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Radiology in the Detection and Prevention of Colorectal Cancer

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Imaging techniques available for detection of colorectal cancer include barium enema, endoscopy, computed tomography (CT), ultrasound, magnetic resonance (MR) and immunoscintigraphy. Technical advances continue rapidly and prompt frequent re-evaluation of the optimal approach to management of these patients. Barium enema and colonoscopy are the main techniques for evaluation of symptomatic patients, although CT may well assume the predominant role within a few years. Variation in quality of barium enemas and colonoscopy poses a challenge for continuing medical education (CME) activities. Screening of asymptomatic individuals has to be considered separately for high, moderate and low risk population. Recommendations have to be made at present in the absence of evidence of effectiveness. Staging of disease pre-operatively is of limited value. Follow-up after surgery should be primarily clinical although endoscopy, CT, MR, ultrasound and immunoscintigraphy all have specific roles in the evaluation of patients suspected of harbouring recurrent disease.

Key words: radiology, endoscopy, colorectal cancer, screening, diagnosis
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TOOLS AVAILABLE

IMAGING METHODS for evaluation of colorectal neoplasms include barium enema, endoscopy,ultrasound, computed tomography, (CT), magnetic resonance (MR), and immunoscintigraphy.

Barium enema (double contrast)

This method can detect up to 98% of colorectal cancers, but detection rates between 75 and 95% are often reported [1–6]. Colonoscopy also has high potential sensitivity, but detection rates as low as 85% have been reported [5, 7]. Polyps of 1 cm diameter and larger are detected colonoscopically in 90% of cases (a fairly consistently reported figure), and on barium enema from 50 to 85% of cases [4, 8, 9]. Major centres tend to report 85% detection, and this figure is still controversial. Polyps of 6 mm or less are overlooked approximately 50% of the time colonoscopically, and in 60–75% of cases on barium enema, but fortunately are of little clinical significance [10]. Complications and fatalities are both more frequent with colonoscopy with mortality around 1 in 5000 [11]. Perforation occurs ten times more often with colonoscopy than with barium enema, but the mortality after such a perforation is three times as great as barium enema. Thus the overall mortality from colonoscopy is approximately three times higher than with barium enema. If barium enema discloses a significant polyp, colonoscopy will also be required. The choice between these two principal methods of detection, therefore, depends on both local skills of practitioners and the patient or subject population mix.

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Computed tomography (CT)

Routine CT examination of the abdomen seldom evaluates gastrointestinal lesions adequately, and a particular effort is required to detect and examine such lesions [12]. Principles to follow include (i) intestinal cleansing, opacification and distension; (ii) imaging during the arterial phase of an intravenous injection of contrast material; (iii) liberal use of thin section (5 mm) scans over the area of interest. Both spiral CT and intravenous glucagon or buscopan facilitate good CT imaging of intestinal lesions. Three-dimensional (3D) CT reconstruction with a spiral scanner has recently been applied to the colon and is very promising. A single breath hold scan of the abdomen is taken after thorough bowel cleansing, and optimal distention of the colon with air, and paralysis of the colon with glucagon. After 3D reconstruction, an algorithm permits a view of the colonic mucosa as seen from within the rectum—similar to the image seen endoscopically. Using a mouse, the viewer can then 'drive' around the colon to the appendix, turn round and 'drive back' inspecting the other side of the haustral folds. At any point, a click on the right button of the mouse provides an axial CT view of the abdomen and that position. This technique is still under development, but initial results indicate that the technique has the potential to replace barium enema (and colonoscopy) for detection of polypoid colonic lesions.

Ultrasound

Intense research is underway for development of intraluminal gut ultrasound contrast agents, and several fluids that are echo-free are under evaluation. Reports from Germany of trans-abdominal ultrasound detection of colon neoplasms, down to 5 mm, stimulated interest in ultrasound as a possible routine colon imaging tool for neoplasm [13]. However, this has not yet become widespread. Problems include the need for thorough

cleansing, the difficulty of removing enough gas from the colon, and the time required of an expert examiner to do a complete study. The CT 3D study mentioned above with only a 30 s scan time, will be hard to compete with. Endorectal ultrasound is, however, very promising. 5 and 7.5 MHz transducers are providing clinically useful evaluation of anal sphincter disease, and of rectal tumour invasion through the wall of the bowel [14, 15]. Higher resolution transducers on long cannulae are under development, and in theory could be inserted through colonoscopes for very high resolution ultrasonic evaluation of colon wall and adjacent structures (kidneys, ureters, pancreas). The clinical utility of this approach is unknown.

Magnetic resonance imaging (MR)

MR is still in evolution for application to colorectal cancer imaging. Intestinal cleansing is required for attempts at detection of tumour, and selection of luminal contrast agents is not yet settled. MR of the liver is as good as CT for metastasis detection, detecting some lesions overlooked by CT and missing some seen on CT [16]. Endorectal coil development is showing great promise for assessment of rectal tumours [17]. Detection and identification of lymph nodes as malignant has not yet reached clinical utility with either MR or CT, and for evaluation of masses found after surgery, a liberal use of fine needle biopsy is helpful.

Scintigraphy, positron electron tomography (PET) and monoclonal antibody imaging

PET scanning with 18F-fluorodeoxyglucose (FDG) was able to detect increased FDG uptake in recurrent cancer (focal soft tissue masses seen on CT) in all 11 patients in one study (MRI distinguished recurrent tumour from scar in 10 of the 11) [18]. Monoclonal antibody scanning (immunoscintigraphy) is also showing great promise. Fortunately, its strengths appear to be in areas of weakness of CT and MR [19, 20]: thus extrahepatic, extraintestinal metastases are well shown. The main use of this technology may, therefore, be in patients in whom carcinoembryonic antigen (CEA) is rising, but initial evaluations with ultrasound, CT or MR are negative or equivocal.

THEIR USE IN DETECTION IN SYMPTOMATIC PATIENTS

The variability in operator expertise, relative costs in different countries, and availability of equipment make it impossible to provide dogmatic recommendations on selection of imaging strategies. Nevertheless, guidelines with some caveats are possible and appropriate.

Patients suspected of having colorectal cancer may be offered barium enema, endoscopy or CT examination. MR is too expensive, inadequate at present, and also inadequately available. Ultrasound has not been shown to have adequate sensitivity. Barium enema is arduous for frail and elderly patients, and colonoscopy can be painful and difficult in patients who have adhesions from previous pelvic surgery. Gelfand and Ott have described a simplified technique which provides good quality double contrast barium enema films in elderly patients [21]. One paper has recommended CT as the initial investigation in frail elderly patients, based on a study of 36 such patients in whom colorectal cancer (CRC) was detected in all 6 patients on CT and in 5 of 6 on barium enema [22]. 11 of 21 patients preferred CT, and 2 preferred barium enema. CT provided four false positive reports of neoplasia, but also revealed pathology in 13 other patients in whom the information modified treatment decisions for some. The barium enemas and CT studies were performed by a mixture of trainees and staff, and were not optimised, so that results reflect general reality rather than potential for either technique (16 of the 37 enemas were of good quality). A comparison of optimised CT against optimal double contrast barium enema using Gelfand's simplified technique, and against colonoscopy would be a valuable guide to management in this group of patients.

Flexible sigmoidoscopy and faecal occult blood have no role as diagnostic tests in symptomatic patients, although flexible sigmoidoscopy has been advocated as a tool to direct patients to either colonoscopy or barium enema [23–25]. This may be particularly helpful when colonoscopy resources are strained.

Either colonoscopy or barium enema are appropriate investigations in symptomatic patients when good quality of both examinations is available. Barium enema will reveal adenomas in approximately 10% of symptomatic patients, and this rate can serve as a quality control. Barium enema will frequently fail to display some section of the colon adequately, most often the sigmoid in the presence of advanced diverticular disease, and in this situation radiologists should indicate their reserve in declaring such segments normal. Most missed cancers and large polyps are visible on the radiographs [5, 6, 26], and double reading of barium enema films should be becoming the norm in appropriate patient populations [5, 27].

Colonoscopy reaches the caecum in 55–95% of patients. Failed or incomplete colonoscopy should routinely be followed by barium enema to examine the right colon, and this can usually be performed 30 min after the colonoscopy. Air is usually used for barium enema and colonoscopy. Carbon dioxide provides greater patient comfort, and is, therefore, preferable [28, 29]. The increase in expertise in cross-sectional imaging has been accompanied by a decrease in the numbers of radiologists performing high quality barium studies, and the maintenance of high standards of barium fluoroscopy is a problem.

It is often difficult for a referring physician to make an informed decision on the quality of barium enemas and colonoscopy available, and factors other than quality usually direct referral practices. There is a need for routine local audit to guide selection when there is little to choose between competing technologies, and when both are highly operator-dependent.

THEIR USE IN SCREENING OF ASYMPTOMATIC SUBJECTS

There is a cascade of risk for colorectal cancer, but it is convenient to divide patients into high, medium and low risk for the purposes of this discussion. High risk patients are those in hereditary non polyposis colon cancer (HNPCC) or adenomatous polyposis coli (APC) families, and those patients with long standing total ulcerative colitis.

High risk

In APC, the disease is often discovered by presentation with symptoms of CRC or by serendipity, since one-third of new cases represent a new mutation. To screen a known family, flexible sigmoidoscopy and examination of the retina have been the mainstay. Once genetic marker detection becomes sufficiently reliable, flexible sigmoidoscopy will only be needed in the family members who have the mutant gene. For HNPCC family members, the major problem is identification since the Amsterdam criteria exclude those in small families. These families have a high preponderance of right-sided tumours, possibly of flat adenomas and probably of mucinous tumours

[30]. Screening should begin at 10 years younger than the youngest affected family member, and not later than 40 years of age. Some recommend starting colonoscopy screening every 2 years starting at age 25 years [31]. Others consider recommending prophylactic colectomy in HNPCC families. There is little information on how best to screen for endometrial cancer in these families, or whether to recommend prophylactic hysterectomy early: the incidence of endometrial cancer is 700 times greater than in the general population, but the tumours tend to be relatively low grade. Total hysterectomy and bilateral salpingo-oophorectomy, once the patient's family has been completed, has been recommended [32]. Hysterosonography, with its ability to show the thickness of the endometrium on each side of the uterus and to show endometrial polyps, may be the best screening tool. It is less invasive than D & C or aspiration cytology, but there are no data on which to base an opinion. Carcinoma of the stomach, small bowel and urinary tract are also integral components to the Lynch syndrome, and there is no evidence as to the merits of screening for these tumours.

Barium enema is probably not the ideal way to screen HNPCC families, since the incidence of adenomas is high, perhaps double that of the general population [32, 33], and many will need to return for colonoscopy. In addition, flat lesions are harder to detect radiologically. The adenomas tend to be large, often villous and likely to contain high grade dysplasia and there is anecdotal evidence that growth of CRC may be quite rapid in HNPCC families, so that 5-yearly screening will be inadequate for this group. However, it is even more important in this group that failed or incomplete colonoscopy be followed by barium enema to assess the right colon.

Screening of members of such families is hard to arrange in a systematic way if it is handled in an *ad hoc* manner. The construction of regional registries, linked nationally, is the only feasible approach to attempting to prevent the 5% or so of CRC that is represented by these families. The organisation of an effective approach to HNPCC is likely to be one of the most rewarding challenges in cancer prevention over the next decade.

Moderate risk

This includes first degree relatives of colon cancer patients, especially those with two colon cancers in the family or patients under 55 years, but who are not HNPCC families. St. John and Rozen have both shown that such individuals have approximately five times the chance of developing colorectal cancer as other members of the general population [34, 35]. Similar risk levels exist in individuals who have had one large adenoma removed, and those who have had one colorectal cancer in the remote past. At least three different strategies would all be reasonable to screen this group of patients: colonoscopy, double contrast barium enema, or full preparation with flexible sigmoidoscopy followed immediately by barium enema if the sigmoidoscopy is negative or shows polyps under 5 mm in diameter, but followed instead by immediate colonoscopy if the sigmoidoscopy shows polyps greater than 5 mm [25, 26]. Considerations such as availability of the technology, quality of local practitioners, costs and simple logistic factors can reasonably dictate which of the three strategies is chosen. Once it has been further developed, CT with 3D reconstruction will probably become the examination of choice for this group.

Low risk

Low risk includes the remainder of the general population, especially those individuals who have reached the age of 50 years in whom the question of screening for CRC may be discussed. The risk of colorectal cancer is around 4–6% in the industrialised world. Colonoscopy at worst might kill 1 in 5000 people screened, and the calculations in favour of colonoscopic screening of 50-year-old executives with normal risk are very dubious. There are no data to permit an unequivocal recommendation of any form of imaging for screening of the normal risk population. Colonoscopy screening research programmes are being started to examine the risks and benefits. Eddy has calculated potential cost-effectiveness of screening the general population, and barium enema every 5 years was the most cost-effective approach, with flexible sigmoidoscopy adding little [37]. Atkin and colleagues have discussed the value of a once in a lifetime flexible sigmoidoscopy at age 55–60 years [38], and demonstrated theoretical benefits of prevention of 5500 colorectal cancers out of 18 000 currently diagnosed each year, at a cost in the U.K. of £30 million, or £8500 per cancer death prevented. Calculations on cost–benefit of flexible sigmoidoscopy, barium enema and colonoscopy screening of normal risk individuals are very sensitive to variations in local expertise and local cost.

With such variability in quality of barium enema and colonoscopy, there must be concerns in establishing widespread screening for high risk groups without some control of quality. Similar concerns with breast screening have led to the establishment of high quality screening centres in many countries. It may be appropriate to apply the same thinking to colorectal cancer screening.

THEIR USE IN STAGING OF DISEASE

Staging of newly diagnosed CRC involves the determination of depth of invasion of tumour, presence of lymph node metastases, and presence of remote metastases, particularly in the liver. CEA determination may be suggestive of extensive disease, but pre-operative certainty requires the use of ultrasound, CT, MR or immunoscintigraphy.

Extension through the bowel

Ultrasound is the best method to answer this question, but only a few reports are available by enthusiasts. These reports show that endosonography is better than CT at predicting perirectal spread, although less effective at demonstrating disease invading the pelvic side wall. The equipment is not widely in use, and results from early studies may not be sustained. Nevertheless, results from 13 studies on the accuracy of rectal endosonography showed a range from 81 to 93% with a mean of 88% [39]. Overstaging is more of a problem than understaging, as obliquity of the beam giving an angled view of the tumour in relation to the bowel wall gives an exaggerated impression of tumour penetration. In addition, the inflated balloon presses benign lesions into the wall of the bowel, and as the muscularis propria becomes difficult to follow it may seem that it has been penetrated. Ultrasound interpretation is harder after radiotherapy as clear delineation of the layers of the bowel is lost—in one study this reduced staging accuracy from 86 to 47% [15]. The current roles for endosonography include:

1. Assessment of small well differentiated cancers being considered for local resection.
2. Examination of large villous adenomas to detect carcinomatous invasion which would be a contraindication to submucosal resection.
3. Evaluation of low lesions for prostatic invasion.
4. Examination of a rectal mass or possible local recurrence, and guidance for submucosal biopsy.

CT is reliable for confirming spread of advanced tumours through the bowel wall, but less useful in excluding such spread. Two large studies have studied CT in staging colorectal cancer. Sensitivity for detection of local extension was 61 and 55%. Most errors were in downstaging local infiltration. Sensitivities for nodal metastases were 26 and 73%, and for hepatic metastases 73 and 79% [12, 40].

MR results are in flux as new coils and pulse sequences are developed. Endorectal coils in particular are producing spectacular images, and can show the layers of the bowel wall [17]. CT at present is superior to MR for detecting local spread, other than in the rectum, but still inadequate.

Lymph node metastasis detection and other extrahepatic metastases

Here endorectal ultrasound has limitations as it can access only perhaps half the lymph nodes removed at surgery for rectal cancer, and cannot distinguish reactive from malignant enlarged nodes. MR is no better than CT at present for detecting nodal metastases: both are limited because of their inability to determine whether an enlarged node is reactive or malignant. Immunoscintigraphy seems to be more sensitive than either CT or MR for nodal metasases (74 versus 75% for CT pelvic disease in one study) [41]. The early enthusiasm for CT in pre-operative staging has not been sustained because of poor accuracy in identification of lymph node metastases and inability to determine local spread. Particular caution should be exercised in describing local invasion in cachectic patients. Conversely, scarring and inflammation may mimic the periclonic fat streaking that is the hallmark of early extracolonic spread.

Metastatic liver disease

Liver metastases are often discovered on ultrasound examination, but the sensitivity of transabdominal ultrasound for small lesions is too low for it to be used to exclude metastases. An attempt at certainty for exclusion of metastases requires a prolonged work-up as described below, and is not indicated pre-operatively for newly diagnosed colorectal cancer. Is there any value in a pre-operative search for hepatic metastasis? Up to 50% of CRC patients will have liver metastases, of whom 5–10% may have a surgically resectable liver lesion. The usual approach is to resect the primary tumour, assess the liver at the time of surgery, and enter apparently cured patients into a follow-up routine that will include serum CEA level estimation.

THEIR USE IN FOLLOW-UP AND DETECTION OF RECURRENCE OF DISEASE

Follow-up after resection of colorectal cancer is for three purposes: (i) treatment of postoperative complications; (ii) early detection of a second primary tumour; and (iii) early detection and treatment of local recurrence or metastasis from the original carcinoma.

Early detection of a second primary

This detection is currently by barium enema or colonoscopy, and perhaps by 3D CT in due course when it is generally available. This surveillance should be early and repeated to ensure that the colon is clear [42], and then every 5 years to detect metachronous tumours. Endoscopic ultrasound can detect anastomotic recurrence after anterior resection of rectal cancer, but its value in surveillance is unknown.

Detection of recurrence

93% of all recurrences present within 4 years, and distant recurrence is more common than local disease. The liver is affected in 13%, lymph nodes in 4%, lung in 3%, peritoneum 2%, bones 0.9%, and brain 0.7% [43]. What data there are on the value of routine postoperative CT are not promising. A CT study on 66 patients after curative surgery found that CT heralded tumour recurrence in only 2 of 33 documented recurrences [42] and others have also documented lack of utility to follow-up CT scanning. However, radiologists would like to see every rectal cancer patient have a CT 3 months after surgery to provide a baseline. This is because the CT scan at 9 months in a patient with pelvic symptoms is often difficult to interpret as an apparent pelvic mass may be either postoperative scarring or recurrent tumour. A 3 month baseline CT scan, it is argued, will expedite the management for those patients who present with symptoms later. There are now data that do show better diagnostic accuracy for interpretation of pelvic findings when there has been an early postoperative CT scan [40, 44]. Apart from this one baseline CT after resection of rectal cancer, there appears to be a consensus that initial follow-up should be clinical, supplemented by CEA and perhaps liver function tests. When these raise concern that there may be recurrence, then imaging is indicated.

When the CEA level rises, the liver should be explored first since this is the most common site for metastases. There are several possible approaches, and Ferrucci has noted that several questions have to be answered for the liver [43], and by extension to any suspected metastases. Are tumours present? How many are there? Are all visible lesions tumours? and, if the lesions are cancerous, are they amenable to surgical resection? To answer the first question one may try ultrasound, CT, MR, and immunoscintigraphy. Ultrasound is readily available and inexpensive. If ultrasound scan shows multiple hepatic metastases no further imaging is required. If ultrasound is negative or equivocal, CT and MR may be considered. A comparison of several CT and MR techniques evaluated for detection of liver secondaries, published in 1989 [44], showed that sensitivities of arterial portography CT (CTAP), delayed CT, lipid-enhanced CT and T1 weighted MR were all comparable at around 85% for all lesions, and 95–97% for lesions over 2 cm in diameter. However, T1 weighted MR was superior, as it had the lowest false positive rate. MR is not readily available in all centres, and a strategy is, therefore, needed for detection and evaluation of hepatic metastases if ultrasound has not resolved the issue. The two common scenarios are: first, a patient with an apparent single metastasis, or two in the same lobe, referred from another hospital for consideration of resectional hepatic surgery; and second, a patient with rising CEA in whom ultrasound or CT examination of the liver has been negative.

Assessment of possible resectable hepatic metastasis

The aim of investigation is to spare the majority of patients unnecessary surgery, by demonstrating the absence of extrahepatic disease and that two contiguous segments of liver can be left in place after resectional surgery. If MR is readily available it should be used. If not, then a graded approach to CT and preoperative assessment may be considered, and can be offered on a 1 day outpatient basis [45]. CTAP is followed by selective angiography of coeliac and superior mesenteric arteries, followed after 4–6 h by delayed CT. Finally, if the lesion still appears resectable two further imaging methods may be useful and will prove a further proportion of patients to be unresectable.

Immunoscintigraphy can demonstrate extrahepatic lesions overlooked by CT or MR, although this is still a controversial area. One study with radioimmunoscintigraphy was disap-

pointing [46] with a low sensitivity (23%), and low positive (33%) and negative (37%) predictive value in detecting extrahepatic recurrence. However, others have found sensitivity for detecting pelvic recurrence to be 75% compared with 57% for CT, and figures for other abdominal extrahepatic sites were 66% and 34%, respectively. Moreover, specificity was greater with immunoscintigraphy. A range of results have been reported with immunoscintigraphy. Gasparini and colleagues [47] report detection rates for local recurrence of 87–100% with Indium 111 FO23C5, and Patt and associates [48], studying 20 patients with elevated CEA and negative radiology, correctly identified the tumour in 19. A wide range of results have been reported with immunoscintigraphy, and it is not clear what place it will have in routine practice. Finally once surgery is undertaken, a few further unsuspected metastases will be found outside the liver, and intra-operative ultrasound will detect a few more intrahepatic lesions overlooked by pre-operative imaging.

Patients with rising CEA and negative imaging

Pulmonary deposits are not rare. Chest X-ray will show most, but is less sensitive than CT. Dual voltage chest radiography is becoming available with computed radiography units and will probably greatly increase the perceptibility of pulmonary lesions on chest X-rays. More often the occult metastasis will be in the abdomen, usually in the liver. Routine investigation will include ultrasound followed by CT or MR imaging depending on availability. If these are negative, immunoscintigraphy may again be helpful. A prospective study of 13 such patients with Indium 111-labelled anti-CEA monoclonal antibody detected tumour recurrence or metastasis in 11. There was one true negative result, and one failure to detect a second caecal primary carcinoma [49].

Follow-up summary

Routine imaging in follow-up has not been shown to be useful, and is very expensive [42, 50–54]. However, clinical follow-up with selective use of imaging when abnormalities are found does detect more recurrent cancers at an earlier and more resectable stage [55]. The routine imaging that is desirable includes (i) endoscopy to examine the anastomosis and to determine that the residual colon is clear of synchronous lesion, repeated once a year and then 5-yearly; and (ii) in rectal cancer patients a 3 month postoperative baseline CT study to facilitate interpretation of any pelvic changes found on a later CT.

If focal symptoms develop, investigation is directed towards the site of symptoms. If CEA or liver function tests cause concern, chest X-ray and abdominal ultrasound may suffice to stop investigation if multiple lesions are discovered. A negative result or an apparent single lesion will direct further study through MR if readily available, or progressive CT (CTAP, angiography, delayed CT). CT will be preferred to MR if pelvic pathology is discovered or suspected. Endorectal coil MR or endoscopic ultrasound may have a role if recurrence after anterior resection of the rectum is suspected. Multiple findings will again make further imaging unnecessary. A negative result may warrant chest CT or immunoscintigraphy, and resective surgery offers the opportunity for final evaluation of the liver by intra-operative ultrasound.

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