MDCT Colonography

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Colorectal Cancer

Colorectal cancer is one of the leading causes of cancer-related mortality in Western countries. In the European Union in 2002, 142,505 individuals died of this disease and in the USA 59,345 individuals [1]. Symptoms of colorectal cancer include hematochezia, changed bowel habits, and a palpable mass. The symptoms often occur late, with poorer outcome than in earlier stages of disease. Most cases are sporadic, but an increased incidence is found in certain conditions, such as familiar adenomatous polyposis and hereditary non-polyposis colorectal cancer (HNPCC). Colorectal cancer is in the large majority of cases an adenocarcinoma and most often presents as a mass or an obstructing apple-core-shaped lesion.

Colorectal cancers are thought to develop from adenomas, through the so-called adenoma-carcinoma sequence. Despite improvements in the treatment of colorectal cancer, there has been almost no decrease in mortality. An important reason for this is the presence of extensive disease at the time of diagnosis. Prevention and early detection of colorectal cancer and of its precursors (adenomatous polyps) by screening are possible and currently offer the only solution to substantially reduce the incidence and mortality of this disease [2].

The prevalence of malignancy in an adenoma is dependent upon polyp size, with a low chance of malignancy in polyps < 10 mm and an increasing risk with increasing size. Adenomas often have a sessile or pedunculated morphology, but some lesions are flat with only a limited elevation or depression with respect to the surrounding colonic mucosa or, rarely, they are in-plane with the surrounding colonic mucosa.

Screening

The development of benign adenoma to a invasive carcinoma is thought to occur over a period of > 10 years. This provides a considerable window of opportunity for the detection of the non-malignant precursor of colorectal cancer, adenoma. The detection and removal (endoscopic polypectomy) of adenomas prevent colorectal cancer. Earlier detection of colorectal cancer is associated with a better prognosis. The presence of a benign precursor, the considerable time window for the development of colorectal cancer, and the available therapeutic options (e.g., polypectomy) have led to the introduction of screening for colorectal cancer.

In patients with increased risk of colorectal cancer, screening (surveillance) will often require colonoscopy at regular intervals, since many of these patients will be found to have relevant lesions. In individuals without increased risk, other screening methods should be considered because of the burden and costs related to colonoscopy. Currently, screening for colorectal cancer is performed in several countries and is being considered in other countries. Other screening techniques are available, including the fecal occult-blood test, sigmoidoscopy, barium enema, and colonoscopy.

Screening Methods

The fecal occult-blood test (FOBT) guaiac is the most extensively employed colorectal cancer screening technique. This test, which requires multiple stool samples after dietary measures have been fol-

(e-ISBN 978-88-470-0802-1 Springer-Verlag Milan Berlin Heidelberg New York). Published online at www.mdct.net

lowed, has a sensitivity for colorectal cancer of approximately 40% and for adenomas of 10–20%; its specificity is 97%. Several large (randomized) trials have demonstrated that biennial guaiac FOBT decreases colorectal-cancer-related mortality by 14% when performed over 10 years [3]. A newer, immunochemistry-based FOBT is simpler to use and shows better sensitivity than guaiac FOBT for colorectal cancer (65–80%) and adenomas (27%), but somewhat lower specificity (95%) [4]. This method is expected to lead to a further decrease in colorectal-cancer-related mortality, but this remains to be demonstrated. Although FOBT has been extensively studied and considered to offer a cost-effective screening method, its poor sensitivity is a major limitation. This has led to the evaluation of other potential screening methods.

Sigmoidoscopy is a feasible technique, with better detection of colorectal cancer and adenomas than FOBT [5]. In a study of 40,674 participants, distal adenomas were detected in 12.1% and distal cancer in 0.3% [6]. Individuals with advanced adenomas in the distal colon (5%) were referred for colonoscopy, which detected proximal adenomas in 18.8% of those referred and proximal cancer in 0.4%. The advantages of sigmoidoscopy over FOBT are its direct inspection of the distal colon and the possibility of biopsies. Its disadvantages are the limited bowel preparation, the need for a hospital visit, and the lack of information concerning the proximal colon. The latter is a substantial limitation which may lead to up to one-third of the cases of advanced neoplasias being missed as compared to detection by colonoscopy [7]. The results on the effect of sigmoidoscopy-based screening on colorectal-cancer-related mortality are awaited.

Colonoscopy is the optimal screening method with respect to the detection of relevant lesions (colorectal cancer, adenomas) and subsequent biopsies. The disadvantages are the burden of bowel preparation and examination, the (limited) chance of complications, and the cost. A recent study in 50,148 volunteers demonstrated that colonoscopy is a safe screening technique with good acceptance [8]. In this cohort, the complication rate was 0.1% (0.01% perforations) and there was no mortality. A substantial limitation of colonoscopy is its acceptance in invitational screening programs.

Computed tomography (CT) colonography has been studied as an alternative, non-invasive, full, colon screening method. The present body of knowledge and the pros and cons of CT colonography are discussed below.

CT Colonography

In CT colonography, a CT scan of the air- or carbon-dioxide-distended large bowel is obtained after bowel preparation (Fig. 1). Initial reports describing the procedure date from the 1990s, with a large number of papers on technical improvements and refinements during the last 10 years.

Bowel Preparation

CT colonography requires bowel preparation since stool in the bowel can mimic or obscure colorectal cancer or polyps. Initially, CT colonography examinations were performed after extensive bowel

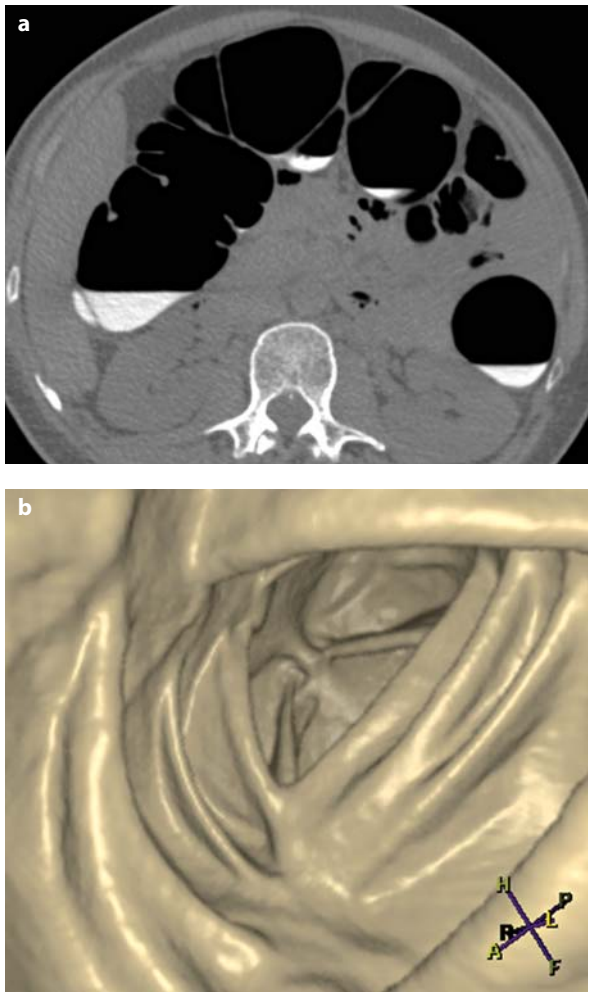

Fig. 1 a, b. CT colonography after extensive bowel preparation and fluid tagging. The transverse colon is well distended at 2D (**a**) and 3D (**b**) (virtual colonoscopy) evaluation. No abnormal finding is seen

preparation, the same as in colonoscopy. In this type of bowel preparation, the colon is cleansed, although fluid or fecal residue often remains. The amount of fluid/residue is influenced by the cathartic regimen used and by patient-individual factors. As polyps beneath the fluid level will not be detected because there are usually no differences in attenuation between lesions of the bowel wall and fluid, the use of fluid tagging has been introduced. This concerns the addition of an iodine or barium contrast agent to the bowel-preparation regimen. Tagging facilitates the identification of cancer or polyps covered by fluid or stool, since it increases the CT value of both. As the beneficial effect is limited, intravenous contrast medium is generally not administered for polyp detection, especially as tagging has become routine. In symptomatic individuals with a suspicion of colorectal cancer, intravenous contrast medium is often used to detect possible metastatic disease, thus allowing a one-shop evaluation of both colon cancer and potential extracolonic spread.

The disadvantage of extensive bowel preparation is that this is burdensome. The extensive bowel preparation needed for CT colonography is considered more burdensome than that for colonoscopy examination [9]. Therefore, alternative approaches have been researched and have led to the combination of limited bowel-preparation schemes and an oral tagging agent. The optimal limited bowel-preparation scheme has yet to be determined, but, in general, it includes combining a low-fiber diet with an iodine and/or barium contrast agent, while stool softeners are administered to increase the homogeneity of the tagged stool. This approach leads to improved acceptance, while the sensitivity of CT colonography does not seem to be negatively influenced [10, 11].

Distension

Bowel distension is mandatory, as a collapsed bowel may mimic cancer, and the detection of colorectal cancer or polyps is impossible in collapsed or poorly distended bowel. Room air can be used, but carbon dioxide is preferable since it leads to better distension and less discomfort (better absorption than room air) [12]. Distension can be obtained by manual rectal insufflation, but the use of an automatic insufflator is preferred. The advantages of the latter are pressure-controlled administration of carbon dioxide and constant intraluminal pressure. This prevents both overinsufflation and gradual collapse of the bowel.

For insufflation, a small flexible catheter suffices. Balloon-tipped rigid enema tubes should not be used because of an increased risk of perforation. In specific situations, such as patients with incontinence for insufflated air or carbon dioxide, a balloon-tipped enema tube can be used when adequate precautions are taken [13].

The use of bowel relaxants is advised. In Europe, butyl scopolamine (Buscopan, Boehringer, Ingelheim, Germany) is used, and glucagon when butyl scopolamine is contraindicated. Butyl scopolamine is not approved as a bowel relaxant in the USA.

Besides insufflation and bowel relaxants, patient position is an important issue. With the patient in the supine position, some bowel segments will be collapsed or insufficiently distended (e.g., rectosigmoid), while distension will be optimal with the patient in the prone position. The combination of supine and prone positioning results in optimized visualization of the large bowel.

Scan Technique and Radiation Exposure

CT- colonography is performed on a multi-detector CT scanner. A minimum of four simultaneous acquired slices is required to permit examination during a single breath-hold and with an acceptable spatial resolution (2.5-mm slice thickness). The increasing availability of 16-, 40-, or 64-slice CT scanners should be taken advantage of. A slice thickness of approximately 1 mm is now routine. Sub-millimeter collimation may not be very beneficial for the detection of polyps with relevant sizes (≥ 6 mm), but may be valuable for other reasons. The truly isotropic resolution is advantageous for reconstructions and for computer-assisted detection because of the inherent 3D nature of the depicted volume of interest. Thereby, flat lesions might be more conspicuous with thin collimation, although this remains to be demonstrated. The disadvantage of a thinner collimation is an increase in noise when other parameters are not adjusted. However, this can be simply counteracted by viewing multi-planar reconstruction (MPR) images with a slightly increased thickness.

Tube voltage is often set to 120 kV, although adjustments for CT colonography may be necessary. This is due to the fact that at lower tube voltage the contrast between tagged bowel content and bowel wall (and thus polyps submerged by bowel content) is increased. The magnitude of this effect will also depend on the size of the patient and may thus allow a substantial reduction of the radiation dose. Most CT scanners nowadays have a lowest setting

of 80 kV, which compared with the tube voltage of 120 kV that is customarily used, results in a three- to four-fold dose reduction [14]. Nonetheless, more research is needed to fully evaluate the optimal tube-voltage setting.

Tube current has been gradually adjusted. Initial scan protocols were based on abdominal CT protocols in which the tube current was chosen to achieve optimized visualization of the enhanced parenchymal organs. For CT colonography, the contrast difference between bowel surface and bowel content is crucial. This is either an air bowel-wall interface or bowel-content bowel-wall interface. In both cases, a lower tube current suffices. Present protocols often use settings of approximately 50 mAs at 120 kV [15]. Reduction seems to be possible to approximately 10 mAs, which for a number of CT scanners is currently the lowest mAs setting possible. Experimental studies have demonstrated the feasibility of CT colonography with even much lower radiation exposure. With a simulated ultra-low dose, CT colonography detection of larger polyps (≥ 10 mm) was unimpaired at settings of 0.4–1.6 mAs, corresponding to effective doses of 0.05–0.2 mSv for two positions [16]. These settings were an order of magnitude lower than what can be realized with present-day scanners. Bowel-preparation regimens with tagging led to a decrease in contrast between bowel content and bowel wall (lesions). Tube-current-reduction study results in untagged CT- colonography examinations or phantoms, cannot be unrestrictedly applied to tagged CT-colonography examinations. However, even in a situation of limited bowel preparation, not all polyps will be covered by the tagging material, and a polyp covered by fecal material when the patient is in the supine position may be uncovered when he or she is placed in the prone position.

In CT colonography examinations with intravenous contrast medium (patients with colorectal cancer), tube current will be used at standard settings in one position. In this situation, the most practical approach is first a prone unenhanced scan with low tube-current settings followed by a supine scan with intravenous contrast medium at standard abdominal settings.

Evaluation Technique

A combination of 2D, including MPR, and 3D readings is used for CT colonography (Fig. 1). The 2D evaluation is primarily performed at a standard colon window (e.g., width 1500, level –150) for the detection of lesions. However, abdominal window settings are used for evaluations that seek to discriminate between a stool and a polyp (Fig. 2). There is no consensus as to whether a primary 2D reading method (3D only used for problem solving) or primary 3D reading method (2D only used for problem solving) should be used, but it is clear that a combination of the two is mandatory [17]. A more intuitive presentation of the colonic surface facilitating evaluation of complex folds is obtained with 3D, whereas 2D yields information on density and homogeneity (differentiation between stool and polyp). In recent years, several 3D display techniques have become available, including enhanced 3D techniques with improved surface visualization. These resolve the problem of the colon surface being obscured by haustral folds [18, 19].

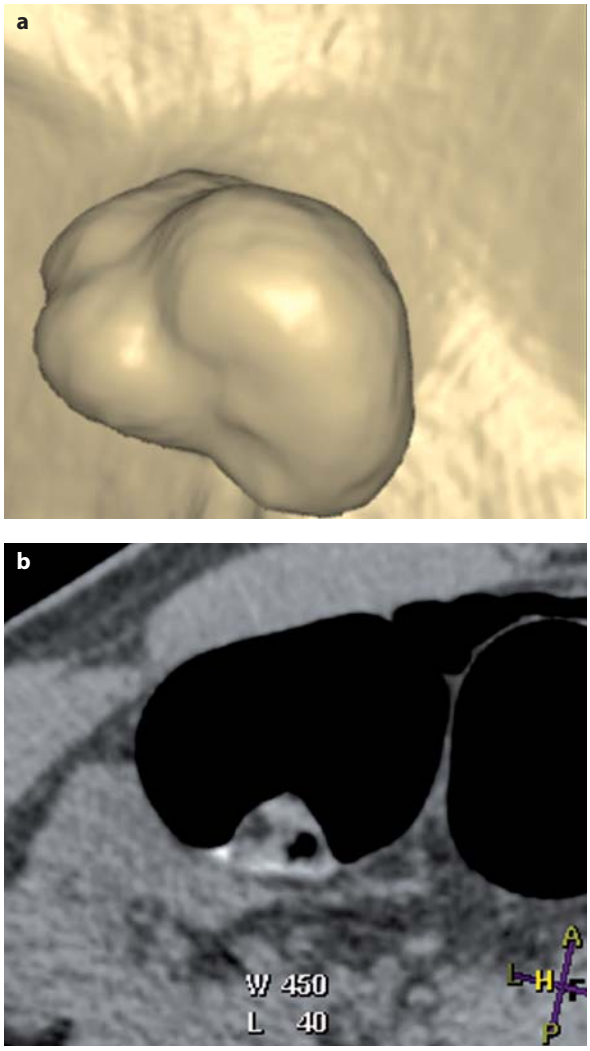

Fig. 2 a, b. At CT colonography with fluid tagging, a polypoid lesion is visible in 3D. The lesion is heterogeneous at 2D evaluation and concerns untagged fecal residue

When limited bowel preparation is used in combination with fecal tagging and the images are evaluated by 3D reading, the tagged substances must be removed from the image beforehand; otherwise, polyps that are covered by fluid or stool remain invisible while stool might be read as a polyp or cancer. The removal of tagged material is done by a procedure usually known as electronic cleansing [20, 21].

Imaging Features

Colorectal cancer often presents as a bulky or obstructing mass or as a polypoid lesion (Fig. 3). Adenomas commonly present as sessile lesions (Figg. 4-6), but can present as pedunculated polyps. A challenge for CT colonography is a colorectal cancer or adenoma presenting as a flat lesion (Fig. 7), which can be slightly elevated or, less frequently, depressed or in-plane. Special attention to subtle changes in wall thickness can lead to the correct diagnosis. Some authors have demonstrated that the detection of flat lesions might be in the range of the sensitivity for the detection of sessile lesions, while others reported decreased sensitivity [22, 23]. Lesions that are only in-plane (no elevation or depression) are rare and cannot be detected by CT colonography. Flat lesions are not only difficult to detect with CT colonography, they can remain undetected at routine colonoscopy; specific measures are needed for improved detection (e.g., dye spray for evaluation of the normal colonic surface pattern disturbed by a flat lesion).

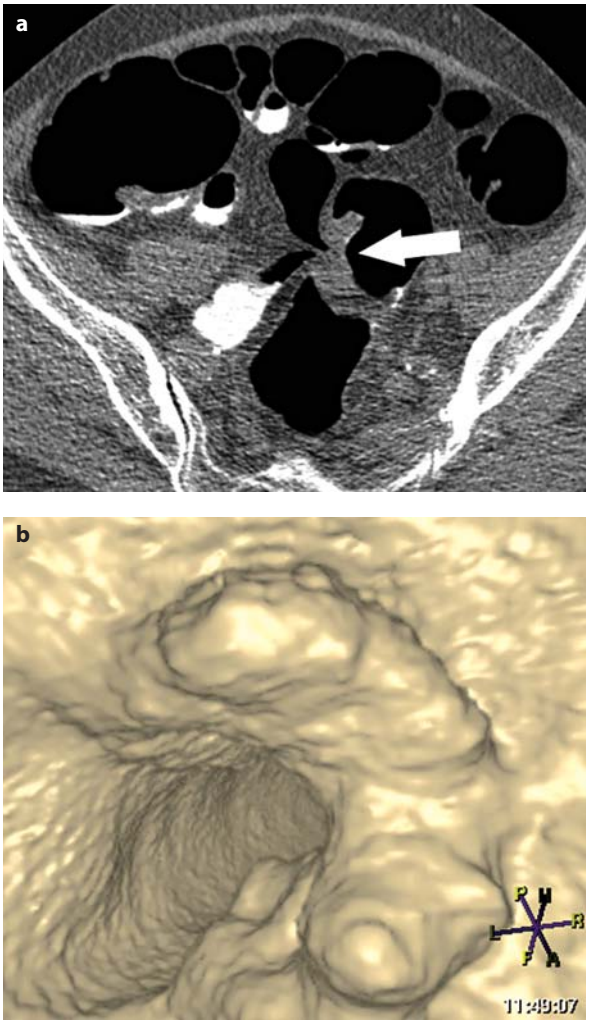

Fig. 3 a, b. Patient with colorectal cancer. CT colonography with the patient in the supine position after extensive bowel preparation and fluid tagging demonstrates the cancer (*arrow*) in the rectosigmoid at 2D (**a**) and 3D (**b**) evaluation

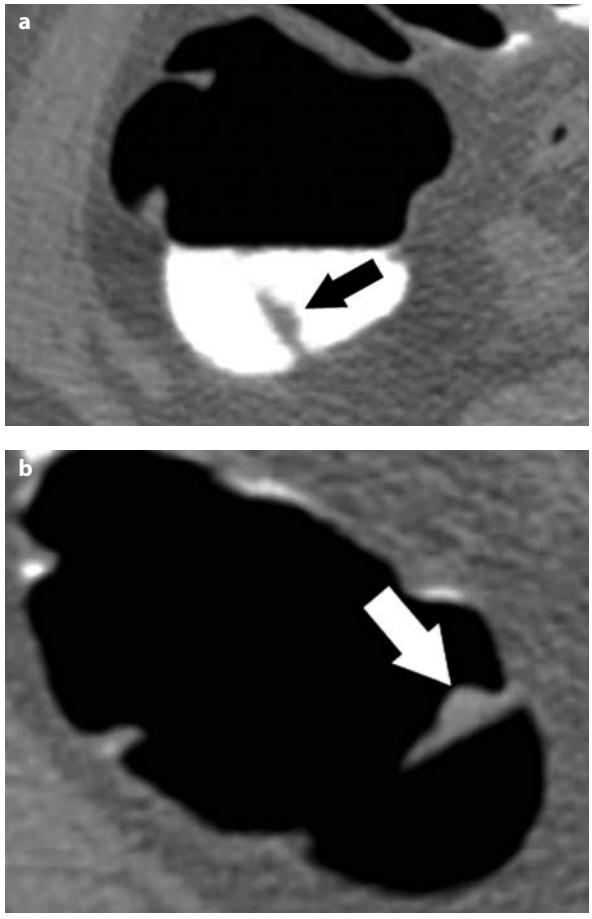

Fig. 4 a, b. Patient with a 15-mm polyp at CT-colonography after extensive bowel preparation and fluid tagging. **a** Two-dimensional image with the patient in the supine position demonstrates the polyp (*arrow*) submerged by tagged fluid. Without tagging, the polyp would not have been identified in this patient position. **b** Two-dimensional image obtained with the patient in the prone position nicely shows the polyp (*arrow*), in this position without surrounding fluid

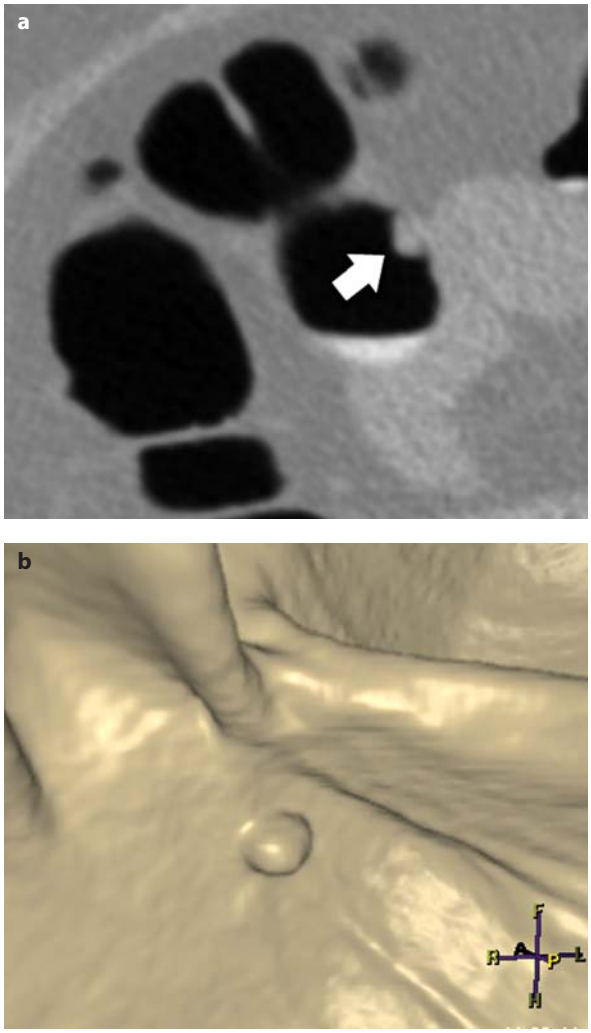

Fig. 5 a, b. Visualization of an 8-mm tubulovillous adenoma (*arrow*) with 2D (**a**) and 3D (**b**) evaluation at CT colonography with the patient in the supine position

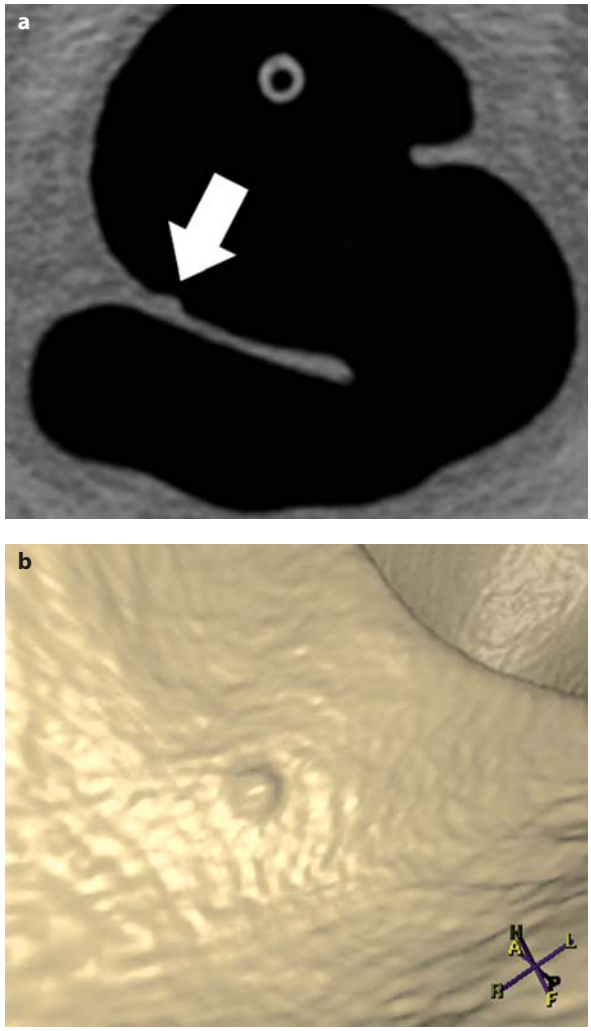

Fig. 6 a, b. A 4-mm tubular adenoma in the rectum (*arrow*). CT colonography with the patient in the prone position with 2D (**a**) and 3D (**b**) evaluation

The major limitation of CT colonography is that no differentiation can be made between a sessile adenoma and a non-adenomatous sessile lesion without malignant potential. Only size is helpful in this respect. Malignancy in adenomatous polyps is present in > 10% of polyps with a diameter ≥ 10 mm and in approximately 1% of the polyps < 10 mm. Small polypoid lesions 1–5 mm in diameter are often non-adenomatous hyperplastic lesions and can be disregarded (except in patients with a large number of small lesions). Polyps 6–9 mm in diameter can be hyperplastic or adenomatous. The chance of a malignant adenoma is very low (a few percent) in this size range. Polyps ≥ 10 mm diameter are often adenomas, with the prevalence of malignancy increasing with increasing size (Fig. 4). Large polyps other than adenomas are rare. Data on the accuracy of CT colonography are thus reported for the size range ≥ 10 mm and ≥ 6 mm or separately for the 6- to 9-mm size range (Fig. 5). Polyps 1–5 mm are often not reported (Fig. 6).

Differentiation between a polyp and untagged stool is done primarily by evaluating the internal structure of the lesion at 2D: polyps have a homogeneous morphology while stool is heterogeneous and may contain air. In tagged examinations, the main discriminating factor is the contrast between tagged material and colorectal cancer and polyps. A helpful but less reliable feature is the lack of change in the relative position of a potential lesion between the two scans [24]. This feature is indicative for a polyp, although bowel segments are mobile and

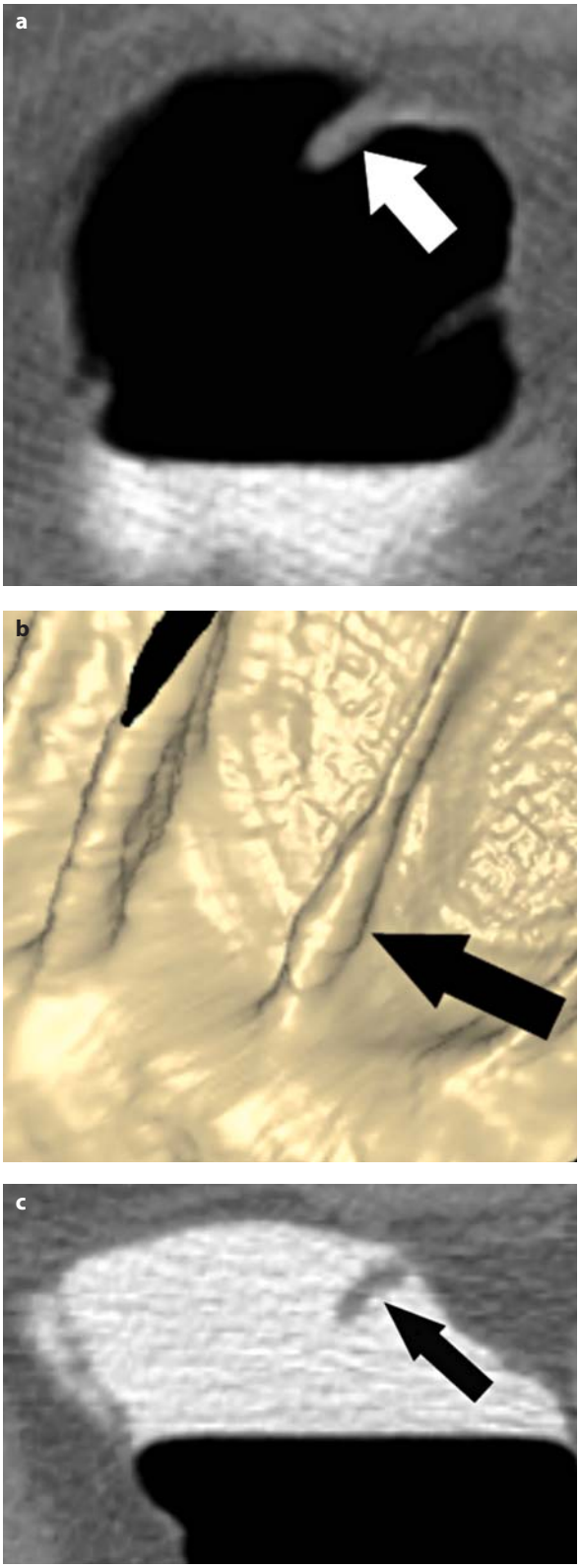

Fig. 7 a-c. Flat lesion at the coecum that proved to be a serrated adenoma. The lesion (*arrows*) can be identified as a thickened fold on 2D (**a**) and 3D (**b**) evaluation. (**c**) With the patient in the supine position, the lesion is submerged by tagged fluid and even more difficult to identify

especially pedunculated polyps can change position. The opposite may occur as well, as sticky stool can be adherent to the colonic wall without being influenced by the effect of gravity.

Computer-aided detection (CAD) has been introduced in CT colonography. Based on their shapes and internal characteristics, colorectal cancer and polyps can be identified. CAD schemes have been designed for application in patients who have undergone extensive bowel preparation or tagged examinations [25, 26]. For the latter, electronic cleansing is frequently carried out prior to the CAD scheme. At present, the role of CAD in identifying lesions that were undetected in the initial read by an observer (secondary read) or in direct applications during observer evaluation (concurrent read) is being assessed.

Accuracy

CT colonography performs well in the detection of colorectal cancer and of polyps with a diameter ≥ 10 mm. It is somewhat less accurate for polyps in the intermediate size range of 6–9 mm. As CT colonography will be used to select patients for colonoscopy, the test characteristics (i.e., sensitivity, specificity, and predictive values) per patient are of primary importance, since patient selection is based on the presence of at least one relevant lesion regardless of the number of lesions present. Colonoscopy is performed for polyp removal by biopsy, with subsequent histopathological evaluation of the lesion. In colorectal cancer, biopsy is performed for histopathology. The per-polyp test characteristics are for this reason less relevant than the per-patient characteristics.

A considerable number of studies reporting on the accuracy of CT colonography have been published. In three systematic reviews of the literature, this technique was shown to have good test characteristics for those findings important at colorectal cancer screening: detection of participants with colorectal cancer and large (often adenomatous) polyps (diameter ≥ 10 mm) [27-29]. These systematic reviews primarily concerned studies in symptomatic populations. For colorectal cancer, the sensitivity was high, namely 95.9%, and the specificity was > 99%. For larger polyps (diameter ≥ 10 mm), sensitivity was 85–92.5% and specificity 95–97.4%. For polyps ≥ 6 mm, per-patient sensitivities of 70, 84, and 86.4% and specificities of 86.1 and 93% have been reported.

The results of three multi-center studies consisting of larger series of participants with average or increased risk [30-32] have been reported and those

of a large series (ACRIN II) are awaited. The largest series (1233 participants) published until now (April 2007) consisted of an average-risk population age 50 years or older [30]. In that screening population, state of the art CT colonography (including fluid tagging, experienced observers) was used. This resulted in a sensitivity of CT colonography for screening participants with one or more adenomatous polyps ≥ 10 mm of 94% and a specificity of 96%. The findings for polyps, irrespective of histopathology, were not reported, although the sensitivity would be somewhat less. The other studies reported inferior results with respect to sensitivity (55%, 59%) for polyps ≥ 10 mm and identical specificity. Differences in the study characteristics included CT colonography technique, use of tagging, evaluation method, and reader experience. The disease spectrum as well as differences in polyp number, polyp size, and polyp morphology will also influence the results. For example, the presence of primarily large lesions in a large number of participants will lead to more favorable results whereas flat lesions can be more difficult to detect than polypoid or pedunculated lesions [23].

More research in larger screening populations is necessary to determine the test characteristics of CT colonography. The ACRIN II study includes 2607 male and female out-patients, age 50 years or older, undergoing screening colonoscopy. Participants are examined by CT colonography directly before colonoscopy and after extensive cleansing and tagging. The results are expected in 2007.

Initial studies on the efficacy of CAD involved small numbers of patients and have yielded promising results: 80–90% per-polyp sensitivity for polyps ≥ 10 mm and a limited number of false-positives [25]. These results were confirmed in a study with a larger number of individuals [26], i.e., 792 screening participants originating from the above-described CT colonography screening study of 1233 participants [30]. The per-polyp and per-patient sensitivities of CAD for adenomas were good: both 89.3% with 2.1 false-positives per patient. CAD for CT colonography was shown to significantly increase per-patient and per-polyp detection and to significantly reduce interpretation times [33].

Safety

CT colonography is a safe procedure; complications are rare (0.02–0.08%). Symptomatic perforations occur in approximately 0.009–0.06% of the individuals who undergo this procedure [34-36] and can be prevented in many cases. Reported perforations are often related to suboptimal technique and indication. The use of a rigid rectal balloon catheter, manual insufflation, or limited experience are related to symptomatic perforations. Other situations that may lead to symptomatic perforations include obstruction or CT colonography performed within a week of a colonoscopy or sigmoidoscopy with biopsy. Perforation has also been reported in patients with inflammatory bowel disease, in whom (as in those with diverticulitis) CT colonography is contraindicated when the disease is in the active phase.

Extracolonic Findings

Apart from colorectal lesions, extracolonic findings (e.g., renal cysts, aortic aneurysms) may be present. The frequency and relevance will depend on the population studied and are highest in populations with symptoms of colorectal cancer. In a recent systematic review of the literature, almost 40% of individuals with symptoms of colorectal cancer also had extracolonic findings [37]. In one-fourth of these patients these consisted of relevant findings, although many of them were already known prior to the CT colonography examination. The prevalence of new, relevant findings was relatively low.

In a screening setting, the number of extracolonic findings most likely will be lower than in symptomatic individuals. In the previously cited CT colonography study in which 1233 asymptomatic subjects were screened, a finding of potentially high clinical importance was detected in 56 persons (4.5%) [30]. Unsuspected extracolonic cancer was proven in only five people (0.4%). It is noteworthy that more extracolonic cancers (n=5) than colon cancers (n=2) were detected in this study. Two patients underwent successful repair of unsuspected abdominal aortic aneurysms. A higher number of extracolonic findings of moderate clinical importance were found, including nephrolithiasis in 98 patients (7.9%) and gallstones in 69 patients (5.6%). The proportions of patients that required follow-up for extracolonic and intracolonic findings (polyps ≥ 10 mm) were approximately similar, 4.5 and 7.5%, respectively. These facts emphasize that extracolonic information resulting from CT colonography screening can be of considerable consequence. Resources consumed as a result of extracolonic findings have been demonstrated to approximately double the costs of diagnostic CT colonography in symptomatic patients [38]. These costs along with the related anxiety and

inconvenience and morbidity should be weighed against the benefits. The frequency of extracolonic findings depends on the radiation dose employed in the CT colonography examination. Reduction of the dose can be expected to lead to a substantial decrease in extracolonic findings [14]. As screening will thus be performed with lower radiation exposure in individuals with fewer extracolonic findings, the associated costs will most likely be lower than in the aforementioned study.

Conclusions

CT colonography is a safe procedure with good accuracy in symptomatic patients – those with colorectal cancer and those with relevant polyps. The technique can be used in patients with incomplete colonoscopy. The combination of CT- colonography and intravenous contrast medium results in a one-stop staging examination in symptomatic patients.

Equivocal results have been obtained in screening, mostly due to suboptimal technique and reader experience in the studies with poor results. The ACRIN II study should provide valuable information on the role of CT colonography in screening. Apart from its accuracy, predictive values, and acceptance, other issues, such as extracolonic findings, will influence the cost effectiveness.

Presently, research is aimed at developing and evaluating CAD, reducing the need for bowel preparation, and lowering the radiation exposure. The latter will reduce the number of extracolonic findings, which is expected to improve the cost effectiveness of screening for colorectal cancer using CT colonography.

Acknowledgment

Ayso H. de Vries MD is acknowledged for providing the figures for this chapter.

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