Imaging of the liver in metastatic disease

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Introduction

The presence of vascular invasion is a prerequisite for visceral metastatic disease and its potential arises once colorectal cancer has invaded into the highly vascularised lamina propria. This network of capillaries drains through branches of the portal vein and thence to the liver. It is therefore not surprising that the liver is a frequent site of metastatic disease and the sole site of metastasis in up to 40% of colorectal patients.

The percentage of patients in whom long-term cure is achievable has increased in recent years and there is a continuing trend of improving survival and cure rates. Technological advances in imaging have played an important part in contributing to this improvement. This has been achieved through more accurate preoperative imaging, leading to rigorous patient selection and improved surgical resection outcomes facilitated by intraoperative imaging [1].

In addition to monitoring of lesions and their response to chemotherapeutic agents, imaging of the liver is of vital importance in the preoperative workup of patients who have disease amenable to hepatic resection. Ideally, imaging should provide:

- accurate delineation of anatomical distribution of metastases and segmental sparing in patients undergoing hepatic resection
- confirmation of absence of widespread multi-segmental micro-metastatic disease within the liver
- confirmation of absence of extrahepatic disease
- discrimination between coexisting benign lesions and metastases
- a method of road mapping the tumour to ensure margins > 10 mm.

The availability of a wide array of imaging technologies presents new challenges in determining the most appropriate, clinically- and cost-effective means of preoperative assessment of these patients. In practice, no one imaging modality will resolve all the above issues of patient selection and this review will focus on how these technologies may complement each other to ensure rigorous patient selection and consequent improved outcomes following hepatic resection for colorectal liver metastases.

Follow-up of patients with colorectal cancer

The relative merits of intensive image-based follow-up versus a less intensive method has been subject to debate; no commonly agreed protocols defining a follow-up regime exist. However, a recent meta-analysis suggested that more intensive follow-up combining CEA (carcinoembryonic antigen) monitoring, outpatient clinical assessment and yearly CT (computerised tomography) scanning improves survival compared with less intensive follow-up that does not utilise CT imaging [2]. The meta-analysis showed that intensive follow-up was associated with a reduced time to first relapse and significant absolute reduction in mortality rate of 9–13%. Since these trials pre-dated the current wider trend of more aggressive hepatic resections and the use of combined therapies which in their own right have improved survival, it is likely that the potential survival benefit from intensive follow-up may be even greater than that identified in the meta-analysis. It is hoped that future planned large multicentre trials will further inform us of the contribution of particular tests and their clinical- and cost-effectiveness in follow-up.

The benefits of serial imaging in patients cannot be underestimated as a method of increasing certainty of the significance of small and difficult-to-characterise lesions by exploiting the fact that metastases have a doubling time of 3 months. Appreciation of this is of particular benefit in the setting of patient surveillance.

Prognostic factors governing outcomes after hepatic resection

The trend in improved survival following treatment for colorectal hepatic metastases may be attributed largely to improved techniques of anatomical

resection [3–5], the availability of intraoperative ultrasonography (IOUS) [6,7], decreased mortality and morbidity in the perioperative period [1], the use of second hepatic resections [8], and the use of chemotherapy [9–12]. In one detailed analysis of the prognostic factors governing survival, three features retained independent prognostic significance [13]:

1. presence of extrahepatic disease
2. > 20% involvement of the liver by tumour
3. tumour-free resection margin < 9 mm.

All of these prognostic factors should be assessable by detailed preoperative imaging which should enable rigorous patient selection. Furthermore, IOUS has an important role in enabling precise localisation and anatomical resection of lesions with tumour-free resection margins.

Extrahepatic disease

It has been shown that patients with solitary unilobar tumours rarely have unrecognised irresectable disease, whereas patients with multiple bilobar tumours are at significantly higher risk of occult hepatic and extrahepatic disease [14]. These issues may influence the choice and intensity of preoperative imaging investigations.

Assessment of extrahepatic disease

The main tools for detecting coexisting extrahepatic disease are PET (positron emission tomography) imaging, CT, and laparoscopy. They are complementary and it is important to recognise that each tool has its limitations and that no single technique will identify all instances of extrahepatic disease.

Serial CT examinations of patients after colorectal cancer remains the most frequent follow-up imaging modality and careful comparison of serial studies allows the distinction between benign non-malignant lesions in lung and liver. In many cases, the unequivocal demonstration of extrahepatic sites of disease by CT or multifocal irresectable liver disease will rule out hepatic surgery in the first instance. For the patients who appear potentially resectable following CT assessment, preoperative FDG–PET (PET with fluorodeoxyglucose) has the greatest potential to alter outcomes by detection of extrahepatic disease not found on conventional imaging (Fig. 1) [15]. By using FDG–PET imaging to select out patients with extrahepatic disease, unnecessary surgery was prevented in 6/43 patients [15]. The precise anatomical location of intrahepatic metastases was not always possible, however, using PET scanning. This may result in exclusion of such patients for resection. On the other hand, the demonstration of isolated extrahepatic disease by PET may result in multiple resections (for example lung metastatectomy and liver resection) that may potentially result in cure.

There are however some limitations of PET and CT imaging, particularly in their ability to identify small-volume peritoneal disease and surface disease on the liver (Fig. 2). In such patients, laparoscopy and IOUS may be the only methods of identifying these types of spread.

The challenge that remains is the identification of disease that may be hard to detect by any imaging modality, namely small-volume nodal metastases and peritoneal carcinomatosis, and failure to detect patients with these forms of spread will doubtless continue to contribute to instances of post-treatment failure.

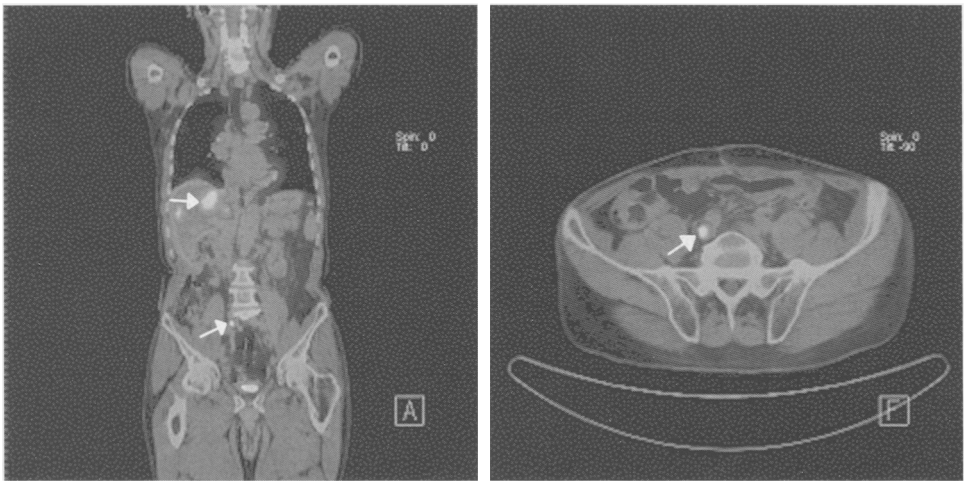

Fig. 1. FDG–PET CT confirms multiple liver metastases shown on conventional imaging, but also shows extrahepatic nodal disease that had not been detected on conventional imaging.

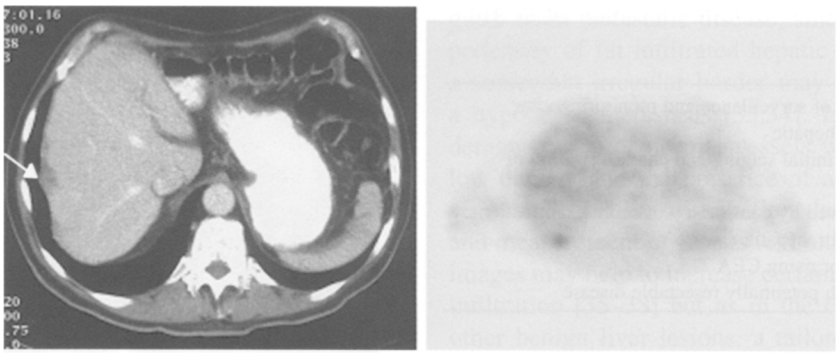

Fig. 2. Small volume peritoneal disease shown on the surface of the liver on CT that was not demonstrated using FDG–PET, which showed a solitary intrahepatic metastasis only.

Transabdominal ultrasound (Table 1)

Transabdominal ultrasound has not been proven to be as accurate as CT or MRI (magnetic resonance imaging) in the detection of liver metastases [16]. This is because assessment of such lesions is limited by the lack of inherent contrast between lesions and the surrounding liver. Although ultrasound is less accurate at detecting metastases than CT, it is cheaper and more widely available and thus for some institutions may provide an effective screening or monitoring technique. However, it cannot be recommended in the preoperative workup of patients considered for hepatic resection, as it is currently insufficiently accurate to predict resectability.

Transabdominal sonography with contrast agents

The ability to improve the conspicuity of metastases using ultrasound contrast agents, on the other hand, appears promising and has been evaluated in a number of small studies. Ultrasound contrast agents comprise tiny microbubbles of gas that interact with the ultrasound beam producing an enhancement of the Doppler signal from blood. Harmonic sonographic imaging allows preferential detection of the signal from the microbubble agents with suppression of the signal from background tissue [17,18]. Delayed post-vascular enhancement of the normal liver, following microbubble contrast agent injection, allows detection of smaller malignant lesions than on baseline imaging [17]. The technique may thus improve the detection rate of metastases by allowing clear distinction between liver parenchyma and metastases. Contrast sonography has been shown to have greater sensitivity than ultrasound in tissue characterisation [19], and in one study, the use of pulse inversion harmonic imaging significantly improved the sensitivity and specificity of ultrasound and demonstrated that the technique was equivalent to helical CT with intravenous contrast in lesion detection [20].

Despite these promising initial studies showing that the technique has the potential to be as accurate as CT in the detection of small liver metastases, ultrasound contrast agents have not gained wide acceptance in the routine assessment of patients with suspected liver metastases, and larger prospective studies verifying its performance in routine clinical practice are required.

Table 1
Transabdominal ultrasound

– may help with lesion characterisation (cysts and cavernous haemangiomas)
– inexpensive tool for surveillance and monitoring therapy
– operator-dependent
– poor sensitivity and specificity
– some areas of liver are difficult to assess

CT detection (Table 2)

Colorectal carcinomas metastasise to the liver by means of the portal venous system. However, they receive their blood supply from the hepatic artery [21]. CT performed during peak level of hepatic parenchymal enhancement will identify the vast majority of colorectal metastases and for many institutions is the modality of choice for the surveillance of patients at risk of developing liver metastases. The technique exploits the relative hypovascularity of colorectal neoplasms compared with normal parenchyma and results in accuracy rates of up to 85% (sensitivity 70%, specificity 94%) [27].

Table 2
Role of CT

– forms the mainstay of surveillance and monitoring after primary surgery or hepatic
– easily available for initial staging and characterisation of hepatic lesions
– specificity is improved by comparison of serial examinations
– demonstration of extrahepatic disease
– first investigation for rising CEA
– defines patients with potentially resectable disease

CT arterioportography (CT–AP)

Initial studies, however, showed that CT arterioportography was superior to conventional CT and until very recently had been advocated as an important preoperative investigation prior to hepatic resection [22–25].

The technique requires the percutaneous placement of an angiographic catheter in the superior mesenteric or splenic artery and continuously obtaining CT images at each level following contrast infusion.

More recently, however, comparisons of spiral CT, and MRI with CT arterioportography suggest that the latter technique is not significantly more sensitive or accurate and indeed may produce false positive lesions caused by perfusion defects. Such defects may be problematic as they manifest as lesions that can easily be mistaken for tumour. In a study by Yamagami et al. [26], non-tumorous areas of decreased portal perfusion of the liver around the falciform ligament was detected in 18/117 patients (15.4%); selective gastric arteriography showed that aberrant gastric venous inflow was responsible for such areas of decreased portal perfusion.

Spiral and multi-slice CT

The improved sensitivity and specificity of helical CT reported by Valls [27] was attributed to thinner 5 mm collimation images compared with earlier CT studies employing slower scan times and 10 mm collimation. The issue of resectability has only been addressed in a few papers. In one series, 54% of patients thought to be resectable on preoperative imaging were excluded by IOUS and laparoscopy. In another series, 78% were correctly identified as resectable representing a trend of improved preoperative assessment which was improved further when a thin collimation technique was used. In this study, 94% of patients selected for hepatic resection by CT were found to be suitable for curative resection with a 58% 4-year survival rate [27]. Thus, higher spatial resolution CT techniques represent an improvement in the selection of patients suitable for curative hepatic resection.

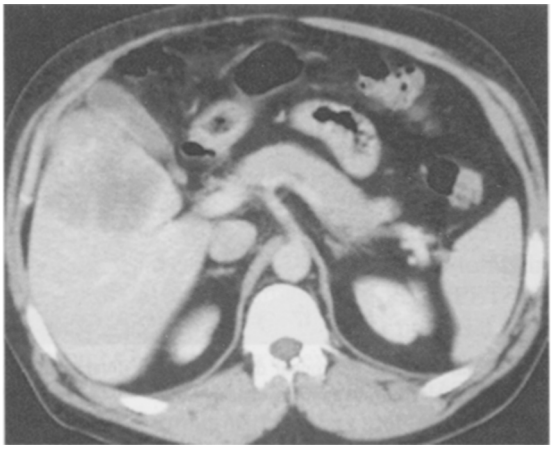

Fig. 3. Contrast-enhanced CT scan showing typical low-density colorectal liver metastasis.

Further improvements in CT technology with multidetector CT has largely negated the need for the more invasive CT–AP. Lesion detection at 10 mm or above is accurate and multi-detector CT techniques achieve this improvement by virtue of its ability to achieve 1 mm isotropic voxel size with consequent improved spatial resolution and multiplanar capability [28].

These recent developments in multi-detector scanners have enabled fast imaging of the entire liver within 10 seconds using new generation multidetector scanners and the potential to image during several phases of hepatic enhancement. However, although studies suggest that triple and biphasic techniques are of value in the assessment of hypervascular metastases, there is little convincing evidence for the value of arterial phase imaging in colorectal metastases [29,30]. Typically, colorectal hepatic metastases are demonstrated as hypodense lesions with rim enhancement (Fig. 3). Larger lesions may contain central necrosis and thus contain a central low density "cystic" nidus.

Lesion characterisation with CT

In addition to identification of liver metastases in patients with colorectal carcinoma, it is necessary to define an approach for distinguishing coincidental benign lesions that can potentially result in a false positive diagnosis.

Of these, cysts are the most commonly detected. Large lesions present little difficulty, as they are well defined, lack any rim enhancement and have no internal architecture. Smaller lesions <10 mm in diameter may be more difficult to characterise. The absence of any ring enhancement and the presence of

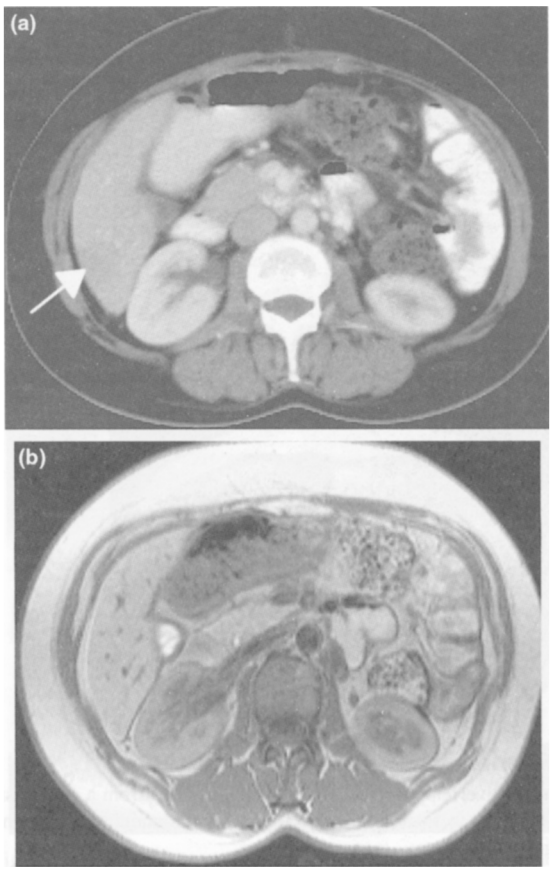

Fig. 4. Focal perfusion defect. (a) CT scan shows an area of low attenuation in segment VI. (b) The corresponding MRI with contrast enhancement shows normal hepatic anatomy with no lesion in the segment, confirming that the low-density lesion on CT was a perfusion defect.

a sharply delineated margin, and very low attenuation are helpful in distinguishing cysts from malignant lesions [31].

Haemangiomas, characteristically these enhance peripherally typically in a nodular fashion with in filling of the lesion and persistence of enhancement [32]. This can be demonstrated by dynamic scanning of the lesion at the same level at 30-second intervals followed by a delayed 20-minute scan which should show persistence of enhancement. Arguably, MRI has superseded CT as the method of choice of characterising potentially benign lesions.

Focal perfusion artefacts (Fig. 4) are another potential source of confusion and usually produce a wedge-shaped defect, which may well relate to anomalous venous drainage. However, unlike metastatic lesions, these are not visible as areas of low density on pre-contrast images and are not visible on delayed images.

When focal fatty infiltration in the liver occurs as isolated areas these can be difficult to distinguish from metastatic disease, since the relative hypodensity of fat infiltrated hepatic parenchyma with a somewhat irregular border may seem identical to a hypodense metastasis [33,34]. In many cases the demonstration of normal vessels within this area of low density and the presence of a straight line, the segmental or lobar distribution, lack of mass effect and measurement of Hounsfield units on unenhanced images may help to increase certainty that this is fatty infiltration [35–38] but as in the characterisation of other benign liver lesions, a tailored MR study can more readily confirm the diagnosis (Fig. 5).

Finally the use of serial CT studies should not be neglected and is invaluable in determining the significance of lesions initially considered suspicious or indeterminate. The addition of a three month interval CT scan to compare with an initial assessment improves specificity from 0.91 to 0.99 [16].

MRI detection of liver metastases (Table 3)

MRI assessment

The workhorse of liver imaging is the T1-weighted gradient echo (GRE) sequence. It allows rapid imaging of the liver in a single breath-hold and can be acquired as a volume in axial or coronal planes enabling the precise anatomical localisation of lesions.

The recommended routines include a T1-weighted GRE. T2-weighted sequences will further aid characterisation and T1 in- and out-of-phase imaging are also rapid sequences which exploit the behaviour of fat-containing tissues during in- and out-of-phase imaging. The sequence thus provides a useful means of further assessing apparent "perfusion defects" seen on CT which in some instances may be due to focal fatty infiltration.

Gadolininum enhancement given as a rapid bolus can be achieved dynamically with images acquired in the arterial, portal venous, equilibrium and delayed

Table 3
Role of MRI

Advantages:
– superior accuracy in characterisation of equivocal lesions
– sensitivity in lesion detection if liver-specific contrast agents used
– multiplanar anatomical definition — dome of liver lesions, relationship to the portal vein
Disadvantages:
– time-consuming, costly
– machine-dependent

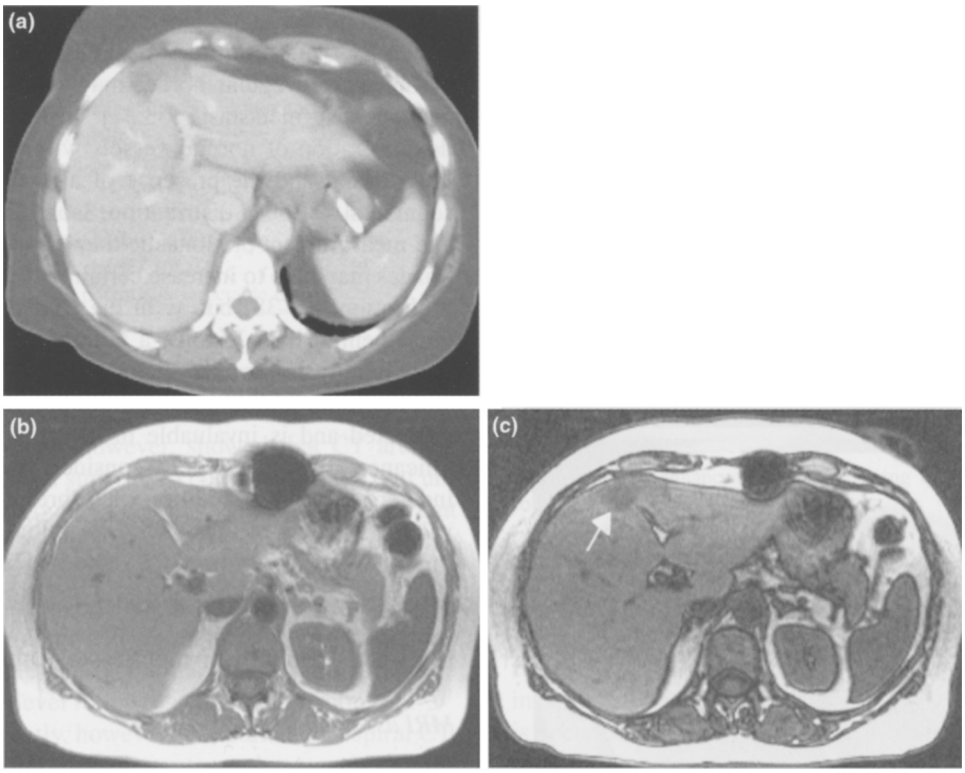

Fig. 5. Focal fatty infiltration. (a) A low-density lesion is seen anteriorly in the liver; appearances are indistinguishable from a metastasis. (b) In-phase and (c) out-of-phase MRI was able to demonstrate that this was due to focal fatty infiltration. A fat-containing area within the liver will show a lowering in signal intensity on the out-of-phase images (arrow).

phases of enhancement. Semelka et al. [39] showed that MRI using dynamic contrast enhancement was superior to dual-phase spiral CT and was significantly superior for lesion characterisation. It was further concluded that in terms of impact on patient management these differences had clinical significance. Thus, the ability of MRI to more reliably characterise structural abnormalities on CT is an advantage that can help in treatment planning and patient selection.

The increased sensitivity and specificity afforded by both superparamagnetic iron oxide (SPIO) and Mangafodipir as liver-specific agents has led to the more widespread use of MRI in the preoperative assessment of patients with liver metastases. One of the first of such liver-specific agents to be evaluated was SPIO. Intravenous infusion of this agent results in uptake by functioning Kupffer cells and darkening of the liver on MR imaging. Thus, metastases that do not contain Kupffer cells fail to take up this contrast and are shown up as relatively hyperintense lesions on SPIO-enhanced T1-weighted gradient echo images (Fig. 6). However, other benign lesions can also show up as hyperdense and care needs to be taken to ensure that false positive lesions are not identified, particularly cysts and cavernous haemangiomas. Comparison with other sequences, especially the heavily T2-weighted sequence and the combined analysis of non-enhanced and SPIO sequences, is more accurate in the characterisation of focal hepatic lesions than review of SPIO-enhanced images only [40]. MRI has shown considerable promise in overcoming the challenge of identifying lesions < 1 cm preoperatively and in a study evaluating the clinical impact of preoperative assessment using SPIO compared with CT arterioportography, it was shown that this technique was at least as accurate as spiral CT–AP. Mangafodipir trisodium (Mn–DPDP) is taken up by the functioning hepatocytes and excreted by the biliary system. Contrast uptake leads to persistent elevation of T1-weighted signal of normal liver parenchyma within 10 minutes of injection. Comparison of T1-weighted images before and after administration of this agent shows a 100% increase in the signal-to-noise ratio of the liver and a 400% increase in conspicuity between the hypointense liver metastasis and surrounding parenchyma [41]. When compared with CT, the use of liver-specific agents increases the sensitivity and accuracy of detection of metastases (Fig. 7). In a study comparing the performance of Mn–DPDP MRI with CT and IOUS,

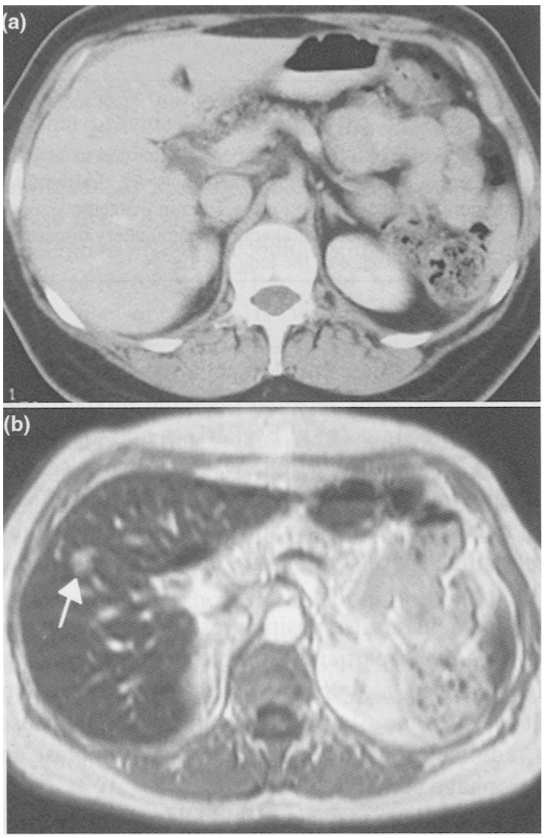

Fig. 6. (a) The CT scan shows no abnormality. (b) Following SPIO administration, the signal intensity of liver is diminished, which renders visible a liver metastasis as a focal high-signal-intensity lesion (arrow).

MRI influenced the operative decision in 74% [42]. However, IOUS still detected further lesions not seen on preoperative imaging, all of which were < 1 cm and compared with pathology sensitivities of CT, MRI, and intraoperative evaluation were 61%, 83%, and 93%, respectively. Nevertheless, recent findings suggest that Mn–DPDP MRI is more sensitive than spiral contrast enhanced CT in the preoperative prediction of the resectability of hepatic lesions [42].

Lesion characterisation

Haemangiomas

These are of low signal intensity on T2-weighted images and can be difficult to distinguish from metastases. Their distinction is made possible on MRI because their T2 values are much greater than those of metastases and if a longer echo time is used (longer TE), haemangiomas remain bright (Fig. 8), whereas metastases diminish in signal intensity. This is quantitatively reflected in the T2 relaxation times, which are in the order of 76 ± 26 ms for metastases and 133 ± 25 ms for haemangiomas [43–45].

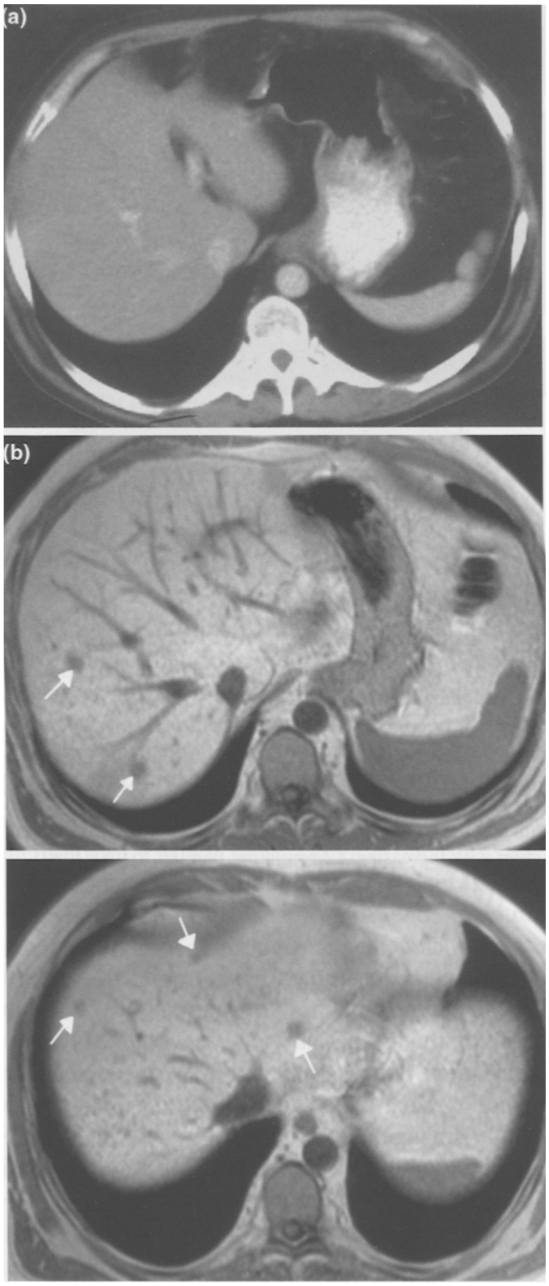

Fig. 7. (a) The CT scan shows no convincing evidence of metastatic disease. Following administration of Mn–DPDP, normal liver parenchyma increases in signal intensity due to hepatocytes taking up Mn–DPDP. Metastases are therefore depicted (arrows) as low-signal-intensity lesions and MRI shows numerous 5–10 mm lesions that were not visible on CT.

Although the T2 weighting characteristics are usually sufficient, dynamic contrast enhancement may be necessary. Haemangiomas characteristically show peripheral nodules of enhancement, slow in-filling and delayed wash-out of contrast compared with metastases that will show rim enhancement.

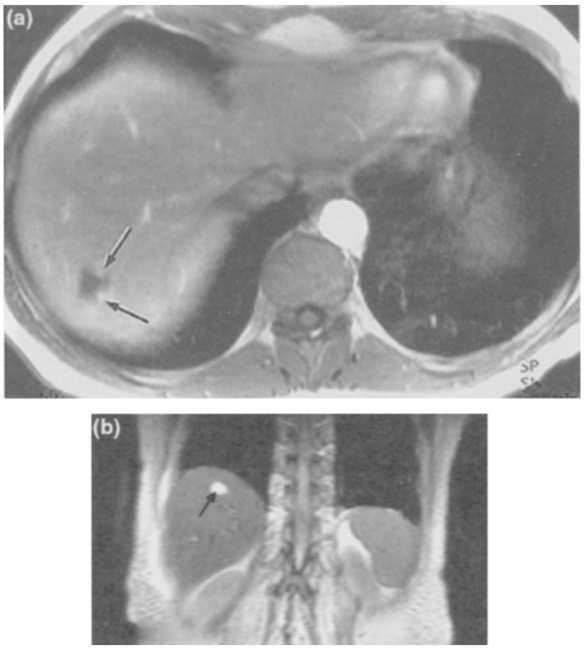

Fig. 8. MRI characterisation of a cavernous haemangioma. (a) Axial gadolinium-enhanced spoiled T1-weighted image during the hepatic arterial phase of enhancement shows the typical enhancement pattern of a haemangioma with peripheral nodules (arrows) enhancing in a discontinuous ring. (b) Coronal heavily T2-weighted scan shows the typical appearance of a cavernous haemangioma, which is of bright signal intensity and becomes brighter with increasing T2 weighting (similar to CSF fluid).

Focal fatty change

Focal fatty change demonstrated on in- and out-of-phase imaging and by fat suppression. When compared with the in-phase sequences, focal fatty regions will drop in signal intensity on the out-of-phase imaging. Other MR techniques may also confirm focal fatty change; e.g. short inversion time (STIR) sequences, water and fat suppression sequences will help to distinguish fat-containing areas.

Cysts

On MRI, simple cysts are of low signal intensity on T1-weighted images. They are bright on T2-weighted imaging and are not associated with any peripheral rim enhancement.

PET imaging (Table 4)

The diagnosis of tumours and metastatic disease using FDG–PET is based on increased regional glucose metabolism exhibited by tumour foci that is essentially independent of tumour size. In a meta-analysis comparing the performance of studies using ultrasound, CT, MR and PET imaging in the detection of gastrointestinal hepatic metastases, FDG–PET was the most sensitive imaging modality [46]. Furthermore, in a study by Park et al. [47], a combined CT and FDG–PET was the most sensitive imaging modality and was found to be cost-effective for managing patients with elevated carcinoembryonic antigen levels who were candidates for hepatic resection.

Table 4
Role of PET imaging

– highly sensitive and specific can detect very small foci of extrahepatic metastatic disease
– provides functional information about tumour and its activity
– false negative rate is high in mucinous tumours, determining peritumoral nodal status, lesions < 1 cm in diameter
– false positive rate after radiotherapy, inflammatory disease and granulomatous disease in the lung

Nonetheless, false positive results can be obtained and this is a particular problem in patients that have received radiotherapy with false positive results seen in the 6 months after radiotherapy caused by radiotherapy-induced granulation, fibroblast and macrophage activity.

The technique may also yield false positive results in the detection of extrahepatic disease, particularly in granulomatous disease and inflammatory processes in the lung. Lesions < 1 cm in diameter may be a cause of false negative diagnosis, micrometastatic disease in lymph nodes and the inability to separate nodes that lie in close proximity to the tumour are all limitations. It has therefore been suggested that in instances in which the findings of FDG–PET would result in the patient being denied potentially curative surgery that some other means of confirming the lesion may help and a careful attempt to localise and characterise a PET-detected abnormality should be sought by conventional imaging. Thus, the use of FDG–PET has transformed the way in which patients are selected for hepatic resection, but it is critical to provide anatomical details with conventional cross-sectional imaging for correct interpretation (Fig. 9).

Table 5
Role of IOUS

– sensitive
– enables intraoperative planning of tumour-free resection margins
– operator-dependent
– not specific
– not a primary staging method

IOUS (Table 5)

Intraoperative ultrasound remains an important tool that provides a road map for the surgeon that helps to ensure tumour-free margins of resection. The technique may identify patients with more segmental disease than thought previously, but with improved preoperative imaging techniques this should occur in < 10% of resections [27].

The use of IOUS is widely advocated as a mandatory procedure during planned resections for metastatic disease within the liver, and despite the improving accuracy of modern preoperative imaging modalities, this technique remains an important component of the peri-operative management that alters the surgical approach in 20–44% of patients [48,49]. Unlike preoperative techniques, IOUS can: identify unsuspected focal metastases as small as 3 mm in diameter, show the relationship of tumour to the vascular pedicle, and localise tumour foci within the liver precisely. All these factors contribute to achieving the optimal surgical approach by guiding the hepatic surgeon towards achieving tumour-free resection margins.

Functional imaging

Traditionally, RECIST (response evaluation criteria in solid tumours) and morphological criteria are used. However, it is increasingly recognised that treated metastases may look like cysts, yet only contain microscopic or non-viable foci, so that morphologically-based RECIST criteria may not be appropriate documentation of response to treatment. This has stimulated interest in functional imaging which may be performed using US, MR, CT or PET. Both MR and US are currently under evaluation as a research tool and there is little known about their use in the clinical setting. CT and PET functional imaging have been validated in clinical settings and are more likely to be readily translated into routine clinical practice.

It has been suggested that intravenous contrast agents may be of value in assessing functional aspects of the liver by measuring intrahepatic resistance and may identify patients at risk of developing diffuse micro-metastatic disease before lesions are visible on conventional imaging. Similarly measurements that do not rely on morphological change alone may be of more value in assessing the response to chemotherapeutic agents.

Quantitative measurements of hepatic perfusion can be achieved during dynamic contrast-enhanced imaging and it has been shown that the liver undergoes changes in perfusion with the development of metastases. These changes comprise an increase in arterial blood flow in relation to total liver perfusion and a concomitant reduction in portal blood flow. Furthermore, such changes have been shown to precede the development of visible liver metastases on conventional imaging and it has thus been proposed that such measurements may be used to identify patients with micrometastatic disease.

A number of techniques of functional imaging of the liver have been validated:

1. PET–FDG imaging
2. perfusion CT
3. densitometric analysis during dual phase spiral CT.

FDG–PET in monitoring disease

^{18}FDG–PET offers a quantitative functional imaging modality that provides a useful adjunct to conventional anatomical and morphological imaging. Because functional imaging is provided using this technique, PET has the further potential role in monitoring response to therapy and in particular of demonstrating whether viable tumour tissue remains after chemotherapy when morphological measures of tumour response may not accurately reflect the degree of pathological response. To this end, quantitative assessment of response may be achieved by measurement of FDG uptake whereby a decrease in uptake indicates a favourable response to therapy. Existing published studies show some variation in techniques of quantitation such as the timing of measurements following chemotherapy, the method of measurement, namely measurement of the standard uptake value (SUV) of ^{18}FDG or the ^{18}FDG tumour to liver ratio [50,51]. Nevertheless, PET appears a useful adjunct to the traditional morphological method of monitoring therapy and, in the future, may play a role in predicting response to therapy.

Perfusion CT

A single slice within the liver is selected and a baseline image taken before rapid intravenous bolus contrast infusion. On completion of the bolus infusion, a series of images are acquired over a 45-second period. This allows perfusion values to be calculated during the arterial and portal venous inflow phases of enhancement. By subtracting the baseline image from the images obtained dynamically and measuring region of interest, values of attenuation over reference structures (the aorta, spleen and liver) both arterial

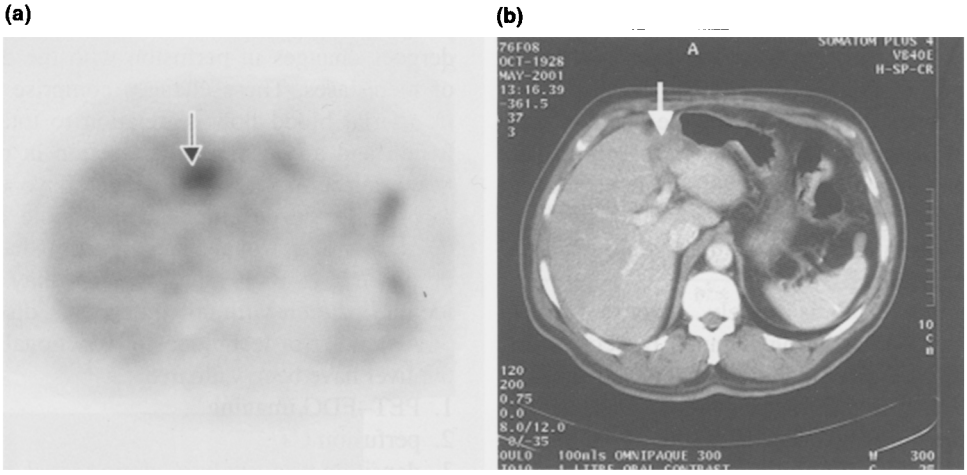

Fig. 9. (a) FDG–PET showing focal area of increased activity in the anterior liver. (b) Corresponding CT image shows anatomical site of lesion adjacent to the falciform ligament

perfusion and portal perfusion measurements can be taken. The time to achieve peak splenic enhancement is used as the cut-off to allow separate measurements of the arterial and portal phases [52].

In a study by Legget et al. [53], 9/11 patients with morphologically evident hepatic metastases showed arterial perfusion >0.25 ml/min/ml compared with only 6/16 patients without obvious metastatic disease. Portal perfusion measurements were very variable, although there was a tendency towards reduced portal perfusion in patients with liver metastases. In a later study of 13 patients, significant correlation was found between prolonged survival and high values of arterial perfusion within the metastasis.

Densitometric analysis

This is a semi-quantitative technique which was first assessed by Platt et al. [54], the technique requires a baseline-unenhanced scan through the liver

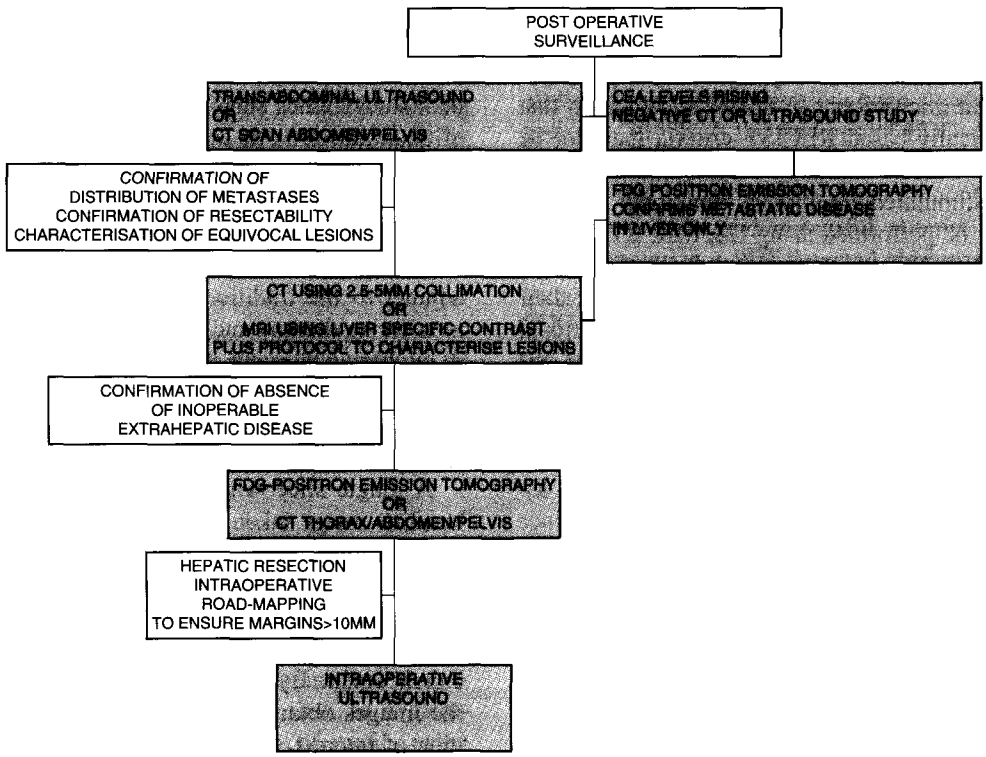

Fig. 10. Algorithm of imaging investigations prior to hepatic resection.

followed by post-contrast-enhanced scans at 25 seconds and 40 seconds. Measurement of the 40 second liver/liver peak ratio using a threshold of 0.6 gave a specificity of 100% for metastatic disease. In a separate study, Platt et al. demonstrated the ability of this technique to identify patients at risk of developing metastases in the subsequent 8 months [55].

Thus, functional imaging has the potential to identify patients at risk of developing metastases; the application of these findings in the clinical setting has yet to be evaluated, however.

In summary

Health economics

The case for clinical- and cost-effectiveness of intensive follow-up of patients with colorectal cancer has been strengthened in recent years by the success of treatment options for patients who develop metastatic disease. Nowhere is this strategy more cost-effective than in the early detection of colorectal metastases to the liver since potentially curable recurrences will be detected by accurate imaging. Furthermore, utilising FDG–PET with CT and MR scanning will lead to measurable benefits that supersede the costs incurred by such techniques.

Imaging algorithm (Fig. 10)

At present, CT scanning with imaging in the hepatic venous phase remains the most useful modality for the surveillance of patients following colorectal surgery. Since the majority of patients develop metastatic disease within the first two years of surgery and it is relatively unusual to demonstrate metastatic disease after the first 5 years, it seems reasonable to intensify postoperative surveillance in the first two years with careful follow-up assessment of patients at risk of developing metastatic disease thereafter. On occasion, the cause of a rising CEA level will not be demonstrated on conventional imaging. In these circumstances, FDG–PET is of value in identifying the focus of metastatic activity. In selecting patients for curative hepatic resection, thin collimation CT or MRI of the liver with liver-specific contrast agents are of critical importance in delineating the distribution of metastases and assessing overall resectability. MRI has a further important role to play in characterising co-existing benign lesions. Finally, FDG–PET provides a highly effective tool in further ensuring accurate selection of patients for hepatic resection by providing confirmation of the absence or presence of irresectable extrahepatic disease. Thus, the use of an accurate preoperative screening technique that reliably selects patients using CT or MRI combined with FDG–PET will ensure that IOUS is reserved to facilitate surgical resection rather than to determine operability at laparotomy or laparoscopy [56].

Future studies

Future studies will be needed to separate the effects of different tests performed during follow-up incorporating assessment of cost-effectiveness and such studies will need to inform us of the intensity and frequency of surveillance imaging. Emerging techniques such as functional CT imaging with contrast enhancement may play a future role in identifying patients with early metastatic disease and together with functional FDG–PET imaging may prove useful as a method of assessing response to therapy when morphological parameters are insufficient.

Judicious use of CT, PET and MRI enables rigorous selection of patients for hepatic resection, preoperative chemotherapy, staged resections and assessment of response to therapy which in turn will continue to improve outcomes and survival in patients with metastatic colorectal cancer.

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