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MULTIDISCIPLINARY SYMPOSIUM: COLORECTAL CANCER

Wednesday 5 October 2005, 14:00–16:00

Colorectal cancer: what the clinician wants to know

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Abstract

Colorectal cancer is a common and lethal disease. The adenoma-carcinoma sequence offers a window of opportunity in which the precursor lesion or early carcinoma can be removed endoscopically to prevent systemic disease. New and advanced techniques to improve endoscopic detection of precursor lesions are being developed. Other, less invasive screening methods are currently being developed and may become of use for population-based screening in the near future. Recently, important developments in the treatment (both surgical and chemotherapeutic) of colorectal cancer have occurred. The extent of the disease (stage) forms the basis for therapeutic decisions and accurate imaging is crucial.

Keywords: *Colorectal cancer; polyps, diagnosis; treatment.*

Introduction

Colorectal cancer is a common and lethal disease. Every year, more than 945 000 people develop colorectal cancer worldwide, and around 492 000 patients die[1]. Despite these sobering statistics, many advances have been made in different aspects of this disease in recent years. In this review we focus mainly on the diagnostic and therapeutic aspects of colorectal cancer.

Pathogenesis of colorectal cancer

The majority of cases of colorectal cancer develop sporadically (88%–94%). The remainder occur in high-risk groups like hereditary cancer syndromes (e.g. hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis) and long-standing inflammatory bowel disease. Furthermore, patients with previous adenomatous polyps or cancer of the colon are also at increased risk for developing colorectal cancer.

Most colorectal carcinomas are thought to arise in pre-existing adenomatous precursors (polyps) that form in the colon when normal mechanisms regulating epithelial renewal are disrupted: the adenoma-carcinoma sequence. As the lesion progresses, genetic changes in various tumour suppressor genes and oncogenes accumulate[2]. However, only a small proportion of all adenomatous polyps progress to cancer and furthermore, the speed of progression varies. For example, the adenoma-carcinoma sequence for sporadic cancers takes an estimated 10–15 years, whereas adenomas in patients with HNPCC might proceed to cancer at a significantly higher speed. To further complicate matters, there is increasing evidence of alternative pathways leading to colorectal cancer and the serrated pathway might serve as an explanation for the occurrence of colorectal cancer in hyperplastic polyps[3]. Thus, it is becoming clear that colorectal cancer is not a single, but rather a very heterogeneous disease from both a genetic and a clinical point of view.

Window of opportunity

The adenoma-carcinoma sequence offers a window of opportunity in which the precursor lesion or early carcinoma can be removed endoscopically to prevent systemic disease. Indeed, there is a significant reduction in the incidence of colon cancer in screened populations by white light colonoscopy plus polypectomy[4].

However, the question arises which polyps should be identified and removed? The National Polyp Study Workgroup introduced the concept of adenomas with advanced pathologic features that serve as risk factors for developing future colorectal cancer[4]. These factors are: adenomatous polyp >1 cm in diameter, polyp with high-grade dysplasia or invasive cancer. Furthermore, villous histology and increasing polyp size also correlate with the development of colorectal cancer[5]. The risk for development of colorectal cancer after removal of small tubular adenomas seems to be low[5,6]. However, in clinical practice most endoscopists also remove smaller adenomas.

For decades hyperplastic polyps were thought to cause no harm. However, now that the serrated pathway for the development of colorectal carcinoma has been described, there is no clear consensus if these polyps should also be removed. The hyperplastic polyps that are large in size and occur in the proximal colon seem to carry a higher risk and should be considered for removal[3].

Diagnosis of colorectal polyps and cancer

Surveillance and screening

Colonoscopy is traditionally considered the optimal examination for the detection of polyps and colorectal cancer. During colonoscopy lesions can be localized throughout the colon, biopsies can be taken for histologic diagnosis, synchronous lesions can be detected and adenomatous polyps and early cancers can be removed in their entirety. However, colonoscopy is not infallible and both polyps and cancers can be missed[7]. The miss rate is inversely related to the size of the lesion and influenced by both the endoscopist and patient-related factors. Furthermore, some cancers also apparently arise from adenomas that are not polypoid. Flat and depressed lesions may account for 12%–40% of all adenomas and early colorectal carcinomas[8,9]. These lesions have a surprisingly high rate of submucosal invasion even when they are small and, needless to say, are more difficult to detect by colonoscopy. Patients with long-standing ulcerative colitis or Crohn's disease have an increased risk for flat dysplasia and cancer that may develop within fields of transformed mucosa which is usually difficult to detect endoscopically[10]. Furthermore, it would be very attractive to be able to immediately differentiate between neoplastic and non-neoplastic lesions during colonoscopy. In this way, only neoplastic lesions could be removed during the same colonoscopy session and other lesions might be left *in situ*, thus reducing time, costs and risk of the procedure.

Chromoendoscopy (application of dye during endoscopy) in combination with magnification endoscopy is one of the techniques with proven success. Rembacken *et al.* and many others have reported this technique to be helpful for both detection and detailed morphological assessment of colorectal lesions[9]. Kudo *et al.* performed pioneering studies, combining high-magnification colonoscopy with chromoendoscopy for the *in vivo* prediction of histology using a pit-pattern classification[11]. Pan-colonic chromoendoscopy showed a significant increase in diminutive adenoma detection[12,13] and detection rates of dysplasia in patients with ulcerative colitis[14]. However, many more, novel endoscopic techniques are currently under investigation and offer promising means of improving endoscopic detection of precursor lesions and colorectal cancer. Amongst these are narrow band imaging, videoautofluorescence endoscopy and confocal microendoscopy. The most successful endoscopic method will probably be a combination of techniques that can both provide wide-area surveillance (a 'red flag technique' like fluorescence endoscopy) and, once a target-lesion is identified, detection methods like narrow band imaging or confocal microendoscopy that can be used to further identify the lesion[15].

Another attractive option may be the coupling of fluorescent dyes to tumour-related antigens as they are in every day use in most pathology labs. Immunoscopy is performed with the use of injected probes consisting of small molecules (enzyme substrates, receptor ligands, monoclonal antibodies, peptides) tagged to a fluorescent dye to achieve high-affinity binding to specific biochemical and molecular markers of disease[16]. In a German study, a fluorescein-labelled monoclonal antibody against CEA (carcinoembryonic antigen) was applied directly onto the mucosal surface during conventional colonoscopy[17]. Fluorescence *in vivo* was present in 19 out of 25 carcinomas and in 3 of 8 adenomas. However, the technique failed in the presence of mucosal ulceration or bleeding. The development of better optical tumour-specific imaging agents could have far-reaching potential in real-time polyp and cancer detection and will definitely complement existing fluorescence endoscopy but possibly also other imaging modalities.

The field of immunoscopy is very close to molecular imaging or may even be considered a form of molecular imaging. In the future other techniques such as magnetic resonance (MR) imaging may be more appropriate than colonoscopy and one could imagine an MR-colography which not only depicts possible polyps but also differentiates their nature through molecular imaging techniques. This would obviate the need for optical colonoscopy as a diagnostic method. Unfortunately, the road to these techniques still seems to be long.

However, in recent years a lot of research has been done on the role of virtual colonoscopy in diagnosing colorectal polyps or cancer. A meta-analysis on 33 studies of 6393 patients showed that computed tomography (CT) colography was highly specific, but its sensitivity was heterogeneous[18]. However, sensitivity improved with increasing polyp

size. The results of MR-colography are less good than CT-colography, but this technique has no radiation exposure, which is of value in the choice of a screening modality. In virtual colonoscopy, patient acceptance seems better than for colonoscopy, and might be improved with less intensive bowel preparation. Important drawbacks of these techniques are the impossibility of obtaining histological biopsies and/or removal of the lesion and therefore this technique seems less attractive for surveillance of high-risk patients.

Population-based screening

Research has shown that population screening by testing for small, invisible traces of blood (faecal occult blood test, FOBT) can reduce mortality from colorectal cancer by 15%–33% [19–21]. Besides FOBT there are other, possibly more suitable methods for screening. Endoscopic screening is expected to reduce deaths to a greater extent than FOBT, but is an invasive investigation that is onerous for the patient and can lead to complications. Development of new, non-invasive imaging techniques like CT-colonography and MR-colonography, and non-invasive screening techniques such as detection of changes in DNA or proteins specific for cancer (proteomics) hold much promise for the future.

Staging

Once a cancer is diagnosed, the extent of the disease should be determined to form the basis for therapeutic decisions. In addition to physical examination, abdominal ultrasound and chest radiography are routinely performed to determine the extent of the disease. The necessity for routine preoperative CT scans is a matter of debate because this method alters the surgical approach in only a few cases [22].

In the case of rectal cancer preoperative knowledge of the depth of invasion and nodal status is critically important for the planning of treatment. Local staging can be done by endorectal ultrasound, CT or MRI. Positron emission tomography (PET) is valuable for detection of recurrent colorectal cancer, but seems to have only little effect on staging of primary cancer [23].

Detection of liver metastases can be performed by either CT or MRI. PET seems to hold promise but its use has not yet been proven in a randomized study [24].

Treatment

There are several modalities for the treatment of colorectal cancer and the decision for a certain therapy relies on the stage of the disease.

Endoscopic therapy

Since there are no lymphatics above the muscularis mucosae, many early malignant lesions can be managed endoscopically [25]. Thus, high-grade dysplasia (sometimes called carcinoma *in situ*) and intramucosal carcinoma are considered non-invasive if these lesions are found within a resected polyp; they require no further treatment if the resection margins are free of cancer. However, when histology of the cancer shows poor differentiation, lymphatic or vascular invasion, cancer at the resection margin, invasion of the submucosa, invasive carcinoma in a sessile polyp or incomplete polypectomy, there is a high risk of residual cancer and surgery should be considered.

Surgery for primary tumour

Traditionally, surgical resection of colonic cancer is based on resection of the intramural tumour together with wide excision of the area of regional lymph drainage, i.e. the mesentery. Hence, for tumours in the caecum, ascending colon or hepatic flexure, a right hemicolectomy is performed. Tumours in the transverse colon are resected through a transverse colectomy or alternatively, by extended right hemicolectomy. For tumours in the splenic flexure or descending colon, a left hemicolectomy is recommended, whereas for sigmoid tumours, a sigmoid colectomy is carried out. Localization of the tumour using double contrast barium enema, white light colonoscopy or virtual colonoscopy is therefore important to define the type and extent of surgical resection. In case of invasion of neighbouring structures or organs, such as ureter, bladder, small bowel or abdominal wall, the colon is resected en bloc with the adjacent structures in an attempt to achieve tumour negative margins. CT scan of the abdomen is helpful in identifying patients with such locally advanced tumours. It should be noted that nowadays, laparoscopic colectomy is equivalent to open colectomy in terms of oncological outcome [26].

Curative treatment of rectal cancer basically consists of local excision, low anterior resection (LAR) or abdominal perineal resection (APR). Full thickness local excision can be performed using the transanal endoscopic microsurgery (TEM) procedure, for superficially invasive cancers (T1). Although the recurrence rate after TEM is higher than after radical resection for more invasive tumours, TEM offers an alternative in patients with significant co-morbidity [27].

The prognosis of patients with rectal cancer has greatly improved by the concept of total mesorectal excision (TME) in combination with LAR or APR, which reduces local recurrences and perioperative morbidity [28]. A standard TME encompasses excision of the rectum including the complete rectal mesentery, proximal and distal to the tumour. The superior results of TME are attributed to improved lateral clearance and decreased

risk of tumour spillage from a disrupted mesentery. Using this technique, local failure rates have dropped from 25% on average, to 4%–7% for Dukes B and C tumours [28].

APR entails rectal excision with complete proctectomy using both an abdominal and perineal approach and requires a permanent colostomy. APR is indicated in patients with rectal tumours involving the anal sphincter musculature or rectovaginal septum, or in patients with poor faecal continence. Otherwise, rectal excision with preservation of the sphincter (i.e. LAR) is the treatment of choice. Large invasive tumours of the distal rectum may be reduced by preoperative radiotherapy or neoadjuvant chemotherapy, converting a planned APR to a sphincter-sparing LAR. Hence, preoperative imaging is important to evaluate rectal tumours in terms of T staging and assessment of local, pelvic invasion.

Surgery for colorectal liver metastases

Partial liver resection remains the gold standard for curative treatment of patients with colorectal liver metastasis leading to a 5-year survival rate of 20%–40% [29]. The large majority (80%–85%) of patients with liver malignancies, however, are unresectable as a consequence of multifocal intrahepatic disease, extrahepatic disease, inadequate functional hepatic reserve, inability to obtain an optimal (0.5 cm) tumour free margin, or involvement of the confluence of the portal vein. It is the primary goal in the work-up of potential candidates for surgical resection, to reliably assess these criteria.

Selection of patients eligible for partial liver resection is nowadays based on the following four criteria: (1) Is the patient fit to undergo major upper abdominal surgery? (2) Are there no extrahepatic metastases (with the exception of lung metastases)? (3) Are all lesions resectable with a tumour-free margin >0.5 cm? (4) Is the volume of the remnant liver sufficient for adequate postoperative liver function?

Accurate imaging is crucial to answer the last three questions. CT and MRI are commonly used to assess the number and location of liver and lung lesions, and possible lymph node metastases. In the presence of lung metastases, pulmonary resection is carried out prior to abdominal exploration and liver resection. When planning liver resection, the segmental division of the liver as described by Couinaud is used to define the borders and extent of liver resection.

When the liver parenchyma is normal, which is usually the case in patients with colorectal liver metastases, up to 70% of total liver volume can be resected without increased risk for postoperative liver failure. The remnant liver has a unique potential to regenerate after resection, thus increasing in volume and function in the postoperative period. In specialized centres, the overall mortality of liver resections for liver metastases is 2%–5%. CT-volumetry of the (remnant) liver is therefore important to select candidates for liver resection. Alternatively, the volume of the future remnant liver can be calculated using patient characteristics. Although frequently used in the Far East for assessment of patients with hepatocellular carcinoma, the indocyanine green (ICG) clearance test is not routinely used in Europe for evaluation of liver function. In recent years, functional imaging of the liver has been examined using scintigraphic techniques (Tc-99m-galactosyl serum albumin or Tc-labelled Mebrofenin), providing simultaneous morphologic and physiologic information of liver segments [30].

Several strategies can be devised to resect liver metastases in patients initially considered unresectable. With neoadjuvant chemotherapy regimens, liver metastases can be downstaged thus offering survival benefits after resection comparable to patients resected on first presentation [31]. In the case of insufficient remnant liver volume, portal vein embolization of the affected liver lobe may be applied, resulting in ipsilateral atrophy and contralateral, compensatory hypertrophy of the future remnant liver [32,33]. Alternatively, in order to preserve as much functional liver parenchyma as possible, liver resection can be combined with local ablative therapies such as radiofrequency ablation [34].

The "two staged" resection entails resection of the liver in two phases with a time interval to allow regeneration of the resected liver before the second resection is undertaken [35].

Chemotherapy

During the past 15 years, sequential advances in chemotherapy after surgical resection (adjuvant chemotherapy) have had a clear and substantial benefit, with the 4-year rate of overall survival approaching 80% [36].

The use of adjuvant fluorouracil-based chemotherapy in patients with Dukes stage III colon cancer is thought to be standard care, but is not routinely recommended in stage II colon cancer [37]. The prospects for a higher rate of cure in patients with locally advanced colorectal cancer are extremely promising, given the emerging evidence that supports therapeutic targeting of growth factors, growth-factor receptors and down-stream pathways [36]. Both bevacuzimab, a vascular endothelial growth factor antibody, and cetuximab, an endothelial growth factor-receptor antibody, have demonstrated benefit in advanced colorectal cancer [38,39]. Oral fluoropyrimidine capecitabine has an improved safety profile and is at least as effective [40].

Palliative treatment for patients with metastatic colorectal cancer aims to improve survival and quality of life and major progress has been made by treatment regimens with new cytotoxic drugs such as irinotecan or oxaliplatin. Now the median overall survival for metastatic colon cancer has been doubled from 10 to 20 months [41].

The present state of generic therapy based on disease stage and histologic site of origin must give way

to molecularly guided, personalized therapies, shifting the risk-benefit ratio of chemotherapeutic intervention towards a clear individualized patient benefit[36].

Follow-up

The main objective of follow-up after curative resection is improvement of survival but psychological support can be given as well. Meta-analyses showed a significant improvement in survival after intense compared with routine follow-up[42,43]. However, how this should be done is not well defined. Colonoscopy is recommended every 3 years to detect metachronous colorectal cancer. Determination of carcinoembryonic-antigen testing every 3–6 months seems the most useful test in patients who had elevated CEA levels before tumour excision[44]. The value of other tests like abdominal ultrasound, CT scan and PET still needs to be determined[45].

When recurrent disease is detected at the previous site of resection, re-resection may be attempted. A selection of patients benefit from a combination of surgery, radiotherapy and/or chemotherapy. Repeat resections are performed for recurrent metastases after partial liver resection. Several series have shown survival curves after repeat resections of colorectal liver metastases, comparable to survival after first resection.

Conclusions

What do clinicians want to know from the radiologist? For population-based screening, further development of virtual colonoscopy is of great value. Preferably this is performed without bowel preparation and air-insufflation and with minimal exposure to radiation. Better imaging of flat and small adenomas and cancers should be made possible. Furthermore, molecular imaging has great potential for both depicting possible polyps and differentiating their nature (e.g. hyperplastic or adenomatous) and should be developed further.

For staging of colorectal cancer, which is the basis for therapeutic decisions, optimal imaging is necessary. The T-stage (with possible local invasion in adjacent structures or organs and/or tumour-related complications such as fistula formation or perforation), and possible lymph node metastases, hepatic metastases and pulmonary metastases should be assessed. Furthermore, the exact location in the colon should be determined and any second primary cancer or polyp be diagnosed. In the case of liver metastases, the number and location relative to the liver segments, possible involvement of major vessels (vena cava, portal vein, hepatic artery) and estimated volume of future remnant liver (when resection is planned) should be assessed.

In the follow-up after curative resection of colorectal cancer, early detection of recurrent disease, both at the site of the primary tumour and in the liver or lungs, might help to further improve survival and the value of the different imaging-modalities should be determined.

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Virtual colonoscopy for colorectal cancer screening: current status

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Abstract

Computed tomography colonography (CTC) (also known as 'virtual colonoscopy') is a noninvasive method of imaging the colon using helical CT. Although CTC has been shown to be useful for certain clinical indications, it has not yet been endorsed as a colorectal cancer screening test. The purpose of this article is to review the current status of CTC for colorectal cancer screening. CTC is an accurate method to detect colonic polyps and to select patients who would benefit from colonoscopy. The major advantages of CTC over conventional colonography include its relatively low risk and greater tolerance by patients. In this article, the CTC procedure and results of clinical trials are reviewed, as well as potential pitfalls related to CTC performance and interpretation. Finally, radiation dose, the discovery of incidental extracolonic findings with CTC, bowel preparation methods, and computer-aided diagnosis are addressed.

Keywords: *Computed tomography colonography (CTC); virtual colonoscopy; noninvasive; colorectal cancer.*

Introduction

Colorectal cancer is the fourth leading cause of cancer death worldwide[1] but is largely preventable. Most colorectal cancers arise from benign adenomatous polyps, which grow slowly. Thus colorectal cancer is highly suited to screening because of its long preclinical phase during which it is detectable and curable[2]. Multiple organizations including the World Health Organization (WHO), the American Cancer Society (ACS), the Agency for Health Care Policy and Research (AHCPR), the US Preventive Service Task Force (USPSTF), and the American Gastroenterology Association (AGA) have issued or endorsed guidelines for colorectal cancer screening. The screening tests endorsed by these organizations include fecal occult blood testing, flexible sigmoidoscopy, air-contrast barium enema, and colonoscopy. Unfortunately, screening programs for colorectal cancer have been only partly successful, owing largely to poor patient compliance with screening recommendations[3,4]. Recent studies indicate compliance rates of only approximately 25%–40%[5–8]. Major obstacles to patient acceptance of colorectal cancer screening with colonoscopy are the requirement for a rigorous bowel preparation, the invasiveness of the procedure and the need for sedation.

Computed tomography colonography (CTC) (also known as 'virtual colonoscopy') was introduced in 1994 as a noninvasive method of imaging the colon using helical CT[9]. Although CTC has been shown to be useful for certain clinical indications, it has not yet been endorsed as a colorectal cancer screening test and is not covered by most third-party payers when used for screening purposes. This article reviews the current status of CTC for colorectal cancer screening.

Advantages and limitations of CTC

CTC has a number of potential advantages compared with conventional fiberoptic colonoscopy. It is a noninvasive technique, requires no sedation, and can be completed in a much shorter time. CTC also appears to be safer than colonoscopy. Colon perforation occurs in 1 : 1000 patients who undergo conventional colonoscopy, and the mortality rate is 1 : 5000[10–15]. Although experience with CTC is much more limited, the morbidity and mortality associated with CTC likely will be similar to those for the air-contrast barium enema (perforation rate of 1 : 10 000 and mortality rate of 1 : 50 000)[16–18]. The only study of morbidity related to CTC reported to date has demonstrated a perforation rate of 3 in 7180 studies (0.04%)[19]. No deaths related to CTC have been reported. In addition, CTC has the potential to eliminate some of the blind spots that can be problematic with conventional colonoscopy. For example, CT colonography is able to demonstrate lesions behind haustral folds and beyond bends in the colon because of its ability to provide an endoluminal view of the colon in both forward and reverse directions

and its ability to demonstrate the colon in both two-dimensional and three-dimensional perspectives. For the same reasons, localization of colonic lesions is more accurate with CTC than with fiberoptic colonoscopy. Finally, CTC is capable of demonstrating clinically important extracolonic abnormalities [20–24].

On the other hand, CTC also has some limitations. Pitfalls that can result in false negative diagnoses include retained fluid, which can obscure lesions, incomplete distension of some colonic segments, and difficulty demonstrating flat lesions. Pitfalls that can result in false positive diagnoses include retained stool and nodular folds, which can be mistaken for polyps. An important disadvantage of CTC compared with colonoscopy is that CTC does not allow biopsy or removal of polyps that are identified. In addition, the sensitivity of CTC for detecting clinically significant polyps has varied considerably in the screening trials performed to date [25–29].
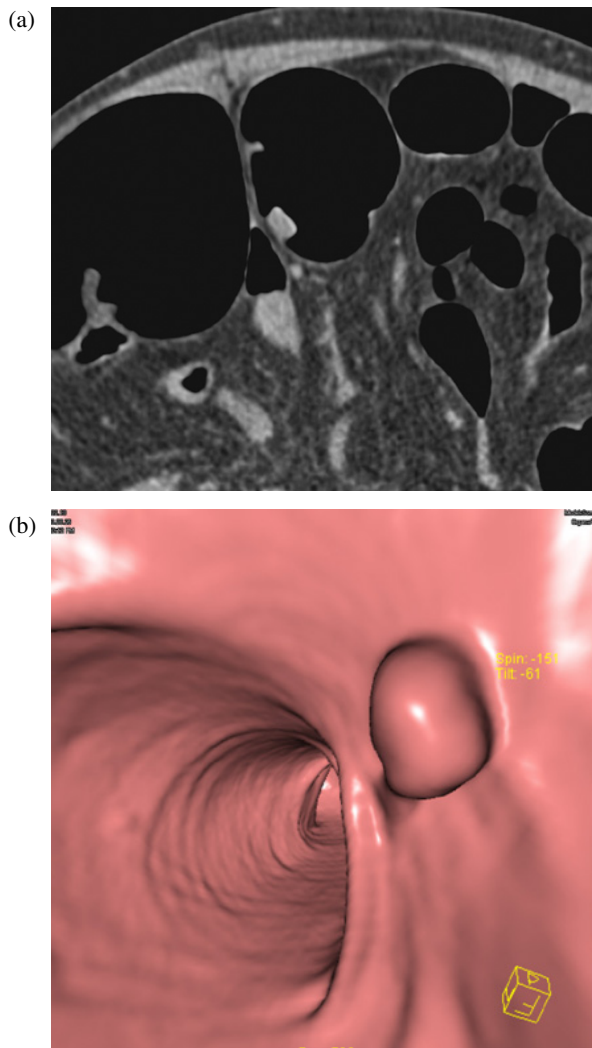
(a)

(b)

Figure 1   **Sigmoid polyp. 2D transaxial (a) and 3D endoluminal (b) images demonstrate a 1 cm sessile sigmoid polyp.**
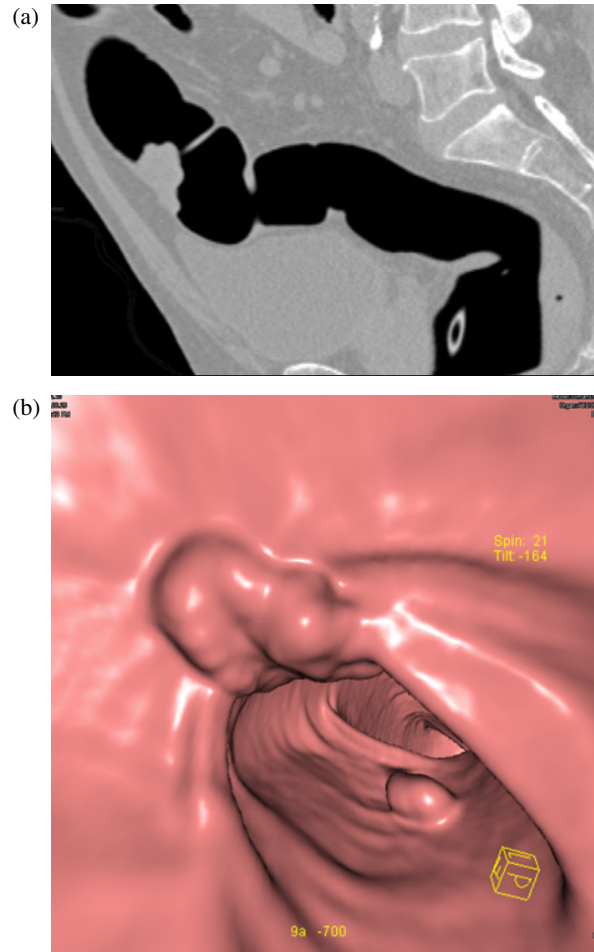
(a)

(b)

Figure 2   **Sigmoid mass and polyp. (a) A sagittal 2D image demonstrates a lobulated mass in the sigmoid colon. (b) The corresponding 3D endoluminal image shows a nearby 9 mm sessile polyp in addition to the mass.**

The standard CTC examination

Currently all patients undergo a standard bowel preparation as for colonoscopy. A recent modification in bowel preparation is the addition of oral contrast agents (see 'Bowel preparation' below). After the patient is placed on the CT scanner table, a small catheter is placed in the rectum, and the colon is insufflated with either room air or carbon dioxide. The main advantage of carbon dioxide is that the gas is reabsorbed very quickly, such that within several minutes the patient no longer feels uncomfortable. When room air is used, patients may remain distended for hours after the procedure. Some radiologists routinely administer a spasmolytic medication to help relax the colon and maximize distension, whereas others do not [30]. Prior to the diagnostic CT examination the standard initial scout view (topogram) of the abdomen is used to confirm that the colon is adequately distended. The patient is then scanned in both the supine and prone positions. No oral or intravenous contrast material

is administered. The entire examination generally takes approximately 10 min.

Technological evolution of CTC

During the 11 years since its inception, CTC has evolved considerably due to rapid advances in CT hardware and software and the experience gained from numerous clinical trials. When CTC was introduced in 1994, only single- and two-detector row CT scanners were available. Using 3–5 mm X-ray beam collimation, it took 30–50 s to scan the patient's abdomen and pelvis, which led to breathing artifacts in many patients. In addition, the spatial resolution of multiplanar and three-dimensional reconstructions was limited by the relatively large X-ray beam collimation. Currently, with 64 detector-row scanners the scan time is reduced to 4–10 s, and the routine detector collimation of 0.6 mm enables extremely high quality multiplanar and three-dimensional reconstructions (Figs 1–3).

Clinical results

Except for one study that was hampered by suboptimal technique and a steep learning curve[31], early CTC trials performed with single detector-row CT scanners demonstrated sensitivities of 68%–92% and specificities of 82%–98% for polyps 10 mm and larger[32–38]. A meta-analysis of these early trials confirmed reasonably high pooled sensitivities by patient and by lesion of 88% and 81%, respectively, with a pooled specificity of 95% for polyps 10 mm and larger[39]. More recent studies performed with four-detector row scanners have demonstrated sensitivities and specificities of 82%–100% and 90%–98%, respectively, for polyps 10 mm and larger[40–43]. It is important to recognize, however, that these trials were not performed on screening populations but on individuals who were at increased risk for colorectal neoplasia. A large single institution screening trial using single detector-row CT demonstrated individual reader sensitivities of 59%–73% and specificities of 95%–98% for polyps ≥10 mm[25]. A smaller single institution screening trial using multidetector-row CT demonstrated a sensitivity of 100% for polyps 10 mm and larger, but in that study only three patients had polyps of that size[26].

Three large multicenter trials comparing multidetector-row CTC and fiberoptic colonoscopy for detecting polyps in patients undergoing colorectal cancer screening have been published[27–29]. In the first study (Pickhardt *et al.*), the sensitivities of CTC and colonoscopy for adenomatous polyps at least 10 mm in diameter were 94% and 88%, respectively. In the second study (Cotton *et al.*), the sensitivities of CTC and colonoscopy for detecting patients with polyps at least 10 mm in diameter
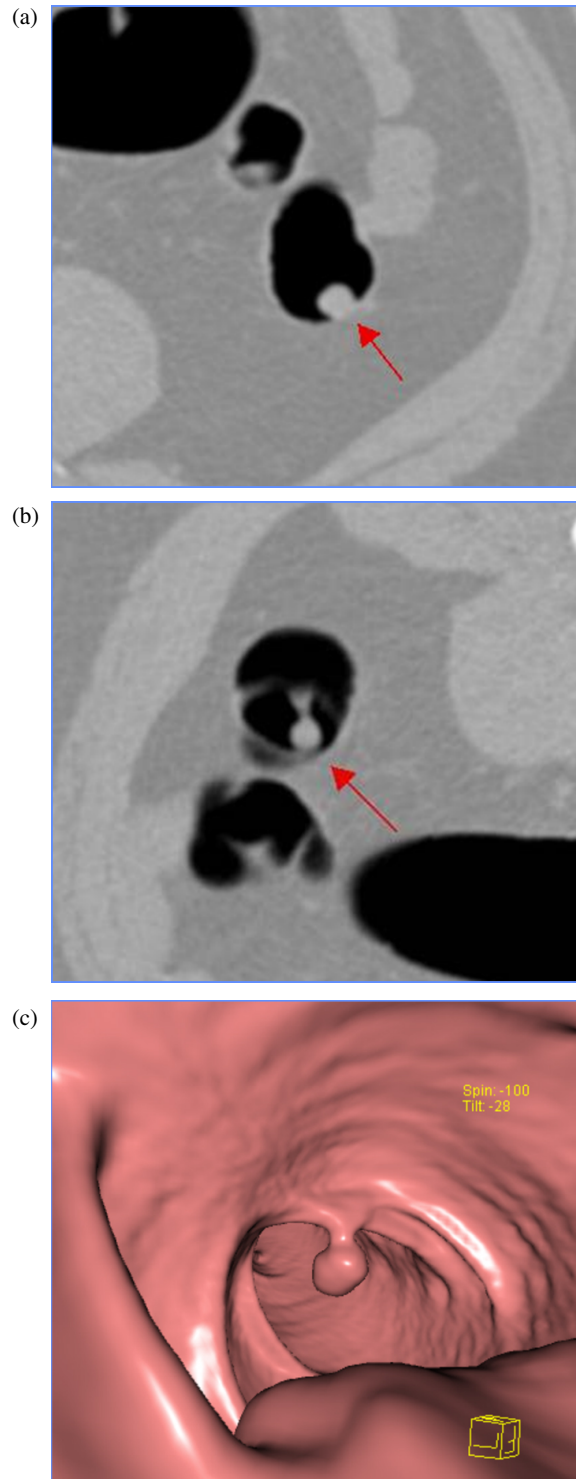
Figure 3   **Pedunculated descending colon polyp. (a) A transaxial 2D image acquired with the patient in the supine position shows a 9 mm polyp (arrow) that appears sessile. (b) A transaxial 2D image acquired with the patient in the prone position demonstrates that the polyp (arrow) arises from a haustral fold and is pedunculated. (c) The corresponding 3D endoluminal view with the patient in the prone position also demonstrates the pedunculated nature of the polyp.**

were 55% and 100%, respectively, and in the third study (Rockey *et al.*) 59% and 98%, respectively. Thus in one study, CTC had a very high sensitivity and outperformed colonoscopy [27], whereas in the other two studies CTC had a low sensitivity, and colonoscopy outperformed CTC by a significant margin [28,29]. These discrepant results may be related to differences in study design and reader experience. In the study by Pickhardt *et al.*, the readers used a primary three-dimensional endoluminal evaluation of the colon, whereas all other studies have used a primary two-dimensional evaluation. In addition, that study employed stool and liquid tagging (discussed later in this article) as part of the bowel preparation of all patients, whereas the other two studies did not employ stool and liquid tagging. Furthermore, the study by Cotton *et al.* suffered from inadequate reader training. Only one of the nine centers involved in that trial had substantial prior experience with CTC, and the only requirement to be a reader was performance of at least 10 CTC procedures (without any test of accuracy). For the institution in that study with prior CTC experience, the sensitivity for polyps ≥ 10 mm was 82%, compared with 24% for the other eight institutions. Also, the study by Cotton *et al.* used two and four detector-row CT scanners, whereas the other two studies used four and eight detector-row scanners.

Current technical issues, controversies and developments

Visualization methods

CTC data are viewed interactively at an image review workstation and can be viewed in two-dimensional (2-D) or three-dimensional (3-D) formats. For 2-D imaging, the reviewer generally scrolls through the image dataset in transaxial, coronal and sagittal planes. For 3-D imaging, the reviewer views the colon from an endoluminal perspective and navigates the entire length of the colon in both directions to avoid missing polyps on the back side of haustral folds. Until the study by Pickhardt *et al.* [27], all published CTC studies had employed a primary 2-D evaluation of the data, with 3-D endoluminal evaluation limited to problem solving and lesion confirmation. However, recent advances in workstation software have transformed 3-D endoluminal navigation of the colon from a cumbersome, time-consuming technique to one that can be performed relatively efficiently. Consequently, many radiologists now use a primary 3-D endoluminal approach as part of their routine CTC image review. Investigational studies currently in progress are evaluating the relative value of 2-D and 3-D image review.

Bowel preparation

In most CTC trials, the investigators have used the bowel preparation prescribed by the gastroenterologists involved in the study. The most common bowel preparations prescribed are a polyethylene glycol solution or sodium phosphate plus bisacodyl. With both preparations residual fluid may be left in the colon at the time of the CTC examination. The polyethylene glycol solution, in particular, tends to produce a large amount of residual colonic fluid, which can obscure a large portion of the colon wall and hide polyps [44]. This problem can be reduced by adding to the bowel preparation oral iodinated and barium contrast agents, which are incorporated into any residual fluid or stool. Residual stool can thus be distinguished from a polyp based on its high density, and polyps can be identified within a pool of residual fluid and fecal matter because of the higher density of the fluid and stool [45]. In an additional step, the high density residual fluid and stool can be removed from the images electronically [46], but this technique can result in subtraction artifacts and is not yet widely available.

Potentially, the use of stool and fluid tagging with or without the additional step of electronic subtraction could enable CTC to be performed with either a reduced cathartic bowel preparation or no cathartic preparation at all [47,48]. A study of CTC without cathartic preparation in over 200 patients demonstrated a sensitivity of 95.5% for polyps 8 mm and larger [48]. The feasibility of such a technique, if confirmed in subsequent studies, could have a major impact on colorectal cancer screening. It is likely that many more individuals would be willing to undergo screening if the requirement for a cathartic bowel preparation were eliminated.

Radiation dose

For clinically indicated diagnostic CT examinations, the benefit to the patient generally outweighs the potential risk from the use of ionizing radiation. However, if CTC is to be used as a screening procedure for patients at average risk of colorectal cancer, the radiation dose must be minimized to maintain the appropriate benefit-risk ratio. Fortunately, CTC can be performed with a relatively low radiation dose because of the inherently high contrast between the colon wall and the gas within the bowel lumen. Studies have demonstrated the feasibility of performing CTC with an effective mA-s (milliampere-seconds) of only 10–50, enabling a complete supine and prone examination to be done with a total radiation dose of approximately 1.0–6.0 milli-Sieverts (mSv) [41,49,50]. Two studies have demonstrated the potential feasibility of even further dose reductions down to 0.2–1.0 mSv [51,52]. A recent study reported that even with the use of a relatively high dose CTC protocol, the estimated absolute lifetime cancer risk associated with the radiation exposure from a CTC

examination would be approximately 0.14% for a 50 year old and approximately, 0.07% for a 70 year old, a large benefit-risk ratio[53]. These estimated risks can be reduced substantially with lower dose protocols like those described above.

Extracolonic findings

The imaging volume for a CTC examination includes the entire abdomen and pelvis as well as the lung bases. Thus one potential advantage of CTC is the ability to demonstrate extracolonic abnormalities that are of potential clinical importance. Studies have demonstrated that 5%–23% of individuals undergoing CTC have potentially important extracolonic findings, 3%–16% undergo further imaging to evaluate the extracolonic findings, and 1%–3% undergo surgery because of the findings[20–24,27]. Thus, on the one hand, this capability of CTC can have an important impact on an individual patient's health. On the other hand, however, the ability to detect extracolonic findings adds to the overall cost and morbidity of the colorectal cancer screening process, because many patients undergo additional medical procedures for what are proven to be benign or falsely positive findings.

Computer aided diagnosis

Computer aided diagnosis (CAD) for CTC is an automated process that detects configurations of the colon wall that might represent polyps. It is a method that has the potential to increase the diagnostic performance of radiologists in detecting polyps and cancers at CTC and to decrease the variability of diagnostic accuracy among readers without significantly increasing the reading time[54,55]. Preliminary studies have demonstrated that CAD programs are capable of identifying some polyps missed by CTC readers, but at the expense of false-positive findings[56]. Such studies indicate that CAD has the potential to reduce perceptual errors with a relatively low false-positive rate, but further improvements in the technology are required. Some of the current challenges faced by CAD researchers are optimizing the tradeoff between sensitivity and specificity, developing programs that detect polyps in patients who have undergone stool and fluid tagging, and insuring that the programs are robust even when ultra-low radiation dose CTC techniques are used.

Obstacles to widespread use of CTC for colorectal cancer screening

Several obstacles to the widespread use of CTC for colorectal cancer screening are evident. The most important obstacle is that the cost of CTC as a screening procedure is not covered by the vast majority of third party payers. Currently in the United States, individuals who undergo CTC for screening purposes pay for the study themselves. Thus, a large percentage of individuals needing colorectal cancer screening cannot afford CTC. Other important issues related to the widespread use of CTC for colorectal cancer screening are the need for reader training and the limited opportunities currently available to acquire it. Experience with CTC trials has taught us that interpretation of these examinations is associated with a learning curve. A retrospective multicenter study demonstrated a trend of better diagnostic performance with more reader experience[57]. How many CTC studies one needs to read before being considered competent and what type of CTC training should be required are issues that have not yet been resolved.

Other challenges

Several additional questions regarding the clinical implementation of CTC as a primary colorectal cancer screening examination need to be resolved[58]. What is the appropriate patient population for CTC screening? What size polyps should be reported? What size polyp threshold should trigger a conventional colonoscopy? What is the appropriate CTC follow-up interval? How should extracolonic findings be reported? These questions and others will require further study and consensus[59].

Conclusion

CTC is an exciting and rapidly evolving technology that shows great promise in the detection of colonic polyps and cancers. Although sensitivities for polyp detection with CTC have varied, one large multi-institutional screening trial has demonstrated excellent diagnostic accuracy for CTC, comparable to that of fiberoptic colonoscopy. Less impressive results for CTC in two other multi-institutional screening trials may be attributable to inadequate reader training and other study design differences. Future screening trials will help clarify the relative roles of 2-D and 3-D image evaluation and likely will establish fluid and stool tagging as important components of the CTC examination. It is likely also that computer aided diagnosis (CAD) will become an integral part of the CTC image review process, further improving the sensitivity of CTC in polyp detection and reducing interobserver variability. Numerous studies already have demonstrated the feasibility of performing CTC with a very low radiation dose.

Further research is needed to determine the feasibility of performing CTC without a cathartic bowel preparation. If feasible, the lack of a cathartic bowel preparation coupled with the relative ease and noninvasiveness of the CTC examination might encourage many more

individuals to undergo colorectal cancer screening, which in turn would result in many saved lives. An important remaining obstacle to the widespread use of CTC for colorectal cancer screening, however, is the lack of coverage of screening CTC by most third party payers, making it an examination that most individuals cannot afford. The results of further clinical trials will play an important role in determining whether professional medical organizations and third party payers will endorse CTC as a legitimate screening test for colorectal cancer.

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Lower gastrointestinal tract tumours: diagnosis and staging strategies*

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Abstract

In patients with colorectal cancer, accurate assessment of tumour extent within and beyond the bowel wall and detection of lymph node and distant metastases are of paramount importance in planning the surgical approach, in deciding whether neo-adjuvant chemotherapy or radiation therapy is necessary, and in determining the risk of tumour recurrence and overall prognosis. The utility of MDCT, MR, transrectal ultrasound, PET, PET/CT is discussed and recommendations for cost-effective imaging in these patients are presented.

Keywords: Colon CT; colon MR; colon ultrasound; colon cancer; colon cancer staging.

Introduction

Colorectal cancer is the third leading cause of cancer worldwide, accounting for nearly 10% of the estimated 700 000 000 invasive cancers occurring annually. There is substantial international variation in incidence rates but these tumours are most prevalent in North America, Europe, and other areas of the world with similar lifestyles and dietary habits. Despite an improved understanding of the development of colorectal cancer and the technical ability to alter its natural history in a large proportion of average and high-risk patients, this cancer remains deadly. Earlier detection of polyps and cancer, aggressive surgery for the primary tumour, and improved multimodality treatment for metastatic disease can improve the prognosis of this neoplasm[1–5].

Screening and diagnosis

The screening for colorectal cancer is one of the most important and controversial public health issues of the day. Questions to be answered include: who to screen? how to screen? how often to screen? when to begin screening? what is the size of the precursor lesion to be targeted?

Table 1   TNM staging system for colorectal cancer

0	Tis	N0	M0
I	T1, T2	N0	M0
II	T3, T4	N0	M0
III	Any T	N1, N2	M0
IV	Any T	Any N	M1

There are a number of screening techniques available for detecting cancers and polyps of the colorectum (Fig. 1):

(1) faecal occult blood test

(2) flexible sigmoidoscopy

(3) air contrast barium enema

(4) optical colonoscopy

(5) computed tomography (CT) colonography

(6) magnetic resonance (MR) colonography.

Since complete visualization of the colon is necessary, the faecal occult blood test and flexible sigmoidoscopy are inadequate examinations. The art of the air contrast barium enema is rapidly fading because of referral patterns and lack of interest. CT and MR colonography

Figure 1 **Colorectal cancer detection. The three major radiologic methods are the air contrast barium enema (A), CT colonography (B), and MR colonography (C).**

appear poised to become competitive with optimal colonoscopy without the need for sedation and only minimal risk of perforation. With developments in faecal tagging, computer aided detection (CAD) and electronic cleansing, CT colonography may become the primary screening test for average risk patients because a rigorous cathartic will not be necessary.

Staging

Once the diagnosis of colorectal cancer has been established by whatever method, accurate staging is of paramount importance in planning the surgical approach, in deciding whether neoadjuvant chemotherapy or radiation therapy is necessary, and in determining the risk of tumour recurrence and overall prognosis. The TNM staging scheme for colorectal cancer is shown in Table 1.

A number of imaging examinations have proven useful for colorectal cancer staging:

(1) multidetector CT

(2) MRI

(3) endoluminal MRI

(4) transabdominal ultrasound

(5) transrectal ultrasound

(6) intraoperative ultrasound

(7) positron emission tomography (PET)

(8) PET/CT.

T-staging

T staging (Fig. 2) assesses the depth of tumour invasion into the wall of the colon, surrounding serosa, fat, and adjacent organs. Transrectal ultrasound is superior to transrectal MR in depicting the depth of mural invasion for rectal neoplasms and both modalities are superior to MDCT and conventional MR. PET and PET/CT have only a limited role in this aspect of tumour staging.
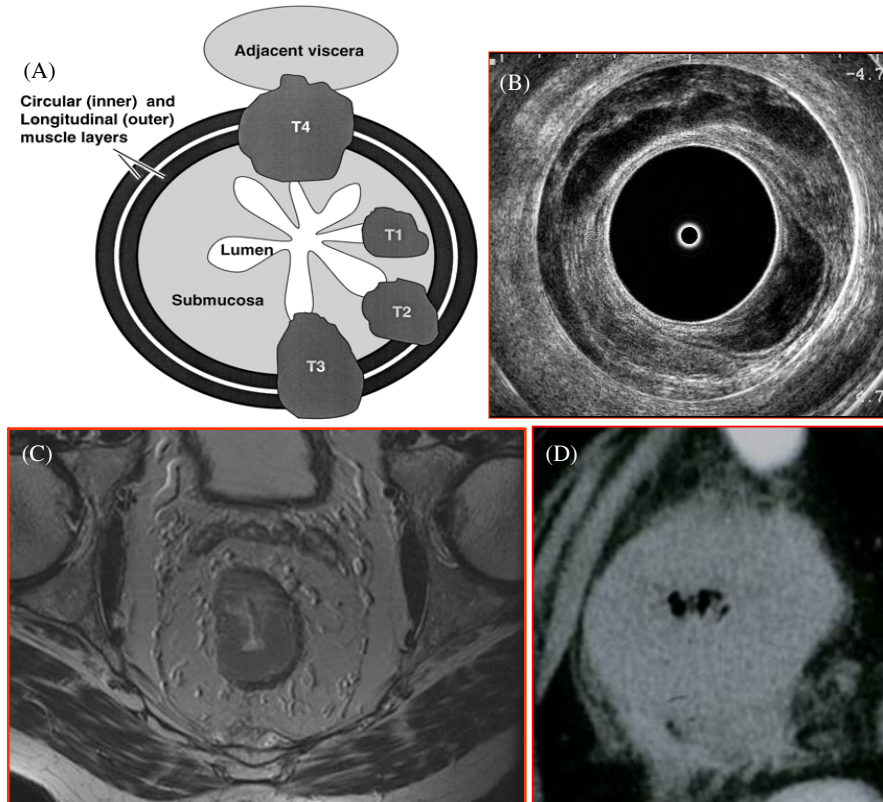
Figure 2 **T staging of colorectal cancer. (A) Schematic drawing. T1, tumour extends into submucosa; T2, tumour extends into muscularis propria; T3, tumour extends through the muscularis propria into the subserosa; T4, tumour extends directly into other organs or tissues. (B) Transrectal ultrasound shows a T1 rectal cancer. (C) Axial MR image demonstrates at T2 rectal cancer. (D) CT shows a T3 cancer of the ascending colon.**
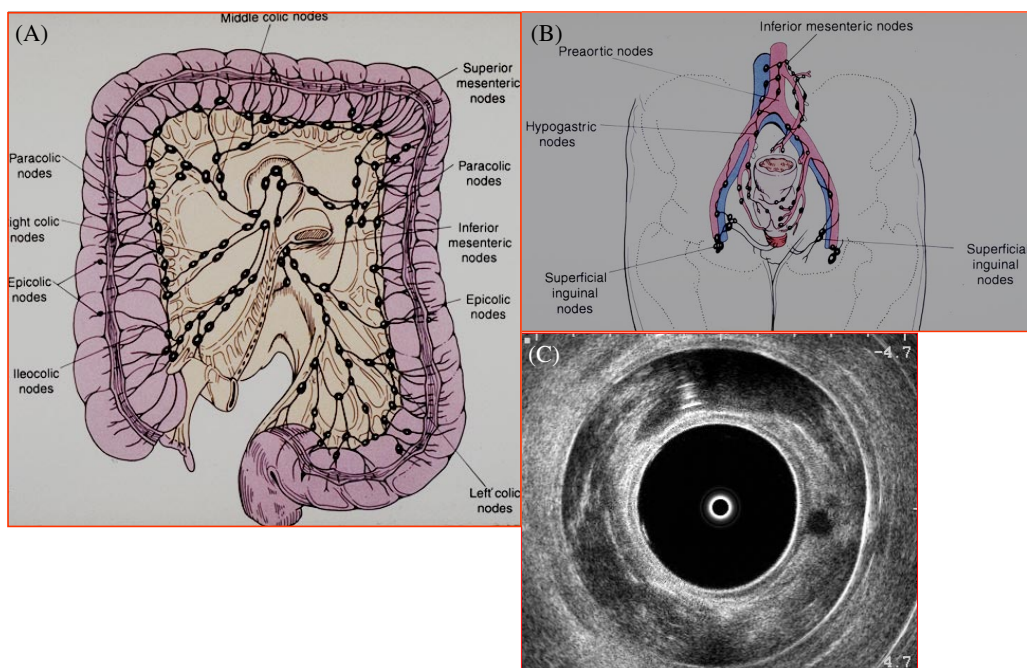

Figure 3 **N staging of colorectal cancer. (A) Schematic diagram depicting the four levels of colonic lymph nodes. (B) Schematic diagram showing lymph node groups typically involved in rectal and anal cancer. (C) Transrectal ultrasound demonstrates a spherically shaped hypoechoic lymph node at 3 o'clock.**

N staging (Fig. 3)

CT and MR detection of malignant lymphadenopathy has traditionally been based on size criteria. Lymph nodes greater than 1 cm are considered abnormal. Unfortunately size criteria are based only on statistical probability. In reality, many nodes smaller than 1 cm are malignant, and nodes larger than 1 cm are caused by reaction to a number of benign inflammatory conditions. Accordingly, CT and MR cannot reliably differentiate benign from malignant adenopathy.

Transrectal ultrasound is superior to MDCT, conventional MR and transrectal MR in the depiction of local rectal adenopathy. PET/CT is superb for detecting regional and distant adenopathy.
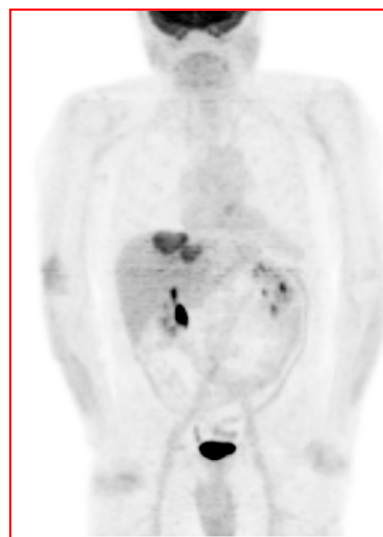
M staging

Once colorectal cancer has become invasive, there are five major routes of metastases that can be assessed with imaging: (1) direct invasion; (2) lymphatic permeation and dissemination; (3) venous embolization; (4) transperitoneal seeding; (5) intraluminal implantation.

MDCT is the standard means of M staging in most situations. It is superior to transabdominal ultrasound and MR in depicting omental, mesenteric and peritoneal disease. PET/CT appears to be the most accurate means of globally evaluating the chest and abdominal cavities for metastatic tumour. Intraoperative ultrasound appears to be the most sensitive technique in the depiction of liver metastases (Fig. 4).

Figure 4   **PET scan showing metastatic disease to the liver.**

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Colorectal cancer: the role of PET/CT in recurrence

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Abstract

Many imaging modalities and scanning techniques, such as contrast enhanced CT, MRI and FDG-PET, are available for assessment of recurrent colorectal carcinoma. In addition, integrated PET/CT is becoming increasingly available. Intuitively, a synergistic combination of scanning characteristics sounds promising. However, the exact clinical value has not yet been fully established. The role of PET/CT image fusion must be weighed carefully against other available modalities. In this review we evaluate the potential of combined PET/CT in recurrent colorectal carcinoma. When available, PET/CT currently appears the diagnostic tool of choice. In the near future, combined PET/MRI may further enhance the diagnostic algorithm.

Keywords: *PET; PET/CT; colorectal cancer; recurrence detection; restaging.*

Introduction

Early detection of recurrent colorectal carcinoma has become more important in the past decade, as the treatment options for localized disease have improved significantly. However, aggressive locoregional interventions (e.g. partial liver resections, radiofrequency ablation (RFA) of liver metastases, resections of pulmonary metastases) are as of yet considered futile in the presence of metastases elsewhere[1]. Therefore, detection of tumour sites throughout the body is needed with high sensitivity and specificity. For patient management with regard to invasive therapy, accurate information about the local extent of the tumour is also necessary.

Tumour visualization is traditionally performed using anatomical imaging techniques such as computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI). Functional imaging may be of additional value. Visualization of metabolism with [^{18}F]fluoro-deoxyglucose positron emission tomography (FDG-PET) is a valuable tool for detection of primary and recurrent colorectal cancer[2–4]. Tumour sites may be detected throughout the body with high contrast resolution. However, exact localization and demarcation of lesions with PET is hindered by its relatively low spatial resolution, and lack of anatomical reference.

The added value of simultaneous contemporaneous FDG-PET and CT has been demonstrated[5]. As a next step, the theoretical benefit of the joint capabilities of CT (anatomical reference) and FDG-PET (accurate tumour detection) have led to the practice of fusion of the images obtained by PET/CT. Although promising[6–8], the technique is relatively new and has limited availability. Furthermore, PET/CT image fusion may suffer from artefacts, and the exact clinical value has not yet been fully established. Therefore, the role of PET/CT image fusion must be weighed carefully against other more widely available modalities.

Integration of PET and CT

When considering the combination of PET and CT, different methods of fusion are available. The most prevailing approach today is 'visual fusion', where two scans are held side-by-side for comparison and correlation. Discrepancies between PET and CT may be resolved with this established technique. When further uncertainties persist, integration of the images can prove to be of additional value. But before attempting to integrate PET and CT images, some specific issues must be considered[9].

Scanning characteristics

Tissues appear differently on PET and on CT images. CT demonstrates anatomy with high spatial resolution, but with low contrast resolution for soft tissues. On the other hand, PET visualizes pathological sites with high contrast resolution, but spatial resolution is limited to 4–7 mm, and surrounding normal anatomical structures are hardly visualized. Due to these characteristics, discrepancies may exist between CT and PET images. Benign lesions may appear unequivocal on CT but may be negative on FDG-PET (e.g. cysts, haemangioma, scar tissue), while intensely FDG-positive lesions may be imperceptible on CT (e.g. local recurrence, liver metastasis). These characteristics complicate visual recognition and correlation. Furthermore, positional differences may exist between PET and CT because of repositioning and/or accidental voluntary motion. Organs may be displaced or changed in size (e.g. bowel motion, gastric emptying, bladder filling between PET and CT scanning). Also administration of furosemide may contribute to such discrepancies. The main problem is respiratory mismatch. PET is acquired during free breathing due to the duration of the scanning procedure (20–60 min), resulting in slightly blurred images in the upper abdomen. For correlation purposes, CT acquisition must be adapted to match these images by scanning during either free breathing or timed unforced expiration[9]. Failure to do this correctly will result in serious localization errors, as the diaphragm (including lower lung fields and upper abdominal organs such as the liver) will be relatively displaced.

Software fusion of PET and CT

When separate CT and PET images are available these may be integrated using specialized software. In such

procedures certain preconditions need to be met. Identical positioning is a prerequisite. The issue of artefacts due to breathing motions needs to be addressed by breathing instructions. The time gap between scans must be limited, in order to avoid discrepancies due to disease progression (or regression) during the interval. Specific software and operator experience are needed. On the whole, the procedure is lengthy, logistically complex, and it has a serious risk of registration errors. Some authors do report adequate results using software fusion, even in the region of the liver[10], but others strongly disagree[11]. It must at least be accepted that the bladder region—and possibly the whole abdomen—has a limited accuracy in image registration.

Integrated PET/CT scanning

A so-called hybrid scanner consists of separate CT and PET scanners placed in line, which acquire scans consecutively without repositioning of the patient. Fusion of images obtained by these two modalities is often referred to as 'hardware fusion', although this term ought to be reserved for situations where multiple images are acquired by a single detector system at the same time. 'Hardware' PET/CT fusion as currently available reduces (but not fully eliminates) many of the above-mentioned positioning problems, but the need for an adequate breathing protocol remains. Other problems such as bladder filling and bowel motion are reduced to acceptable levels. When compensating for all sources of errors, a fusion error below 10 mm is generally achievable in the abdomen[12]. In specific cases this accuracy may not be reached, for example when a patient is not able to comply with breathing instructions. This source of error is important when considering the liver, as the result may be misplacement of liver lesions in the lung or vice versa, albeit in a low percentage of scans[13].

When using a hybrid PET/CT scanner, the CT images can be used for attenuation correction of the PET images. Although convenient, as the total scanning time can be reduced by ±35%, any artefact in the CT images may cause secondary artefacts in the PET images. Examples of such artefacts are false-positive hotspots related to attenuating metal such as prosthesis or clips[14], and hotspots related to intravenous/oral contrast[15]. Further discrepancies between the PET images and the CT images may result from bowel movement[16], or when the patient accidentally moved between the two scans.

Balancing the benefits

Integration of PET and CT can provide synergistic benefit regardless of the technique applied. Hybrid PET/CT is more expensive than software fusion, but it delivers a fast, logistically easy and more reliable image correlation. A definitive advantage of hybrid PET/CT is

that visual fusion and software fusion may be impossible or inadequate when demanded *ad hoc*[11]. In the case of unexpected findings, integrated PET/CT scanning will provide adequate images, while software image fusion is likely to result in suboptimal results.

Interpretation

While fused PET/CT images do appear straightforward, the above-mentioned characteristics indicate that the images may not be easy to interpret. The true benefit of integrated PET/CT not only depends on integration of images, but also on the integration of expert opinions. Therefore, it is strongly advised that joint reading sessions take place with the radiologist and nuclear medicine physician with the appropriate clinical input from clinical oncologists and/or surgeons.

PET/CT in detection of recurrent colorectal carcinoma

In the follow-up of colorectal carcinoma, or in suspected recurrence (e.g. detectable CEA level, residual or newly formed tissues), the clinically relevant questions to be answered include: where are the potentially malignant tissues localized, is a specific lesion malignant or not, and what is the local extent of a specific lesion? An important role of imaging is to guide the rational use of additional invasive diagnostic procedures (e.g. liver biopsy, colonoscopy, etc.). A second role is demarcation of lesions to guide locoregional therapy. The role of PET/CT in relation to other imaging modalities depends on the indications for the procedure.

Local recurrence

CT is not very accurate for early detection of local recurrence of colorectal carcinoma, due to the distorted local anatomy after operation. Selzner *et al.* demonstrated a sensitivity of only 53% for CT, and a much better sensitivity for FDG-PET of 93%[7]. Such excellent sensitivity in detection of local recurrence also applies in the evaluation after external beam therapy[17]. The lack of anatomical reference hampers exact localization and evaluation of the extent of local pathology on PET alone. Since these data are essential when considering therapeutic intervention such as re-excision or irradiation, PET/CT may be of great value. An example of local recurrence detection and localization is provided in Fig. 1. Therefore, for the detection and evaluation of local recurrence, it is advised to perform PET/CT when available rather than PET alone.
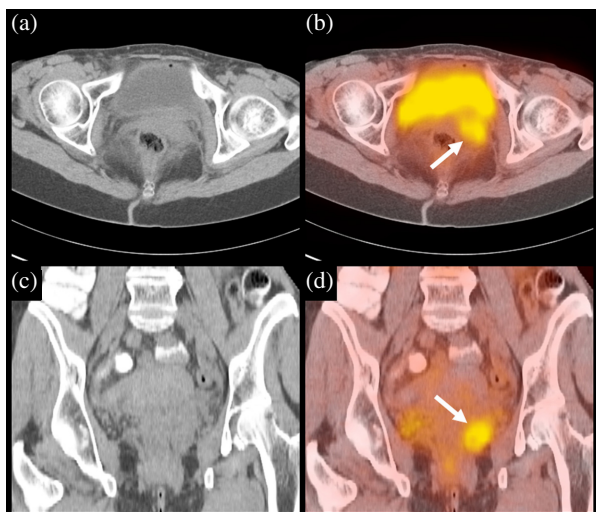
Figure 1 **Image fusion of contrast-enhanced CT and FDG-PET. The images show axial and coronal slices of CT (a, c) and PET (b, d) through the abdomen. On the CT images, the pelvic recurrence is difficult to appreciate due to extensive tissue masses. Within these masses, the PET image clearly shows a pathological lesion consistent with local recurrence of malignancy behind the bladder (white arrow). Image fusion with CT provided sufficient anatomical reference to guide a surgical approach.**

Lymph node metastases

Abdominal lymph node metastases from colorectal carcinoma tend to be small. Many involved lymph nodes are below 1 cm in diameter, thus explaining the poor sensitivity of CT. Some of these small metastases can be detected by FDG-PET, albeit with a poor sensitivity of 29%, but with a high specificity of 88% [18]. Problems arise when a hotspot on PET may correlate with several anatomical structures including activity excreted in the urinary tract, blood vessels and bowel polyps, or be the result of physiological bowel uptake. In these cases, PET/CT can adequately identify a hotspot, and settle the diagnosis. Fig. 2 illustrates PET/CT localization of a pathological lymph node.

Liver metastases

Ruers *et al.* demonstrated that FDG-PET as a stand-alone modality improves diagnostic work-up in patients with liver metastasis when added to conventional diagnostic imaging. Furthermore, it has an impact on and improves therapeutic management [4]. Integrated PET/CT can provide further value especially in the postoperatively distorted liver with scar tissue and artificial materials, where sensitivity and specificity are relatively low for both CT and MRI [19,20]. After local ablative therapy, PET may detect recurrence of liver metastasis earlier than

CT [3,21], but correlation with CT is needed for more exact localization [8]. Conversely, CT may be false-positive at the rim of the lesions because of hyperperfusion after RFA, while FDG-PET remains reliable [22]. MRI using enhancement with manganese containing contrast may further improve detection of liver metastases and provide additional information on the nature of liver lesions [23]. Fig. 3 demonstrates that FDG-PET is not affected by scar tissue and artificial materials. For the detection of liver metastasis after hepatectomy a sensitivity of 100% and specificity of 89% was demonstrated for PET/CT, while the specificity of contrast enhanced CT dropped to 50% for this specific patient category [7]. An example of recurrent metastasis in the liver resection area, not recognized on CT and MRI but detected by FDG-PET and localized by image fusion, is shown in Fig. 4. For the evaluation of liver metastases, PET/CT appears to be the technique of choice.
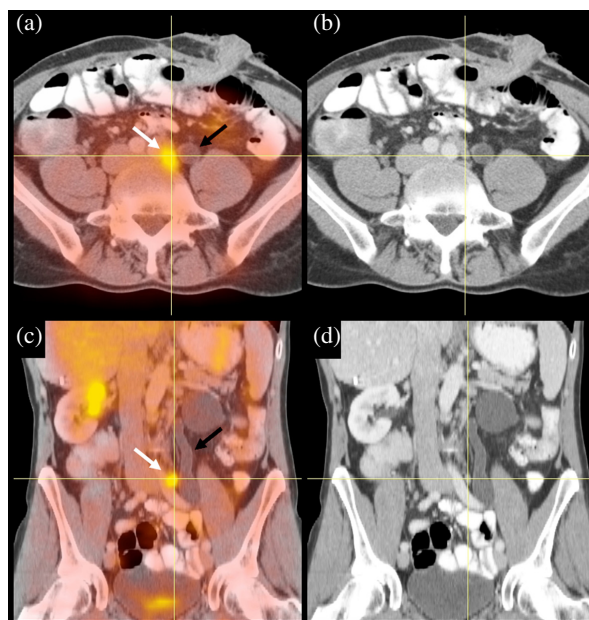

Figure 2 **Image fusion of contrast-enhanced CT and FDG-PET. The images show transverse slices (a, b) and coronal slices (c, d) through the abdomen of a patient who previously underwent primary resection of a sigmoid carcinoma. The PET image clearly showed a pathological lesion (white arrow), but the cause remained unclear as no clear lymph node was found, and the dilated ureter suggested another explanation (black arrow). Image fusion with CT could demonstrate correlation with a lymph node that was overlooked before.**

Extrahepatic metastases

Whole body imaging as a standard procedure is a major benefit of FDG-PET, thus providing information on extrahepatic metastases, which has a direct impact on patient management. Lai *et al.* demonstrated that 29%
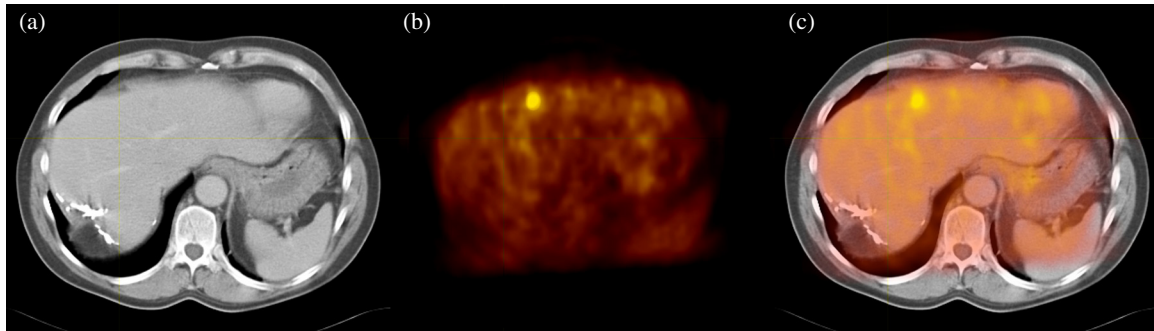
Figure 3   **Image fusion of contrast-enhanced CT and FDG-PET. The images show transverse slices of the abdomen through the liver, from CT (a), PET (b) and PET/CT (c). PET shows a clear metastasis in the ventral border of the liver that is hardly visible on CT, indicating the high sensitivity of FDG-PET, but also illustrating the need for correlation with anatomical imaging. Furthermore, the image illustrates that FDG-PET is unaffected by the extensive residual changes and surgical clips posterior in the right liver lobe, after partial liver resection.**

of patients with liver metastases appeared inoperable because FDG-PET detected extrahepatic metastases [2].
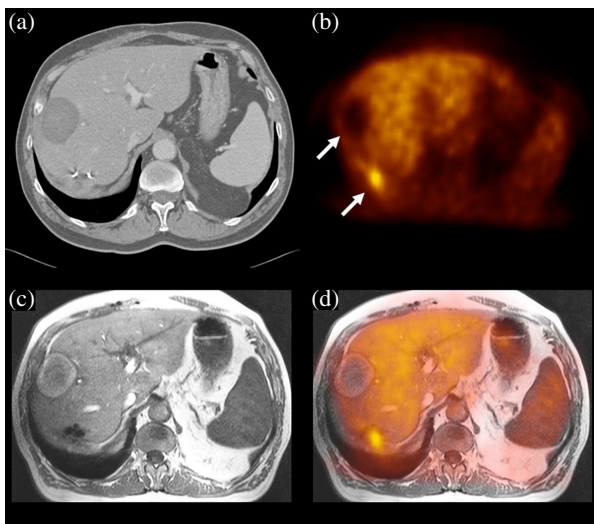

Figure 4   **Software image fusion of CT, MRI and FDG-PET. The images show transverse slices through the liver of a patient who underwent prior RFA treatment (upper arrow) and liver resection for liver metastasis of colon carcinoma. Both CT (a) and MRI (c) are difficult to interpret in the region of the surgical clips. The PET image (b) clearly shows a recurrent liver metastasis (lower arrow), which could be localized only after image fusion with MRI (d). This permitted guided locoregional therapy.**

In recurrent colorectal carcinoma, most extrahepatic distant metastases will be pulmonary. Detection of these metastases is of particular importance as surgical intervention may still be possible, by combining liver surgery with resection of a limited number of pulmonary lesions [24,25]. Both CT and FDG-PET have demonstrated high sensitivity for pulmonary lesions, but PET may

be particularly helpful in discriminating benign from malignant lesions [26]. FDG-PET has also demonstrated added value in detection of other extrahepatic distant metastases such as bone metastases [27]. In unexpected extrahepatic lesions detected by PET, exact localization may be very hard without correlative anatomical imaging as provided by PET/CT. This also applies to the detection of unexpected second primaries, which may occur in approximately 1% of cases [28].

Lesion characterization

Regardless of the type of lesion as seen on imaging, differentiation of benign from malignant disease is always a challenge. Both CT and FDG-PET can contribute to the final diagnosis, but a combination of both modalities delivers the strongest diagnostic tool [29,30]. Given this asset, we consider PET/CT the best option when atypical lesions need to be characterized at the highest possible level of accuracy, especially in cases where a definitive diagnosis through pathology cannot be obtained.

Future developments

The true clinical value of FDG-PET—and the added value of the application of PET/CT scanners—should ideally be clarified by prospective clinical trials. But a true comparison between separately acquired PET and CT images, visual fusion, software fusion, and integrated PET/CT images can hardly be achieved, as this implies the acquisition of multiple scans with a high cumulative radiation burden to the patient. As a result of the rather limited scientific evidence, the current choices for implementation of FDG-PET in diagnostic strategies appear rather random, and large variations exist among institutes. This also applies to the application of

hybrid PET/CT scanning for various specific questions. Nevertheless, scientific evidence about the diagnostic values of PET and PET/CT are increasing rapidly, and eagerly awaited.

New PET tracers

Besides visualization of glucose metabolism with FDG, PET scanning may be applied for *in vivo* non-invasive evaluation of other tissue characteristics using tracers other than FDG. For example, DNA synthesis activity may be quantitatively assessed using [^{18}F]fluoro-deoxy-L-thymidine (FLT), as a reflection of cell proliferation and tumour growth[31]. The exact clinical applicability of FLT, as well as several other tracers currently under investigation, is at present even less clear than the utility of FDG-PET. It is to be expected that many new tracers will accumulate selectively in pathological lesions, and will show poor or no normal tissue activity. These images may therefore be uninterpretable without integration of PET and CT.

Integration of PET and MRI

The combination of PET and CT is not the only possibility, nor is it a perfect solution. On theoretical grounds it is preferable to combine PET with (functional) MRI, for better soft tissue evaluation with a relatively low radiation burden. An excellent example of the application of PET/MRI fusion is accurate delineation of malignant lesions in the liver, to allow optimally guided locoregional therapeutic intervention. The PET/MRI fusion procedure is already possible when using software fusion; an example is shown in Fig. 4. It is expected that integrated PET/MRI scanners will become clinically available in the next 5 years.

Conclusions

The combination of PET and CT is currently proving itself as a valuable tool in the diagnostic strategy for detection of recurrent colorectal carcinoma, especially in the field of staging before surgical re-interventions. This has an impact on diagnosis and choice of therapy. The application of separate PET and CT is not to be considered 'second class', when visually correlated adequately. Although unbiased supporting literature is currently limited, hardware integrated PET/CT using a hybrid scanner does seem to be able to improve diagnostic accuracy over correlated stand-alone PET and CT in several specific cases. As software image fusion is prone to error, this technique should be used with caution and should be reserved for specific applications.

The largest benefit from integration of PET and CT images depends on the integration of knowledge. This implies joint consensus reading by a multidisciplinary team. This will be of even greater importance when new PET tracers and new MRI applications enter the clinical field.

With the increasing availability of integrated PET/CT scanners, it is to be expected that clinical use and experience will rapidly expand. However, a critical review of indications and added value of these techniques are a prerequisite for rational application and maximum diagnostic yield.

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Liver metastases of colorectal cancer: US, CT or MR?

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Abstract

In contrast to other extrahepatic malignancies many colorectal cancers can be cured even when there is metastatic spread to the liver. The diagnosis of liver metastases relies totally on imaging to decide which patients may be surgical candidates. The diagnostic value of ultrasound with contrast agents, multidetector CT and MR imaging with non-specific gadolinium chelates and liver-specific contrast agent is discussed. Nowadays MDCT is the mainstay of staging and follow-up of these patients, because it provides good coverage of the liver and the complete abdomen and the chest in one session. MR imaging has been shown to be superior to helical CT in the preoperative assessment of colorectal liver metastases. Large studies are needed to define the role of MDCT vs. MRI staging in patients referred for resection of liver metastases.

Introduction

Metastastic disease to the liver is a very common clinical situation in oncology. The liver is one of the most common sites of metastatic spread of epithelial cancers, second only to regional lymph nodes. The true prevalence of metastatic disease is unknown, but approximately 20%–25% of patients with colorectal cancer have liver metastases at the time of diagnosis. Studies based on autopsy results showed that up to 70% of colon cancer patients have liver metastases at autopsy.

The early detection of liver metastases is of utmost importance in patients with cancer. In general, the presence of liver metastases indicates non-resectability of the primary tumour for oncologic reasons, except for tumour palliation (i.e. to relieve obstruction of the gastrointestinal tract). In these patients, chemotherapy is the method of choice. For a few malignancies, resection of liver metastases has been shown to improve the survival of the patients[1]. Colorectal cancer is one of a few malignant tumours in which the presence of limited synchronous liver metastases (i.e. occurring at the time of diagnosis of the primary tumour) or metachronous metastases (occurring after diagnosis of the primary tumour) warrants surgical resection. Exact knowledge of the number, size, and regional distribution of metastases is essential to determine their resectability. Based on the number and localization of the liver metastases and considering all other clinical parameters of the patient, only about 30% of colorectal patients with liver metastases may undergo resection. However, the 5-year survival of these patients is between 30% and 48% in comparison to a survival of less than 5% of patients with liver metastases not amenable to liver surgery[1–4].

It is the task of radiologic imaging to evaluate the liver to assess the presence or absence of liver metastases in surgical candidates and to evaluate the success of chemotherapy in others. Although transabdominal sonography is widely used to assess the liver, it has some limitations: it needs considerable operator expertise and often reveals equivocal results in patients with (chemotherapy-induced) fatty infiltration of the liver. These problem cases are then often referred for a computed tomography (CT) or magnetic resonance (MR) imaging examination. With the introduction of multidetector CT (MDCT) imaging, the use of CT in oncologic patients to 'screen' for lung, liver, and lymph node metastases in the body has dramatically increased. MR imaging is still limited in the anatomic coverage, although the recent introduction of multi-channel MR coils with wider coverage and the moving-table MR technique has re-established the 'competitiveness' of MR with MDCT with regard to patient throughput. One of the advantages of MR in liver imaging is the better soft tissue contrast, which reveals better characterization of focal liver lesions in question. The development of a liver-specific MR contrast agent has further improved the diagnostic yield of MRI in lesion detection and characterization.

In this review, the role of MR imaging with non-specific gadolinium chelates and liver-specific MR contrast agents is demonstrated. The CT and MR imaging features of liver metastases is presented. Emphasis is placed on the role of MRI in comparison to CT in the assessment of patients with extrahepatic cancer and limited liver metastases, who are surgical candidates.

Ultrasound

The development of ultrasound (US) contrast agents (SonoVue®, Bracco, Milan, Italy; Levovist®, Schering, Germany, etc.) has dramatically increased the potential of sonography in the assessment of focal liver lesions. The use of contrast agents allows perfusion mapping of focal lesions, thus enabling characterization of focal lesions. In the study of von Herbay *et al.*, the use of contrast-enhanced US (CEUS) improved the sensitivity and specificity of US in the differentiation of malignant vs. benign from 78% to 100% and from 23% to 92%, respectively[5]. Bernatik *et al.* investigated the diagnostic yield of CEUS vs. helical CT in the detection of liver metastases. CEUS showed 97% of lesions seen by CT[6]. However, no histologic standard of reference was available to determine the true sensitivities of both methods. CEUS now has an established role in the evaluation of equivocal lesions seen at conventional US and in monitoring treatment response after local therapy
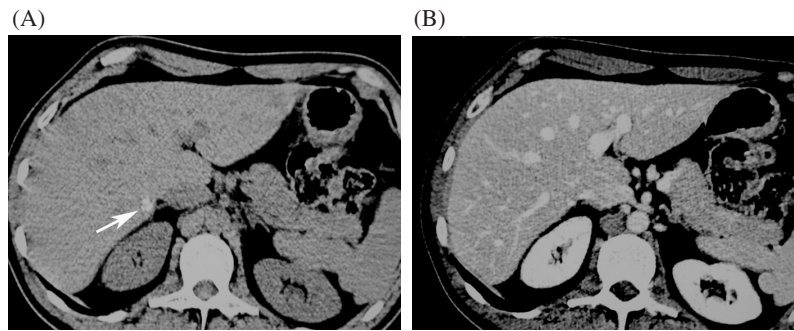
Figure 1   **Value of unenhanced CT in detection calcified metastases. (A) The unenhanced scan clearly depicts a small calcified metastasis (arrow), which turned out to be vital tumour at surgery. (B) The lesion is hardly seen in the portal-venous phase.**

of tumours. However, due to the limitations in the visualization of segmental distribution and 3D-shape of metastases, it is limited in the preoperative assessment of patients with colorectal liver metastases. However, contrast agents have improved the diagnostic yield of intraoperative US with an impact on surgical strategy[7].

Multidetector-row CT

Helical and multidetector-row CT (MDCT) are the most commonly used imaging modalities for detection and characterization of hepatic metastases. Using a helical CT with a single detector row and a scanning speed of 0.8–1 s per rotation, it is impossible to scan the entire liver in a truly arterial phase, before contrast material inflow from the portal vein is encountered.

With the advent of four-row detector scanners in 1998, coverage of the liver within one breathhold of 10–14 s became feasible, which decreased the likelihood of motion artifacts due to breathing during scanning. Currently, 40–64-row MDCT scanners with 0.6 mm detector configuration are on the market. Rotation time has come down to 0.33 s with the latest generation. Therefore, the liver can be scanned with submillimetre collimation within one breathhold of not more than 2–3 s. Due to isotropic voxels, image reformation in any plane is possible without a loss of spatial resolution.

Several studies have assessed the value of using thin slices to improve detection of small metastases. In the study of Weg *et al.*, 2.5 mm thick slices were significantly superior to 5, 7.5 and 10 mm thick slices[8]. In the study of Kopka *et al.*, a slice thickness of 3.75 mm proved superior to 5 mm in terms of lesion characterization and superior to 7.5 mm in terms of detection and characterization[9]. When the slice thickness is decreased to 1 mm, no further improvement in lesion detection is seen, but there is a considerable increase in image noise with subsequent degradation of image quality[10]. Therefore a slice thickness of 2–4 mm is recommended for axial viewing. Not surprisingly, differences between

imaging protocols were most prominent when small liver lesions ($\leq$10 mm) were evaluated[9]. However, in addition to those 2–4 mm thick slices obtained for viewing, submillimetre slices are obtained for 3D-image reconstructions.

There has been an ongoing debate, how many scans are necessary for a CT examination of the liver. The value of an unenhanced scan lies primarily in the characterization of small lesions as being solid or cystic. However, in patients with colorectal cancer, liver metastases are calcified in 11% at initial presentation[11]. These lesions are much better seen on unenhanced scans than on portal-venous phase scans (Fig. 1). Arterial-phase scans are of great importance in the diagnosis of hypervascular metastases and in the differentiation between these lesions and haemangiomas, especially in case of early and completely enhancing haemangiomas. The increased temporal resolution of MDCT has led some investigators to add an early arterial phase to their protocols, which is only useful in patients with HCC, if ever[12]. Colorectal liver metastases are hypovascular in the vast majority, but arterial-phase scans may increase lesion conspicuity in a small number of cases (Fig. 2)[13]. Portal-venous phase scans are most reliable in detection of colorectal liver metastases, with a reported sensitivity of 85.1% for helical CT[14].

MR imaging

MR imaging is commonly used as the definitive imaging modality for the detection and characterization of liver lesions[15]. Use of MR units with a field strength of $\geq$1 T is preferable, and phased-array torso coils are now standard in body MR imaging. The standard MR imaging protocol should always include unenhanced T1- and T2-weighted and contrast-enhanced pulse sequences. In liver MR imaging a set of T1-weighted in-phase and opposed-phase gradient-recalled echo GRE images is acquired to assess the parenchyma for the presence of fatty infiltration or focal sparing of diffuse fatty infiltra-

tion. For T2-weighted imaging, the turbo-spin echo (TSE; or: fast spin echo, FSE) with fat suppression are preferred over the single-shot TSE pulse sequences, which lack inherent soft tissue contrast due to long echo trains. For detection of focal lesions a TE of approximately 80–100 ms is chosen. In addition, heavily T2-weighted pulse sequences with a TE of approximately 160–180 ms may help in differentiation between solid (metastasis, hepatocellular carcinoma (HCC), etc.) and non-solid lesions (e.g. haemangioma, cyst) (Figs. 3 and 4)[16,17]. After the acquisition of unenhanced pulse sequences, contrast-enhanced pulse sequences are always obtained.

Figure 2 **Need for bi-phasic contrast-enhanced scan for detection of mixed vascularity metastatic adenocarcinoma: the arterial-phase scan demonstrates hypovascular and hypervascular metastases (arrows). Incidental note is made of a large metastasis in the spleen.**

MR contrast agents

Nowadays, two different groups of MR contrast agents for liver imaging are available: First, the non-specific gadolinium chelates and second the liver-specific MR contrast agents. The latter group can be divided into two subgroups, the hepato-biliary contrast agents, and the reticulo-endothelial (or Kupffer cell) contrast agents.

Non-specific gadolinium chelates

The liver and liver-lesion enhancement patterns obtained with non-specific gadolinium chelates (extracellular contrast agents) are similar to those obtained with iodinated contrast agents used in CT. Several agents with similar properties are on the market, including gadopentetate dimeglumine (Schering, Berlin, Germany), Gd-DTPA-BMA (GE Healthcare, Oslo, Norway), Gd-DOTA (Guerbet, Aulnay-sous-Bois, France), and Gadoteridol (Bracco, Milan, Italy). The standard dosage of non-specific gadolinium chelates is 0.1 mmol/kg b.w. After i.v. bolus injection dynamic T1-weighted GRE sequences are obtained at least in the arterial phase, portal

venous phase and equilibrium phase (3–5 min post). Colorectal liver metastases are typically hypovascular. In the arterial phase, they are often isointense or minimally hypointense; maximum lesion-to-liver contrast is reached in the portal-venous phase, when a ring enhancement is present (Fig. 4)[18]. The equilibrium phase is important, because it helps with lesion differentiation (e.g. haemangioma vs. metastasis). Haemangiomas show persistent pooling of contrast material during the equilibrium phase, whereas most metastases appear hypointense or centrally isointense with peripheral wash-out of contrast material (Fig. 3)[17].

Liver-specific contrast agents

Hepatobiliary agents

Hepatobiliary agents represent a heterogeneous group of paramagnetic molecules of which a fraction is taken up by hepatocytes and excreted into the bile. Mangafodipir trisodium (Teslascan®, GE Healthcare) is taken up by hepatocytes and results in signal intensity increase on T1-weighted images (a so-called 'T1 enhancer')[19], and a fraction is also taken up by the pancreas, which has been used for pancreatic MR imaging[20,21]. Focal non-hepatocellular lesions (i.e. metastases) do not enhance post-contrast, resulting in improved lesion conspicuity (Fig. 5). Mangafodipir-enhanced MRI has been show to be superior to unenhanced MRI and helical CT for detection of liver metastases[21,22].

Gd-BOPTA (Multihance®, Bracco) and Gd-EOB-DTPA (Primovist®, Schering) are hybrid contrast agents, which carry a lipophilic ligand[23]. After i.v. bolus injection these agents show biphasic liver enhancement with a rapid T1 enhancement of the liver similar to that seen with non-specific extracellular gadolinium agents. Then hepatic signal intensity continues to rise for 20–40 min (Gd-EOB-DTPA) and 60–90 min (Gd-BOPTA), reaching a plateau after about 2 h because of hepatocytic uptake. This results in increasing contrast between liver and non-hepatocellular tumours[24].

Reticuloendothelial agents

All reticuloendothelial system (RES) agents are superparamagnetic iron oxide-based contrast agents (SPIO). They are predominantly phagocytosed by the Kupffer cells in the liver and the spleen and cause local field inhomogeneities, which result in shortening of T2 relaxation times and decreased signal intensity of liver tissue. Currently, two SPIO agents (Endorem®, ferumoxide, Guerbet; Resovist®, SHU 555A, Schering) are available. SHU 555A (Resovist®) can be administered as an i.v. bolus and dynamic T1-weighted sequences can be obtained to assess tumour vascularization. SHU 555A has fewer side effects than ferumoxide (Endorem®). After
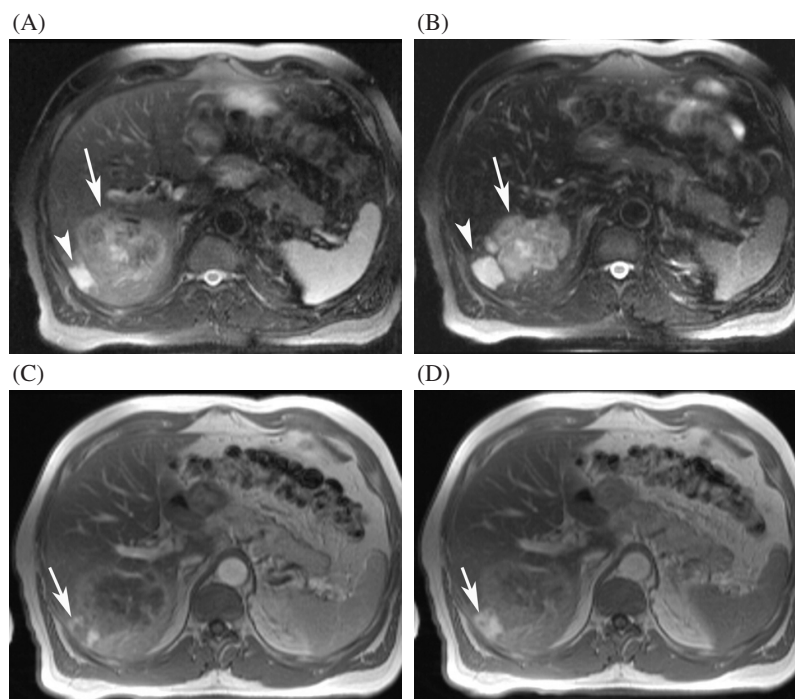
Figure 3   **Value of T2-weighted images and non-specific gadolinium chelates in lesion characterization in a patient with a history of haemangioma in segment 6. (A) The T2-weighted TSE image reveals a moderately hyperintense lesion, suggestive of a metastasis (arrow). There is a second small lesion adjacent to the metastasis, which is very hyperintense on T2-weighted images (arrowhead). (B) On the SPIO-enhanced image, there is better delineation of both lesions. (C), (D) The dynamic gadolinium-enhanced images in the arterial and the delayed phase show peripheral nodular enhancement with pooling in the smaller lesion, indicative of haemangioma (arrow). Patient had developed a colon cancer metastases close to this previously known haemangioma.**
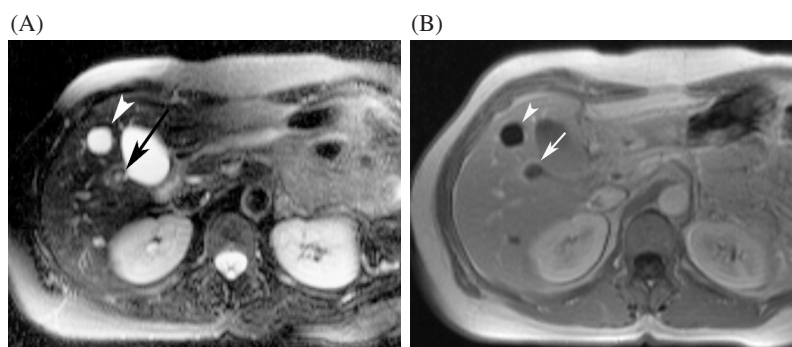

Figure 4   **Small metastasis and cyst: differentiation with T2-weighted TSE and non-specific gadolinium chelates. (A) The T2-weighted TSE image shows a small cyst, which is very bright (arrowhead). There is a second lesion, which is moderately hyperintense (arrow). (B) The gadolinium-enhanced T1-weighted GRE image shows lack of enhancement of the cyst (arrowhead). The other lesion displays a ring enhancement, which is suggestive of metastasis (arrow).**

SPIO administration, the liver parenchyma containing Kupffer cells shows a marked reduction in signal intensity on T2-weighted images, whereas liver metastases remain hyperintense on T2-weighted images. Thus, due to the decreased SI of normal liver and no signal loss of metastases, the lesion contrast is markedly improved on post-contrast T2-weighted images[25] (Fig. 6). RES agents are also useful in differentiation of metastases from focal liver lesions from benign hepatocellular lesions (such as focal nodular hyperplasia (FNH) or adenomas) and haemangiomas, because the latter show uptake of contrast material with subsequent
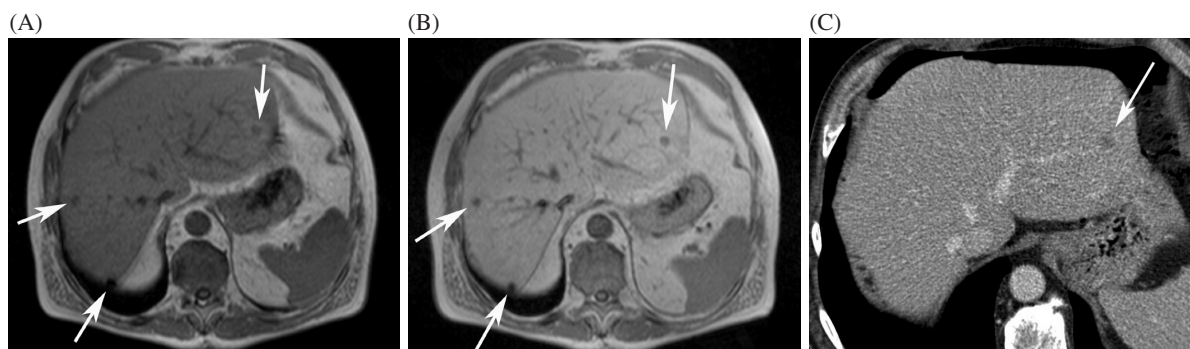
Figure 5 **Comparison of mangafodipir (Teslascan®)-enhanced MRI and CT. (A) Unenhanced T1-weighted MRI shows some lesions in the liver (arrows). (B) There is much better delineation of the metastases on the mangafodipir-enhanced images. (C) On the contrast-enhanced MDCT, only one metastasis in the left lobe is seen. The other lesions were also not seen on adjacent slices.**

signal intensity loss[25]. SPIO contrast agents have a predominant T2 effect, although there is also a T1 effect, which may be used for perfusion imaging of metastases.

Detection of liver metastases: which imaging modality?

In a time of limited resources in health care, there has been considerable debate which imaging modality offers the best non-invasive examination of the liver, offering both detection and characterization of local liver lesions. The use of multiple diagnostic modalities is both costly and time-consuming.

A meta-analysis has compared the diagnostic value of US, CT, MRI and PET in the detection of gastrointestinal cancer metastases derived from studies published in the literature[26]. Surprisingly, this meta-analysis found that FDG-PET (with CT) is the most sensitive method for detection of metastases, with a mean weighted sensitivity of 90%–92%[26]. However, several studies in this analysis assessed metastases per lesion, which yields lower sensitivities than studies assessing metastatic load per patient. Seventy-three percent of MR studies in this analysis used per-lesion analysis, whereas only 22% of PET studies did so. The reliance on a per-patient analysis in most of the PET studies is likely to inflate the sensitivity of this method (e.g. detection of only one of four metastases present would be considered a correct positive diagnosis). So, inhomogeneities of the studies analysed make it difficult to draw conclusions[26].

Accordingly, the issue of when to use which imaging method is still not solved. The answer likely depends on local equipment, availability, and operator expertise. MDCT scanning is well established and is often the first choice for a 'screening' liver examination at many institutions. The MDCT technique has improved small lesion detection by reducing respiration-related artifacts. Shortened scan time of MDCT enables exact multiphase scanning of the chest and abdomen with improved lesion

characterization, but increases the radiation exposure on the other hand. MDCT has the big advantage of 'one-stop-shopping' in imaging of the liver and extrahepatic disease (both abdominal and thoracic). This ensures that MDCT will continue to have an important role in staging and screening.

Several studies have reported MRI to be more sensitive and more specific than dynamic CT and helical CT. Ferumoxide-enhanced MRI has been shown to detect more, especially small, metastatic lesions than contrast-enhanced CT[27]. Small lesions, which are detected at a greater frequency with this technique, are particularly difficult to characterize exactly. Gadolinium-enhanced MRI may be helpful in characterization of these lesions, particularly for small haemangiomas, cysts, and biliary hamartomas. Liver-specific MR contrast agents are helpful in the differentiation between FNH and hypervascular liver metastases. The wide array of MR pulse sequences and MR contrast agents available makes MRI the most powerful tool for non-invasive lesion characterization[15].

Preoperative assessment of surgical candidates

The majority of liver metastases are non-resectable because of extrahepatic disease or extensive liver involvement. With increasing surgical expertise in liver resection, indications for resection of limited metastatic disease have expanded in recent years. To prevent unnecessary laparatomies in patients referred for surgery, meticulous preoperative assessment of metastatic liver involvement should be performed[27].

The ideal preoperative imaging modality should combine (1) high sensitivity and (2) high specificity, with a low false-positive rate for metastases detection and characterization. It should provide (3) precise anatomic information of the tumour location in relation to the major anatomic structures. In most oncologic centres,
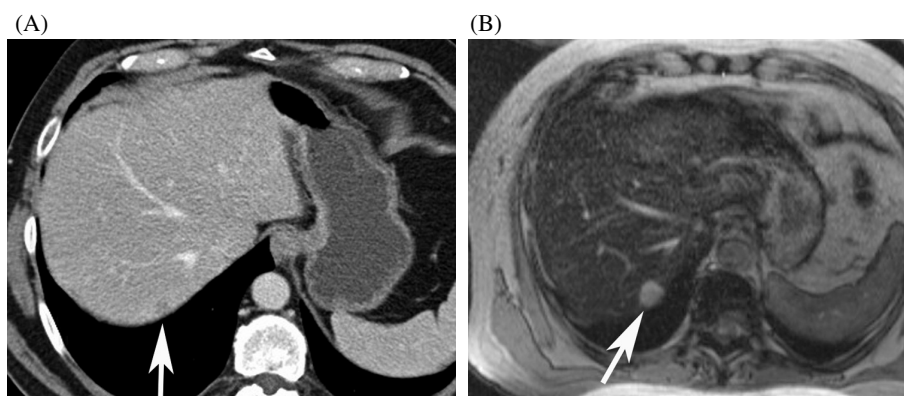
Figure 6 **Comparison of SHU 555A (Resovist®)-enhanced MRI and MDCT. (A) On the contrast-enhanced MDCT, a metastasis is only faintly seen (arrow). (B) The SHU 555A-enhanced T2-weighted image depicts a 1.5 cm metastasis in segment 7.**

contrast-enhanced CT and/or MRI are the mainstay of preoperative staging in patients with liver tumours. However, in the study of Zacherl *et al.*, helical CT either showed either false-positive and false-negative diagnoses in 42% of patients referred for surgery [28]. In comparison to preoperative staging the surgical strategy was changed by intraoperative US in 22.8% [28].

Recently, two prospective studies on the use of CT and MRI in surgical candidates with colorectal liver metastases have been reported [22,29]. Mann *et al.* compared mangafodipir-enhanced MRI helical CT in preoperative assessment of liver metastases for resectability [22]. He found MRI to be more sensitive than helical CT in the preoperative assessment of the resectability of hepatic lesions (Fig. 5). MRI detected significantly more lesions than helical CT (sensitivity 83% vs. 61%), but intraoperative US detected a few subcentimetre metastases not seen by MRI. The extent of metastatic disease was under- or overestimated in only 10% of patients by mangafodipir-enhanced MRI [22]. Van Etten *et al.* found the ferumoxide-enhanced MRI technique at least as accurate as CT during arterioportography (CTAP) in preoperative assessment of colorectal liver metastases [29]. Both methods were equivalent in 81% of patients, and CTAP showed more lesions in another 11%. However, this influenced further management in only 2%. In 8%, ferumoxide-enhanced MRI showed more lesions than CTAP, and this influenced the clinical decision in 4%, rendering these patients with widespread disease non-resectable [29]. Up to now no studies comparing MRI with MDCT have been performed.

In summary, contrast-enhanced multi-phasic MDCT is a robust and accurate technique to assess liver and extrahepatic disease in patients with colorectal cancer. In patients with limited metastatic disease to the liver, MR imaging enhanced with liver-specific contrast agents is recommended for preoperative assessment.

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