Clinical Radiology

The Royal College of Radiologists

Recommendations for cross-sectional imaging in cancer management
Liver metastases and primary liver cancer

April 2022

Contents

Clinical background

The liver is the organ most frequently affected by metastatic disease, second only to lymph nodes.[1] The management of liver metastases depends on various factors: number/location of lesions, the site (and therefore prognosis) of the primary tumour, and presence or absence of other sites of metastatic disease. For most tumour types, the presence of synchronous liver metastases will render further management palliative. However, for some, particularly colorectal and neuroendocrine tumours, long-term survival and even cure is possible in a subset of patients. Curative treatment may also be considered in selected cases from other malignancies, particularly if there has been a long interval between treatment of the primary tumour and representation with liver metastases.

Surgical resection and ablative techniques are currently the only potentially curative treatment options. Palliative treatments on the other hand include stereotactic body radiotherapy (SBRT), selective internal radiation therapy (SIRT) and systemic chemotherapy. Cardiovascular fitness, the segmental distribution of lesions and vascular involvement are major determinants for resection, with lesion size and number influencing selection for ablation. Metastases within both lobes of the liver are not an absolute contraindication to either resection or ablation.

Who should be imaged?

Patients who have neoplasms with a propensity to metastasise to the liver, as indicated in the appropriate sections of these guidelines, with the aim of detecting metastases. The most common primary tumours metastasising to the liver are colon, breast, lung, pancreas and stomach, but this list is far from exhaustive. Focal liver lesions in this context require accurate characterisation if their nature will affect subsequent treatment (this may require magnetic resonance imaging (MRI), a period of observation or biopsy if the diagnosis remains unclear).

Malignant disease confined to the liver (or with limited extrahepatic disease that does not exclude curative treatment options) in patients deemed fit for resection or ablative therapy should be imaged, with a view to detect the number and location of individual lesions to aid in treatment planning.

Staging objectives

- To determine the presence of liver metastases in patients with a known primary malignancy (see appropriate sections).

- To evaluate whether the liver lesion is benign, a primary malignant liver neoplasm or metastatic and thereby contributing to the decision as to whether no treatment, radical surgery, other local therapies or systemic chemotherapy is required.

- To identify the distribution (number and location) of malignant lesions and their relationships to the major vascular structures if the lesions are being considered for resection, ablation, SBRT or SIRT, or following neoadjuvant treatment.

- To identify other sites of metastatic disease in patients being considered for resection or other liver-targeted therapies.

- To avoid biopsy if the lesion(s) are potentially resectable and the patient is a candidate for liver resection.

- To identify the need for percutaneous-targeted biopsy, which is generally required for systemic chemotherapy, absence of a known primary or appropriate temporal relationship to a prior primary.
- To identify the presence of parenchymal liver disease and its consequences as this has a bearing on the nature of the liver lesions and treatment options.

Staging

The liver is usually examined as part of the general staging of patients with malignant disease (see guidelines appropriate to the primary tumour and *iRefer: Making the best use of clinical radiology*[2]). In general, computed tomography (CT) is used for this purpose. Dedicated liver MRI is indicated if there is diagnostic doubt or to increase the sensitivity for small malignant liver lesions present in patients who are candidates for curative treatment. Liver MRI is now widely accepted as the optimal imaging modality for detecting liver metastases, particularly subcentimetre lesions not visible on other forms of imaging.[3] The use of liver-specific MRI contrast agents, such as gadolinium ethoxybenzyl dimeglumine (gadoxetic acid, Gd-EOB-DTPA, Primovist), has an incremental value over CT and MRI with more traditional gadolinium chelates/extracellular contrast agents in the detection of liver metastases with greater sensitivity and specificity.[4–6] Liver MRI is required as a baseline in all patients undergoing neoadjuvant treatment to allow comparison with post-treatment scans. This aids with characterisation of small lesions and for showing the full extent of liver involvement at the outset, both crucial for future surgical planning. Liver MRI is also a valuable technique in the post-ablation setting, to assess for any residual or recurrent disease at the ablation site.

The role of preoperative fluorodeoxyglucose positron emission tomography-CT ([18]FDG PET-CT) in patients with colorectal liver metastases is currently uncertain with no clear survival benefit and a lack of randomised studies to support its routine use.[7] In selected patients being considered for curative treatment, PET-CT can be used to help characterise equivocal findings detected on other imaging, in restaging of patients with recurrence being considered for radical treatment and in high-risk patients with unfavourable primary tumour histology.[8]

Contrast-enhanced ultrasound, multiphasic CT (including dual energy/spectral CT) and MRI can all be used to characterise focal liver lesions identified as incidental or indeterminate as part of initial staging, and this will depend on availability and local expertise. However, in most instances, liver MRI with contrast medium usage will usually be the imaging modality of choice in the context of known malignant disease.

CT technique

- Oral administration of 750 ml of water over 30 minutes as a negative contrast agent to fill the stomach, duodenum and proximal small bowel.
- 100–150 ml of intravenous iodinated contrast medium injected at 3–4 ml/sec (ideally using weight-based volume).
- Bolus tracking helps to optimise the timing of acquisitions.
- The potential phases of enhancement that can be used are unenhanced, late arterial, portal venous and equilibrium phases, but the number of acquisitions needs to be restricted due to dose considerations (should be tailored to the underlying disease process if this is known).

- Multidetector computed tomography (MDCT) through the liver in the portal venous phase is the single most useful phase and is commenced at 65–70 seconds post-injection.
- Using MDCT, slice thickness will depend on scanner capability. In general, sections are acquired at 0.5–0.65 mm and reformatted at 2–5 mm for viewing.
- Additional late arterial phase (approximately 30–35 seconds post-injection) may be used for neuroendocrine tumours, hepatocellular carcinomas (HCC) and renal cell carcinomas, which are all typically hypervascular (as are the benign lesions such as focal nodular hyperplasia and hepatocellular adenoma).

Some populations of liver metastases from melanomas, thyroid carcinoma and some breast cancers are also hypervascular. However, the frequency of liver metastases, only visible on the arterial phase that will change the overall stage and affect management, is extremely low; thus, additional arterial phase imaging in these patient groups is not routinely recommended.

MRI technique

As breathing artifacts are problematic for liver imaging, strategies to overcome this need to be used in all patients. The appropriate strategy will depend on MRI machine specification but could include: breath-holding, navigator assisted, respiratory-ordered phase encoding, respiratory compensation and compressed sensing (local MRI physicist input is crucial for image optimisation).

A multichannel surface coil should be used in all cases. The field of view will in general be the whole liver. Parallel imaging techniques can be used to reduce the acquisition time in patients who have difficulty with breath-holding or to increase spatial resolution.

There is little general consensus on optimal liver protocols. Most would agree that the basic sequences that should be undertaken include T1W and T2W sequences. T1W sequences should be performed using spin- or gradient-echo (GRE) sequences with the spins 'in-phase' (such that liver–spleen contrast is maximised). Opposed-phase GRE sequences should also be obtained routinely as valuable means of assessment of the fatty liver and detecting fat within focal lesions. The Dixon method of fat suppression has advantages over other techniques including reduced susceptibility to artifacts and ability to quantify the amount of fat. T2W sequences with moderate and heavy weighting are useful for lesion characterisation. The use of T2 fat saturated or short tau inversion recovery (STIR) sequences maximises background liver to lesion depiction.

The use of liver-specific MRI contrast agents given intravenously is widely accepted to be of value in lesion detection (and characterisation of hepatocellular lesions) – see staging section earlier. The use of liver-specific contrast agents is recommended in all patients with liver metastases who are being considered for curative treatment (including before and after neoadjuvant treatment). Liver-specific contrast agents require protocol modification, with the timing of the hepatobiliary phase dependent on the agent used. Radiologists using these agents should familiarise themselves with their appropriate usage.

Diffusion-weighted imaging (DWI) should also be routinely performed. Although DWI-MRI is less sensitive than Gd-EOB-DTPA MRI for detecting liver metastases, the combination of both techniques has been shown to give the highest value of per-lesion sensitivity.[9] It also has an important role in differentiating cysts and haemangiomas from other lesions.

Protocol for imaging of liver metastases

Sequence	Plane	Slice thickness	Principal observations
Fast gradient-echo (GRE)/fast spin-echo (FSE)	Axial/coronal/ sagittal	10 mm	Overview and planning sequence
GRE T1W (in- and opposed-phase and Dixon)	Axial	3–6 mm	Demonstrate and eliminate the effects of intrahepatic fat and characterise lesions
T2W – FSE with moderate and long echo time (TE) **Alternatives include STIR and T2 fat sat**	Axial	3–6 mm	Identify and characterise cysts and haemangiomas
DWI (with suggested b values of 50, 200, 500 and 750)	Axial	5 mm	Identify malignant liver lesions and characterise cysts
Dynamic contrast study T1W GRE fat sat*	Axial (± oblique coronal for vascular relationships)	2.5 ± 1 mm	Characterise and identify tumours to demonstrate vascular relationships

* Unenhanced, arterial, portal venous phases. Equilibrium phase obtained with a ten-minute delay may be of value in characterising haemangiomas and cholangiocarcinomas. If a liver-specific contrast agent is used (highly recommended if curative treatment is an option), an acquisition at the appropriate hepatobiliary phase will be required (1–2 hours for gadobenate dimeglumine [Multihance] and 10–20 minutes for Gd-EOB-DTPA [Primovist]).

PET-CT

^{18}FDG PET-CT is a useful complementary technique to MRI for hepatic lesion detection. Liver metastases are generally FDG-avid and therefore readily detected by PET-CT. Sensitivity is dependent on how avid the tumours are; highly avid metastases detectable in the order of 5 mm in diameter can be detected in such tumours as colorectal cancer but it should be remembered that normal liver uptake of ^{18}FDG can be heterogeneous. Mucinous metastases have variable uptake of ^{18}FDG and may be non-avid.

Follow-up

Follow-up is conducted:

- To assess response to chemotherapy and is, therefore, performed at a frequency to correspond with the chemotherapy regimes
- When there is clinical or serum marker evidence of recurrence
- After surgery or ablative therapy to identify small-volume recurrent disease within the liver or lungs that may be amenable to further resection/ablation.

Tips

- The arterial phase is relatively short and optimal timing is affected by cardiac output. To optimise dynamic contrast-enhanced CT or MRI in which an arterial phase is required, either a test bolus or a delay triggered from aortic enhancement thresholds can be used.

- Lesion-liver contrast in CT in the arterial phase is dependent upon the rate of delivery of iodine; therefore, relatively high flow rates and volumes of contrast are helpful (for example, 4–5 ml/sec), whereas liver-lesion contrast in the portal venous phase is more dependent upon the total iodine dose.

- The arterial phase is prone to transient perfusion effects, which may mimic hypervascular lesions.

- In patients with fatty livers, the sensitivity of CT to hypovascular lesions is reduced; depending on the clinical issues to be addressed, MRI should be considered.

- MRI using a liver-specific contrast agent and DWI gives the highest sensitivity for detection of liver metastases and should be performed in all patients being considered for curative treatment.

- The distribution of Gd-EOB-DTPA differs from other gadolinium chelates as it is rapidly cleared from the blood pool and taken up by hepatocytes. This will affect the appearance of lesions such as haemangiomas and requires consideration when characterising lesions.

- DWI is not adversely affected by hepatocyte liver-specific contrast agents.

- Chemotherapy may affect the imaging characteristic and performance in the detection of metastases using all imaging techniques.

Primary liver cancer

Clinical background

Worldwide, liver cancer constitutes a major health problem being the fifth most common cancer and the second most frequent cause of cancer-related death globally.[10] In the UK, the incidence of liver cancer is much lower with HCC, the most common of the primary liver neoplasms, accounting for only 1.6% of all primary malignancies.[11] However, the incidence of both HCC and cholangiocarcinoma (the second most frequent primary liver neoplasm) continues to rise within the UK and this is partly due to increasing rates of liver cirrhosis, an important risk factor for HCC.[11] Sporadic HCCs, arising in the absence of liver cirrhosis, tend to be large at presentation with a dominant tumour mass, with or without satellite nodules, and occur in an older population. Fibrolamellar HCC is a distinct primary liver tumour occurring in young adults without liver cirrhosis and with normal serum alpha-fetoprotein levels.

The prognosis of HCC is dependent on the stage at which the tumour is detected, therefore early detection and accurate diagnosis is important in the management of HCC. Surveillance of high-risk patients (those with cirrhosis, advanced fibrosis or non-cirrhotic hepatitis B infection)[10] using six-monthly ultrasound plus/minus serum alpha-fetoprotein measurements is undertaken in many parts of the UK. Differentiating HCC from dysplastic nodules, the precursors of HCC, can be difficult using only non-invasive techniques. In the absence of chronic liver disease or with cirrhosis and good functional reserve, resection is the treatment of choice. In the presence of cirrhosis and poor functional reserve, liver transplantation can be offered depending upon lesion size, number and the absence of major vascular invasion. Other therapies include percutaneous ablative therapies, transarterial chemoembolisation, SBRT and systemic treatment.

Who should be imaged?

Patients at high risk of developing HCC in whom ultrasound and/or serum alpha-fetoprotein measurements indicate the possibility of an underlying neoplasm require further imaging. In those with nodules <1 cm detected at ultrasound, enhanced four-monthly surveillance is advised initially.[10] If the lesion(s) remain stable over a one-year interval then the patient can revert to routine six-monthly ultrasound surveillance. If there is an increase in size or number of nodules then further characterisation is needed. Unlike most other cancers, HCC can be diagnosed non-invasively with imaging without mandatory pathology confirmation. Further characterisation using non-invasive criteria can be applied to cirrhotic patients for nodule(s) ≥1 cm, in light of the high pre-test probability. This can be performed with multiphasic CT, dynamic contrast-enhanced MRI or contrast-enhanced ultrasound. CT or MRI should be used first given their higher sensitivity and ability to analyse the whole liver.

Guidelines from several major international organisations include criteria for the non-invasive diagnosis of HCC in patients with cirrhosis using the dynamic contrast characteristics of HCC when compared with benign liver nodules.[10,12] Most recently, a group of experts supported by the American College of Radiology developed and revised the *Liver Imaging Reporting and Data System (LI-RADS) version 2018*, a system where features of liver nodules are used to give a score as an indicator of the probability of a particular nodule being an HCC.[12] LI-RADS includes the dynamic contrast characteristics, size and growth of a nodule supplemented with ancillary MRI findings.

Patients who are potential candidates for curative treatment require all lesions to be characterised and mapped. In the absence of an extrahepatic primary tumour or with features of a primary hepatic neoplasm, malignant liver lesions also require full staging.

Staging objectives

- To identify the presence and location of the primary tumour and to detect multifocal liver involvement.

- To note the presence of vascular invasion.

- To note whether parenchymal liver disease and portal hypertension are also present.

- To evaluate whether the liver pathology is benign, premalignant or primary malignant and consequently to decide whether radical surgery, ablative therapy or palliation is required.

- To avoid biopsy if the lesion(s) are potentially resectable or if alpha-fetoprotein is significantly elevated.

- To accurately assess the extent of biliary and vascular involvement in hilar cholangiocarcinomas (including portal venous/hepatic veins/hepatic arteries), which is crucial for determining resectability.

- To determine the full extent of disease including deposits in the lymph nodes, lungs, bones, adrenal glands and peritoneum.

Staging

CT technique

- CT of the chest, abdomen and pelvis is the investigation of choice.

- Oral administration of 750 ml of water.

- 100–150 ml of intravenous iodinated contrast medium injected at 3–4 ml/sec (ideally using weight-based volume).

- Bolus tracking helps to optimise the timing of acquisitions.

- MDCT with acquisition through the chest with dual-phase acquisition of the liver commenced at 30–35 (late arterial) and 65–70 seconds (portal venous) post-injection with the last acquisition continued through the pelvis.

- Using MDCT, slice thickness will depend on scanner capability. In general, sections are acquired at 0.5–0.65 mm and reformatted at 2–5 mm for viewing.

- If arterial anatomy is required prior to resection, an additional early arterial acquisition at 18–20 seconds with 1 mm collimation can be acquired, although this is not routinely advocated.

- For treatment-naive patients undergoing CT, unenhanced imaging is optional; however, it is required in the post-treatment setting.

Protocol for imaging of primary liver tumours

Sequence	Plane	Slice thickness	Principal observations
Fast gradient-echo (GRE)/fast spin-echo (FSE)	Axial/ coronal/ sagittal	10 mm	Overview and planning sequence
T2W 2D and 3D MRCP	Oblique coronal	40 mm and 1 mm respectively	For biliary tract tumours to assess extent of biliary involvement
GRE T1W (in- and opposed-phase and Dixon)	Axial	3–6 mm	Demonstrate and eliminate the effects of intrahepatic fat and characterise lesions
T2W – FSE with moderate and long echo time (TE) **Alternatives include STIR and T2 fat sat**	Axial	3–6 mm	Identify and characterise cysts and haemangiomas
DWI (with suggested b values of 50, 200, 500 and 750)	Axial/coronal	5 mm	Identify malignant liver lesions and characterise cysts
Dynamic contrast study T1W GRE fat sat*	Axial (± oblique coronal for vascular relationships)	2.5 ± 1 mm	Characterise and identify tumours to demonstrate vascular relationships

* Unenhanced, arterial, portal venous phases. Equilibrium phase obtained with a ten-minute delay may be of value in characterising haemangiomas and cholangiocarcinomas. If a liver-specific contrast agent is used, an acquisition at the appropriate hepatobiliary phase will be required (1–2 hours for gadobenate dimeglumine [Multihance] and 10–20 minutes for Gd-EOB-DTPA [Primovist]).

MRI technique

MRI has advantages over CT particularly for the evaluation of focal liver lesions in the cirrhotic liver. It provides a greater number of parameters by which to assess nodules including presence of intra-tumoural fat/haemorrhage and diffusion characteristics. MRI contrast agents may be extracellular or hepatobiliary; the latter enable both extracellular and hepatobiliary phase imaging. Both Gd-EOB-DTPA (Primovist) and gadobenate dimeglumine (Multihance) may be used in hepatobiliary phase imaging, though gadobenate requires longer delays (1–2 hours for gadobenate vs about 20 minutes for Gd-EOB-DTPA). Late arterial phase imaging is strongly preferred over early arterial phase imaging to maximise the likelihood of depicting hypervascularity, which is a major feature of HCC (although it is now possible to perform multiple arterial phase acquisitions during a single breath hold).

When compared with CT or MRI with extracellular contrast agents, MRI with Gd-EOB-DTPA permits detection of arterialised HCCs in the dynamic phases as well as detection of small non-arterialised HCCs in the hepatobiliary phase, which increases sensitivity for diagnosis of small lesions (<2 cm).

For cholangiocarcinomas, particularly hilar tumours, MRI can provide better assessment of the extent of biliary and vascular involvement and can be used in selected cases when CT is not definitive. Extracellular MRI contrast agents are generally used over hepatobiliary agents as there is often biliary obstruction, which could impede the dynamic and delayed phases if the latter was chosen.

PET-CT

[18]FDG PET-CT has variable efficacy in hepatobiliary tumours. It is not used routinely in HCC imaging because of its limited sensitivity (about 50–70%).[13] Performance is better for larger tumours, poorly differentiated tumours and metastatic HCCs, which have a greater tendency to be FDG-avid. The introduction of novel radiotracers shows promise in optimising the sensitivity of PET for HCC, among which choline has been studied the most with higher sensitivity for HCC.[14] Variable uptake of [18]FDG is seen in cholangiocarcinoma, although certain histological subtypes such as mass-forming cholangiocarcinoma can demonstrate sensitivity in the region of 85%.[15] False-positive [18]FDG uptake is seen in acute cholangitis and inflammatory uptake is also observed following biliary stent insertion. Therefore, when [18]FDG PET-CT is used for the assessment of cholangiocarcinoma, it is preferable to perform the PET-CT study prior to biliary stent insertion.

Follow-up

Imaging follow-up is conducted:

- After surgery or ablative therapy to identify small-volume recurrent disease that may be amenable to further resection/ablation
- To assess response to chemoembolisation/SBRT/systemic treatment
- To assess the significance of indeterminate hypervascular lesions

Tips

- With dynamic extracellular small molecular weight contrast medium enhancement, it is important to have an unenhanced acquisition of the same sequence to identify true arterial enhancement; in liver cirrhosis, dysplastic nodules are often of high signal intensity. If there is a nodule bright on T1 pre-contrast a subtraction can be performed from the arterial phase to determine if there is arterial enhancement.

- Subcentimetre hypervascular lesions only identified on the arterial phase in patients with cirrhosis should be interpreted with caution – not all hypervascular lesions will be small HCCs.

- While the majority of HCCs are hypervascular, a minority are hypovascular.

- HCCs may take up liver-specific contrast agents, while poorly differentiated tumours usually do not; evaluation of all sequences with appropriate clinical parameters, including serum alpha-fetoprotein levels, is important in characterising focal liver lesions.

- A GRE T2W acquisition can be helpful to demonstrate intratumoural haemorrhage, which is rarely seen in tumours other than HCC or hepatocellular adenomas.

- Enlargement of lymph nodes is common in the presence of cirrhosis and, therefore, caution should be used in interpreting such periportal nodes as being involved.

- When evaluating hilar cholangiocarcinomas, the oblique coronal plain is advantageous in demonstrating the relationship of the tumour to the hilar vascular structures.

- With cholangiocarcinomas, it is preferable to fully stage the tumour before the insertion of a biliary stent as the stent may cause the production of fibrosis, which may mimic the primary tumour leading to overstaging.

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