guideline, colonoscopy remains the preferred screening strategy and CTC is considered only an alternative technique.[65] In the U.S. Preventive Services Task Force guideline, CTC is not even recommended arguing that its risks and benefits are not yet known.[66] In Spain, the *Guía de Práctica Clínica de Prevención del Cáncer Colorrectal* (Clinical Practice Guideline for the Prevention of Colorectal Cancer) reports that CTC shows good results in the detection of polyps ≥6 mm, but argues that CTC should not be used in colorectal screening until there is more research on their benefits, costs and acceptability.[67] In other words, there is no common consensus. Among the causes of this disparity are hot topics like the fact that CTC is not intended for the detection of polyps <5 mm and the clinical management of polyps of 6–9 mm in size that allows their surveillance. Other arguments against CTC are the low sensitivity in the detection of flat lesions (even though a definition of flat lesion for all the techniques should be established in the first place) and the lack of knowledge of the harms associated with radiation. These are all complex issues that need to be addressed by the different groups of experts in order to reach consensus. We think that we have come a long way regarding global acceptance of CTC as screening technique. Most studies now focus in the creation of models that simulate if the implementation of the technique would

be feasible, in terms of resources and infrastructure both technological and of availability of trained professionals. The greatest effort should center on the creation of a joint screening program that would include all the areas involved in the diagnosis of colorectal cancer, combining all the validated techniques to find the most effective, sustainable and with the highest population adherence algorithm.

Conclusion

CTC has high sensitivity in the detection of colonic lesions when the colon is properly prepared and distended and when the reader has the proper training and software. Although already established as the technique of choice after incomplete colonoscopy, its role in the colorectal cancer screening algorithm, together with the rest of validated techniques, has yet to reach consensus.

Authorship

Responsible for the integrity of the study: MP.
Conception of the study: MP.
Design: MP.
Acquisition of data: MP.
Analysis and interpretation of data: not applicable.
Statistical analysis: not applicable.
Bibliographical research: MP.
Drafting of the paper: MP.
Critical review with intellectually relevant contributions: MP, AD, JRAC.
Approval of the final version: MP, AN, JRAC.

Conflict of interest

The authors declare no conflict of interest.

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