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Clinical Radiology
The Royal College of Radiologists

Recommendations for cross-sectional imaging in cancer management, Second edition

Liver cancer

Faculty of Clinical Radiology

Contents

Liver metastases

Clinical background

After lymph node metastases, the liver is the most common site of metastatic disease[1] and consequently, liver metastases represent the commonest form of malignant liver disease.[2] The prevalence of benign liver tumours is also high,[3] and it is clearly important that benign liver lesions are distinguished from malignant disease. Liver metastases usually indicate that the malignant disease is disseminated and resection of the primary tumour with curative intent is no longer feasible and treatment is usually with systemic chemotherapy. In patients in who the primary lesion has been or can be eradicated and the liver is the only site of disease, surgical resection or an ablative therapy may be considered. Liver resection and ablation are most commonly performed for colorectal metastases and neuroendocrine tumours but may be appropriate 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. 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 absolute contraindications to either resection or ablation.

Who should be imaged?

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 also require characterisation when their nature will affect the nature of the treatment given.

Malignant disease confined to the liver 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 the planning of physical therapies.

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 or 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 or ablation.
- To identify other sites of metastatic disease in patients being considered for resection or ablative 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 in the 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 when appropriate clinical areas are imaged (see guidelines appropriate to the primary tumour and *iRefer: Making the best use of clinical radiology*[4]). In general, CT is used for this purpose. Dedicated liver MRI can also be used to increase the sensitivity for small malignant liver lesions present in patients who are candidates for resection.

^{18}FDG PET-CT is likely to be of value in patients with colorectal cancer being considered for resection as it can identify patients with extra-hepatic disease which may preclude hepatic surgery.[5] Contrast-enhanced ultrasound, multiphasic MDCT, and MRI can all be used to characterise focal liver lesions identified as incidental or indeterminate as part of initial staging.[4] However, in most instances, liver MRI with contrast medium usage will usually be the imaging modality of choice in the context of malignant disease.

CT

- Oral administration of 1 litre of water or iodinated contrast medium.
- 100–150 ml of intravenous iodinated contrast medium injected at 3–5 ml/sec.
- 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.
- 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, using a 64-row MDCT sections are acquired at 0.5–0.65 mm and reformatted between 2–5 mm for viewing.
- Additional late arterial phase (approximately 30–35 seconds post-injection) may be used for neuroendocrine tumours, hepatocellular carcinomas and renal cell carcinomas which are 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

As breathing artefacts 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, and respiratory compensation.

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 that have difficulty with breath holding or to increase spatial resolution.

It is to be noted that there is little general consensus with regard to optimal liver protocols, mostly due to compromises that need to be made because of the MRI scanner being used.

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 sequences with the spins ‘in-phase’ (such that liver–spleen contrast is maximised). Opposed-phase gradient-echo (GRE) sequences should also be obtained routinely as valuable means of assessment of the fatty liver and detecting fat within focal lesions. 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.

Extracellular small molecular weight contrast medium given intravenously is of value in lesion characterisation and detection (see injection protocol below).

Diffusion-weighted imaging increases the sensitivity for focal liver lesions and has a role in differentiating cysts and haemangiomas from other lesions.

Protocol for imaging of liver metastases

Sequence	Plane	Slice thickness	Principle observations
Fast gradient-echo (GRE)/fast spin-echo (FSE)	Axial/coronal/sagittal	10 mm	Overview and planning sequence
GRE T1W (in- and opposed-phase)	Axial	3–6 mm	Demonstrate and eliminate the effects of intrahepatic fat and to characterise lesions
T2W – (fast) spin-echo with moderate and long TE. Alternatives include STIR and T2 fat sat	Axial	6 mm	Identify and characterise cysts and haemangiomas
Diffusion-weighted imaging	Axial or coronal	5 mm	Identify malignant liver lesions 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 and 10–20 min for gadoxetic acid).

Liver-specific contrast agents have both characterisation and detection roles. Some studies have demonstrated that liver-specific contrast media have advantages over non-specific small molecular weight chelates in specific circumstances, including prior to liver resection. Liver-specific contrast agents require protocol modification, with the timing of the hepatobiliary phase dependent on the agent used.

Suggested basic sequences and those for use with extracellular small molecular weight contrast medium given intravenously are given in the table below. Sequences and timings related to liver-specific contrast agents vary widely and radiologists using these agents should familiarise themselves on their appropriate usage.

PET-CT

^{18}FDG PET-CT is a useful complementary technique to MRI for hepatic lesion detection (see also comments above). Liver metastases are generally FDG-avid and therefore readily detected by PET. 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. ^{18}FDG PET-CT is a valuable technique in the post-radiofrequency ablation setting, being an early indicator of complete/incomplete tumour destruction and an effective modality for follow-up. CT and MRI are less sensitive than ^{18}FDG PET-CT in this situation. Mucinous metastases have variable uptake of 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 which 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. (Remember the axiom: 'Fat is your foe on CT, but your friend on MRI!')
- The distribution of gadoxetic acid 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.
- Diffusion-weighted imaging 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

Hepatocellular carcinoma (HCC) is the most common of the primary liver neoplasms.[6] Although it is the fifth most common malignancy worldwide, it represents only 1% of primary malignancies in the UK.[6] The incidence of both HCC and cholangiocarcinoma (the second most frequent primary liver neoplasm) is rising within the UK.6 HCC often occurs on the background of liver cirrhosis which adds to the difficulty in obtaining an accurate diagnosis and in local staging. 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.

Surveillance of high-risk patients with cirrhosis using ultrasound and 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 and transarterial chemoembolisation.

Who should be imaged?

Cirrhotic patients at high risk of developing HCC in who ultrasound and/or serum alpha-fetoprotein measurements indicate the possibility of an underlying malignant cause; the intension being to detect and characterise liver lesions.4 All patients with focal liver lesions, and who are potential candidates for curative treatment, require all lesions to be characterised and mapped. In the absence of an extra-hepatic primary tumour or with features of a primary hepatic neoplasm, malignant liver lesions 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 determine the full extent of disease including deposits in the lymph nodes, lungs, bones, adrenal glands and peritoneum.
- To note whether parenchymal liver disease and portal hypertension are also present.
- To evaluate whether the liver pathology is benign, pre-malignant 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.

Staging

CT

- CT of the chest, abdomen and pelvis is the investigation of choice.
- Oral administration of 1 litre of water or iodinated contrast medium.
- 100–150 ml of intravenous iodinated contrast medium injected at 4–5 ml/sec.
- MDCT with acquisition through the chest with dual-phase acquisition of the liver commenced at 30–35 and 65–70 seconds post-injection 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.

Protocol for imaging of primary liver tumours

Sequence	Plane	Slice thickness	Principle observations
Fast gradient-echo (GRE)/fast spin-echo (FSE)	Axial/coronal/sagittal	10 mm	Overview and planning sequence
GRE T1W (in- and opposed-phase)	Axial	6 mm	Demonstrate and eliminate the effects of intrahepatic fat and to characterise lesions
T2W – (fast) spin-echo with moderate and long TE. Alternatives include STIR and T2 fat sat	Axial	6 mm	Identify and characterise cysts and haemangiomas
Diffusion-weighted imaging	Axial/coronal	5 mm	Identify malignant liver lesions 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 and 10–20 min for gadoxetic acid).*

Values of $CTDI_{vol}$ should normally be below the relevant national reference dose for the region of scan and patient group (see Appendix and Radiation protection for the patient in CT in Section 2).

MRI

MRI has advantages over CT particularly for the evaluation of focal liver lesions in the cirrhotic liver.

Hepatocyte liver-specific contrast agents may also be of value in characterising focal liver lesions. Gadobenate and gadoxetic acid are both T1 agents which can be used dynamically with a T1W GRE fat sat sequence. Uptake of these contrast media in the hepatobiliary phase is variable with HCC but in the majority reduced.

PET-CT

^{18}FDG PET-CT has variable efficacy in hepatobiliary tumours. The sensitivity for detection of hepatomas is in the range of 50–70%.[7] Performance is better for larger tumours and metastatic HCCs have a greater tendency to be FDG-avid. 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%.[8] 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 which may be amenable to further resection/ablation
- To assess response to chemoembolisation
- 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

- Sub-centimetre 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 over staging.

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