Imaging in colorectal cancer

Introduction

Worldwide, one million patients are diagnosed with colorectal adenocarcinoma annually, making it one of the most common malignancies. In the UK, colorectal cancer is the fourth most common malignancy after breast, lung and prostate cancer, with 41 581 new cases in 2011 (Cancer Research UK, 2014).

Around 30–40% of patients presenting with metastatic disease will have metastases confined to the liver at the time of diagnosis (Lafaro et al, 2013). Taking into account patient and technical factors, 20–30% of these patients will have potentially resectable lesions (Simmonds, 2000). In the UK, almost 10% of patients diagnosed with colorectal cancer will die within a month of the diagnosis, which is poor compared to survival results in Europe (National Cancer Intelligence Network, 2012). Therefore early detection and accurate initial staging with multidisciplinary team management is central to improving patient outcome.

From the initial diagnosis of metastatic colorectal cancer, patients without treatment only have a mean survival of 8 months, with a median improvement of only 3.7 months with chemotherapy (Simmonds, 2000). However, when the liver is the only site of colorectal metastasis, the patient may still have a good prognosis after complete surgical resection, or other targeted liver therapy such as radiofrequency ablation or selective internal radiotherapy treatment. Therefore it is essential that any pre-surgical imaging identifies the extent of tumour within the liver and the presence of any extrahepatic disease to allow accurate staging and localization as this can improve survival to 30% at 5 years (Simmonds et al, 2006).

Gold standard treatment of hepatic metastases in a patient with colorectal carcinoma is complete resection of the metastases which increases 5-year survival from 5% to between 22 and 67% (Adams et al, 2013). Incomplete resection, on the other hand, has no impact on survival, hence the importance of accurate, sensitive imaging.

Liver metastases are commonly evaluated by computed tomography with subsequent further interrogation by magnetic resonance imaging, ultrasound and/or positron emission tomography as locally determined.

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Screening

Screening aims to decrease mortality through earlier detection of lesions. In the UK, the 5-year survival rate of patients diagnosed at the earliest stages of colorectal cancer is over 90% compared to 6.6% in patients diagnosed with advanced disease (National Cancer Intelligence Network, 2012). The current UK national screening programme for colorectal cancer offers screening to both men and women aged 60–69 years once every 2 years and uses the faecal occult blood test, which reduces mortality (Hardcastle et al, 1996; Kronborg et al, 1996).

Patients testing positive for faecal occult blood should then undergo colonoscopy. However, because of issues such as compliance and tolerance, colonoscopy may not be suitable for all patients. An alternative method of assessment in high-risk patients with positive faecal occult blood within screening programme is computed tomography colonography (National Institute for Health and Care Excellence, 2011).

Currently computed tomography colonography or virtual colonoscopy (*Figure 1*), which uses volumetric computed tomography data and reconstruction software to produce three-dimensional images of the colon (Johnson and Dachman, 2000), shows promise as a potential tool with a high sensitivity (93.8%, 95% confidence interval 82.8–98.7%) and high specificity (96.0%, 95% confidence interval 94.8–97.1%) for adenomas >10 mm (Pickhardt et al, 2003).

Following bowel cleansing and/or faecal tagging, carbon dioxide or air is insufflated via the rectum, and the abdomen and pelvis are scanned within a single breath hold with prone and supine acquisition. However, computed tomography also carries the risks associated with radiation exposure (Brenner and Hall, 2007). Furthermore, the technique is limited by the adequacy of bowel preparation and gaseous insufflation, and there are problems with detection of flat lesions (van Gelder et al, 2005). Current available data indicate that the risk of perforation from computed tomography colonography is lower, from 0.005–0.03%, compared to 0.06–0.19% in colonoscopy (Berrington de Gonzalez et al, 2010).

Diagnosis

Colonoscopy remains the key diagnostic investigation in colorectal cancer as it can directly visualize the whole colon and allows tissue biopsy or removal of smaller polyps at the same time. Larger known polyps can also be removed on a second colonoscopy via endoscopic mucosal resection. Colonoscopy is recommended by the National Institute for Health and Care Excellence (2011) for patients who do not have major comorbidities. While colonoscopy has a high sensitivity (87.5%, 95% confidence interval 74.8–95.3%) for detecting adenomas >10 mm (Pickhardt et al, 2003), it is associated with substantial risks, particularly bowel perforation (Macrae et al, 1983), and may be incomplete.

Barium enema has traditionally been considered the radiological alternative to colonoscopy in patients presenting with

symptoms suggestive of colorectal cancer. However, Halligan (2013) showed that barium enema is not as sensitive in the detection of colorectal cancer as computed tomography colonography. This study also showed equivalent detection rates for colonoscopy and computed tomography colonography and recommended that barium enema be abandoned. Although already becoming less common, worldwide a significant number of barium enemas are still performed. It is likely that eventually the barium enema will become an obsolete technique, limited to use only in exceptional circumstances.

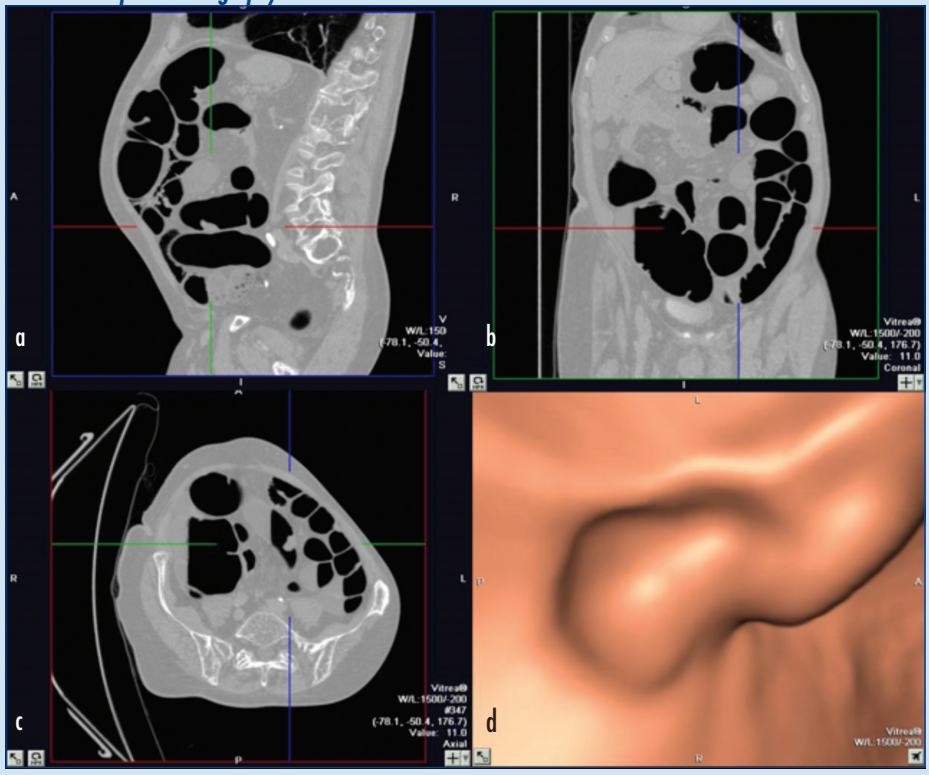
Computed tomography colonography is a radiological alternative to colonoscopy for the detection of colorectal lesions (Fenlon et al, 1999). Computed tomography colonography has a high sensitivity (pooled per-polyp sensitivity of 66%; 95% confidence interval 64–68%), which increased with the size of the polyp, and specificity of 83% (95% confidence interval 81–84%)(Chaparro et al, 2009). Computed tomography colonography is less invasive and allows the detection of abnormalities outside of the colon, but with it comes a risk associated with radiation exposure; an absolute lifetime risk of cancer of 0.14% for a 50-year-old (Brenner and Georgsson, 2005). Limitations of computed tomography colonography when compared to colonoscopy are chiefly inability to obtain tissue and it cannot be therapeutic (i.e. polypectomy).

Early studies suggested patient preference for colonoscopy over computed tomography colonography (Akerkar et al, 2001). However, the technique has since been refined with insufflations of carbon dioxide instead of gas and the latest Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) results showed almost equal patient satisfaction. In the short term, patients reported less satisfaction and more associated worry with colonoscopy than computed tomography colonography, but at 3 months, they were more satisfied with the way results were conveyed at colonoscopy (Halligan, 2013).

The relationship between computed tomography colonography and colonoscopy may evolve in a similar way to that seen between magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography where the radiological test delineates the anatomy and locates the abnormality while the more invasive test retrieves tissue. This relationship is already in place in some institutions in the United States. Computed tomography colonography also has the advantage of staging any detected tumour at the same sitting.

If a suspicious lesion has been identified on any modality, it is imperative to obtain a tissue sample, ideally of the primary lesion, or of a likely metastatic lesion if there are difficulties accessing the primary lesion. The tissue sample allows a histological diagnosis to help guide further management.

Figure 1. Computed tomography colonography demonstrating a polyp within the colon. a. Sagittal view. b. Coronal view. c. Axial view with patient lying on their right. d. Virtual reconstruction of the polyp from the computed tomography data.



Staging

Currently the most widely used staging system in colorectal cancer is the tumour nodes metastasis (TNM) staging system (*Table 1*) (Edge et al, 2010). This has largely replaced the modified Dukes criteria (*Table 2*) (Astler and Coller, 1954) which classifies staging mainly based upon surgically resected specimens.

Computed tomography remains the mainstay of most oncological imaging as it provides information on the tumour size and location, adjacent spread, nodal involvement and the presence of metastasis (*Figure 2*). Owing to its relative widespread availability and rapid image acquisition ability, high spatial resolution and the lack of intra-operator variability, a full body staging computed tomography scan is usually performed as the initial staging imaging modality for suspected cancers. Computed tomography is accurate in identifying whether the cancer has invaded beyond the muscularis propria (i.e. T2 *vs* T3 disease), but it is limited in the detection of malignant lymph nodes (Dighe et al, 2010).

Computed tomography of the thorax, abdomen and pelvis allows evaluation for metastatic disease. Computed tomography has high sensitivity for detection of pulmonary deposits (and is useful in follow up of non-specific nodules). High speed data acquisition from multi-detector scanners allows evaluation of the entire liver in specific vascular phases – a common site of metastasis. Contrast-enhanced imaging modalities exploit the unique dual supply of blood to the liver, with 80% derived from the portal vein and 20% from the hepatic

Table 1. TMN staging system for colorectal metastases

Primary tumour	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	Tis	Carcinoma in situ, i.e. intraepithelial or invasion of lamina propria, but not through muscularis mucosa into submucosa
	T1	Tumour invades submucosa
	T2	Tumour invades muscularis propria
	T3	Tumour invades through the muscularis propria into the peri-colorectal tissues
	T4a	Tumour penetrates to the surface of the visceral peritoneum
	T4b	Tumour directly invades or is adherent to other organs or structures
Regional lymph nodes	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1–3 regional lymph nodes
	N1a	Metastasis in one regional lymph node
	N1b	Metastasis in 2–3 regional lymph nodes
	N1c	Tumour deposit(s) in the subserosa, mesentery or non-peritonealised pericolic or perirectal tissues without regional nodal metastasis
	N2	Metastasis in 4 or more regional lymph nodes
	N2a	Metastasis in 4–6 regional lymph nodes
	N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis	MX	Metastases cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Metastasis confined to one organ or site (e.g. liver, lung, ovary and non-regional node)
	M1b	Metastases in more than one organ or site, or the peritoneum

Table 2. Modified Duke's criteria for colorectal cancer staging

Stage	Pathological description
A	Confined to mucosa
B1	Through muscularis propria but does not penetrate it
B2	Penetrates through muscularis propria
C1	Local lymph node involvement but tumour itself still confined to bowel wall
C2	Local lymph node involvement and tumour penetrating through the bowel wall
D	Distant metastases

From Astler and Coller (1954)

artery, to differentiate between normal liver parenchyma and malignant metastatic lesions which are almost always hypovascular compared to background liver.

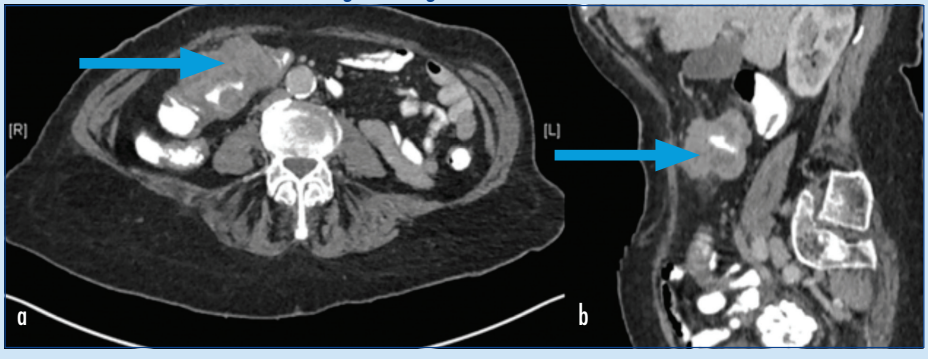
While contrast-enhanced computed tomography is used first line in the detection of liver metastases, up to 15% of lesions may be missed on computed tomography staging (Valls et al, 2001) although further imaging is not usually undertaken where staging computed tomography demonstrates no hepatic disease. Magnetic resonance imaging, ultrasound and positron emission tomography may be used to evaluate indeterminate liver lesions and/or define disease burden before complete resection, and are also used, alone or in combination, to evaluate liver metastases.

Ultrasound offers a real time non-invasive technique for assessing patients with rectal cancers and/or suspected liver metastasis. In rectal cancers, endorectal ultrasound can be used to help stage local tumour invasion (Edelman and Weiser, 2008). However, this is not currently in widespread use within the UK.

In suspected liver metastases, ultrasound provides a fast and effective modality for guiding the biopsy of visualized lesions. However, it is highly operator dependent and may have low sensitivity and specificity depending on the operator, with a high false negative rate of greater than 50% (Ong and Leen, 2007) in dynamic liver ultrasound. With the development of intravenous microbubble contrast agents, the sensitivity of detecting individual metastasis increases so that 92% of sub-centimetre lesions are identified compared to 54% in a non-contrast enhanced baseline study (Albrecht et al, 2001). An alternative is the use of intra-operative ultrasound which remains the gold standard for detection of hepatic metastatic lesions with up to 98% sensitivity and 95% specificity for lesions as small as 2 mm in diameter (Schmidt et al, 2000).

For rectal tumours, multiplanar magnetic resonance imaging is the mainstay of local staging. T2-weighted magnetic resonance imaging is commonly used to demonstrate the extent of local tumour invasion through bowel wall layers (*Figure 3*) as it provides excellent soft tissue image resolution (Iyer et al, 2002). Intravenous contrast medium is not required for this. Magnetic resonance imaging of the rectum is also commonly used for restaging post neo-adjuvant therapy for planning resection.

Figure 2. Computed tomography post positive oral contrast demonstrating a soft tissue mass within the transverse colon in (a) axial and (b) sagittal images.



Magnetic resonance imaging is one of the most effective modalities in characterizing potential liver metastases. With the development of new sequences, better hardware, body array coils and software analysis, magnetic resonance imaging is particularly useful in the characterization of indeterminate lesions identified on other modalities (Ong and Leen, 2007). Licensed for use in Europe since 2004, gadolinium-ethoxybenzyldiethylenetriaminepentaacetate (Gd-EOB-DTPA) is commonly used as a hepatobillary contrast agent in contrast-enhanced magnetic resonance imaging for detection of hepatic metastases from colorectal carcinoma as it allows hepatocyte-specific uptake. Together with using diffusion-weighted imaging sequences, it allows improved per lesion detection of liver metastases.

Positron emission tomography is a functional technique that uses the differential glucose metabolism and tracer uptake of tumour cells compared to normal healthy tissue. The most commonly used tracer is 18F-fluorodeoxyglucose (FDG). It is not used in the primary staging of colorectal cancer, but is very useful as an adjunct imaging modality in preoperative staging of colorectal cancer in the presence of metastatic or recurrent disease (Brush et al, 2011). The sensitivity and specificity of FDG-positron emission tomography for the detection of colorectal metastasis were reported to be as high as 95% and 100% (Ogunbiyi et al, 1997).

With the added functional imaging information from whole body 18F-FDG positron emission tomography, up to 25% of patients have avoided inappropriate surgery compared to those who underwent computed tomography staging, as a result of its increased sensitivity in picking up extrahepatic disease (Arulampalam et al, 2004).

Colorectal cancer metastases are often very 18F-FDG avid (*Figure 4*) and with the clinical importance of confirming resectable disease most of the reported literature on FDG-positron emission tomography and positron emission tomography/computed tomography comes from studies involving colorectal metastasis (Sacks et al, 2011). However, because of the resolution limitation of positron emission tomography, metastatic lesions measuring less than 5 mm are usually poorly visualized.

Follow up

Following initial surgery with curative intent, approximately 30–40% of patients will develop recurrent disease within the first 2 years (Kruse et al, 2013). The National Institute for Health and Care Excellence (2011) recommends that routine follow up should include at least two computed tomography scans of the chest, abdomen and pelvis within 3 years, combined with carcinoembryonic antigen (CEA) tests every 6 months and colonoscopy at 1 and 5 years following treatment. While the sensitivity and specificity of CEA is low, raised CEA levels in patients post-curative surgery are associated with tumour recurrence in 90% of patients (Kruse et al, 2013).

In the absence of any clinical symptoms but with only the presence of a rising CEA, computed tomography follow up has a low sensitivity and specificity in identifying the source of the rising tumour marker. These follow-up studies do not significantly improve mortality (P=0.06) but have an increased rate of detection of asymptomatic recurrence and improved reoperative rates with curative intent for the sites of recurrence (Tjandra and Chan, 2007).

Magnetic resonance imaging of the pelvis and perineum may also be performed for patients with resected rectal cancer under surveillance with rising CEA levels. Magnetic resonance imaging is better able to differentiate between local recurrence from scar tissue than computed tomography based on tissue signal characteristics, but there are still limitations to the size and specificity of tumour recurrence detection (Ito et al, 1992).

In patients with rising CEA levels where no clear tumour recurrence has been identified on computed tomography or magnetic resonance imaging, positron emission tomography/computed tomography is a valuable tool in the localization of tumour recurrence. As a functional imaging modality, it can localize focal areas of increased metabolic activity and has an overall sensitivity and specificity of 95% in detecting metastases in patients with rising CEA levels (Cohen, 1997).

Figure 4. a. The liver metastasis is very subtle on the unenhanced computed tomography image but (b) demonstrates avid 18F-fluorodeoxyglucose uptake on the positron emission tomography/computed tomography fused image in keeping with a metabolically active colorectal metastasis. The increase in uptake seen around the right atrium is physiological and not significant.

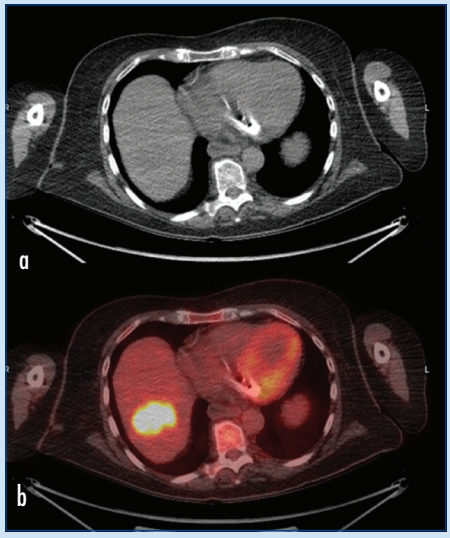
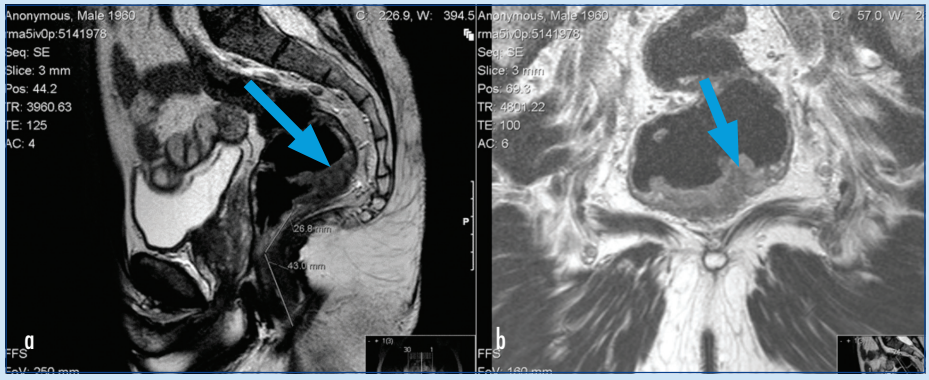


Figure 3. Multiplanar high resolution (a) sagittal and (b) axial T2W images of a low rectal tumour. A sagittal image is used for measuring the height of the tumour from the anal verge and helps determine which operation is appropriate. The axial image (to the tumour, not patient) demonstrates no invasion beyond the muscularis propria in keeping with local staging of T2.



Conclusions

Radiological imaging plays a key role in the detection, evaluation and management of colorectal malignancies. Computed tomography colonography provides an accurate alternative for patients intolerant of colonoscopy with an equivalent detection rate. Contrast-enhanced computed tomography remains the mainstay of colorectal cancer staging because of its widespread availability, rapid image acquisition, high spatial resolution and reproducibility. Magnetic resonance imaging and/or ultrasound may be used to assess indeterminate liver lesions detected on computed tomography or to assess disease burden where it would change management. Functional imaging using positron emission tomography/computed tomography is a useful adjunct for assessing extrahepatic metastasis both pre- and post-treatment. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Imaging plays a key role in the multidisciplinary management of patients presenting with colorectal cancer.
- Computed tomography colonography is a valuable, accurate, alternative screening tool for patients who are unable to tolerate colonoscopy within screening programmes.
- Contrast-enhanced computed tomography remains the mainstay of colorectal cancer staging because of its widespread availability, rapid image acquisition, high spatial resolution and reproducibility.
- Magnetic resonance imaging plays a central role in the local staging and assessment of rectal cancer, and is particularly useful for characterizing indeterminate liver lesions that may be suspicious for metastatic colorectal cancer.
- Positron emission tomography is a functional imaging modality which allows the identification of metastases, particularly extrahepatic metastases not visualized on other modalities, thereby potentially significantly altering the management of patients with metastatic disease.