

REVIEW

The early detection of liver metastases

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Abstract

Early detection of liver metastases improves outcome in patients treated by chemotherapy, and is also associated with better survival in patients treated surgically. Large liver metastases (greater than about 1–2 cm in size) should be detectable by optimum quality CT or MRI techniques with a high level of accuracy. Microscopic metastases (smaller than 1–2 mm in size) are rarely detected by anatomic imaging methods, but are also rarely discovered at surgery or pathology. Alterations in perfusion caused by angiogenesis in microscopic lesions can sometimes be detected using radionuclide or doppler perfusion techniques. Currently, attention is focused on the early and correct diagnosis of lesions in the size range 2 mm to 2 cm. In this size range, superparamagnetic iron oxide (SPIO) enhanced MRI is probably superior (60% sensitivity) to dual phase CT (45% sensitivity) when compared with surgery and intra-operative ultrasound. Recent developments in CT and MRI promise some further improvement. The value of ultrasonic contrast agents has been shown in efficacy studies, but they are yet to be assessed against state of the art CT and MRI.

Keywords: *Liver; metastasis; diagnosis; imaging.*

Why look for early metastatic disease?

The discovery of liver metastases is no longer an indication for terminal care. In addition to continuing improvements in chemotherapy, the unique regenerative capacity of the liver parenchyma offers a basis for resection of liver tumours which can include large and extensive metastases. However, it is clear from surgical studies over the last few years that the best outcome for liver surgery is achieved when the volume of disease is small, particularly when lesions are few in number or solitary, and when the lesions are localised to a single lobe. All these factors point towards early detection as a useful contributor to improved long-term outcome. New types of palliative and possibly curative treatments for liver metastases, including thermal and radio-frequency ablation, also require accurate and early detection of tumours, and finally, the accuracy of information for staging, stratification for treatment and prognosis is improved by the early detection of liver disease.

When should we look for liver metastases?

This question breaks up into two parts, both controversial. Firstly, which primary tumours have a significant incidence of liver metastases at the time of initial presentation so that examination of the liver should be part of the initial staging work-up? This clearly includes primary cancers of the gastrointestinal tract, lung, advanced breast cancer (stage 2B or above) and lymphoma; we should probably also include melanoma and testicular tumours. A further group of tumours shows relatively infrequent liver metastasis, but the liver should be examined if there is advanced local disease or lymph node metastasis at the time of presentation—this includes renal and ovarian tumours, also carcinomas of the prostate, bladder and uterus, and sarcomas.

The second part of this question relates to the likelihood of metastases developing after initial treatment of the

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primary tumour. How often should we examine the liver and with what methods? The doubling time of colorectal metastases has been shown from follow-up studies to range from 60–200 days, but occasionally we see much faster growth rates, and in other cases tumours appear indolent over a long period of observation before suddenly exploding into rapid growth. A reasonable compromise is to carry out abdominal CT together with clinical review and measurement of tumour markers at intervals of six months over the two years following initial treatment (e.g. in colorectal cancer). However, the evidence for improved long-term survival of patients undergoing surveillance, compared with those reviewed only when symptoms recur, is not yet sufficiently conclusive to define a standard of care.

How to look for metastases

Optimum CT technique requires thin slices and contrast enhancement. Maximum attenuation in liver parenchyma occurs approximately 30 seconds after the end of contrast injection, whatever volume is used. The maximum intensity of enhancement is greater with faster rates of injection. Depending on the size of the patient, 100–150 ml of contrast medium of 300 mg iodine concentration is appropriate, injected at 4–5 ml s⁻¹. Arterial phase acquisition should begin about 25–30 seconds from the beginning of the injection, and portal phase about 60–70 seconds from the start of injection. Dual phase acquisition is worthwhile for patients with carcinoid or pancreatic islet cell primaries, and for those with renal or adrenal primaries. There is also a significant minority of metastases from breast and colorectal cancer which is hypervascular in the arterial phase and less easily detected in the portal venous phase; whether the additional benefit of dual phase acquisition justifies its routine use in all patients with these pathologies remains arguable. Patients with primary hepatocellular lesions should also have dual phase examinations.

Optimum technique for MRI requires breath-holding T2 acquisitions using gradient echo sequences with superparamagnetic iron oxide (SPIO) enhancement. Published studies have shown this technique to be more sensitive than other sequences for detecting small lesions, but the recently developed 3D breath-hold T1w sequences, which are suitable for use with dynamic gadolinium enhancement, may offer an equally effective alternative.

Results with 'large' lesions

With metastases greater than 1–2 cm in size, current optimum CT and MR techniques should yield a very high detection rate. In a recent study of colorectal cancer metastases, using correlation with surgery, intra-operative ultrasound and histology, 99% of lesions of 1 cm or larger were detected on pre-operative MRI with SPIO

enhancement. The same patients also underwent dual phase contrast-enhanced CT which detected 94% of lesions in this size range. Occasional metastases will have similar signal or attenuation characteristics to those of the normal adjacent liver, but most of these will be detected using contrast enhancement. Currently, SPIO-enhanced MR appears marginally better than dual phase CT. Multi-detector CT producing improved resolution, and breath-hold 3D MR sequences with gadolinium both offer possible further improvements, yet to be confirmed. However, the lower limit of size for diagnosis by these methods is likely to remain at about 2–3 mm.

Results with 'small' lesions

It is in the size range of 2 mm–2 cm that the choice and execution of optimum imaging techniques is now critical. With dual phase CT using single detector technology, the typical detection rate for lesions <1 cm is 30–40%. With SPIO-enhanced MRI, we expect to detect about 60% of lesions smaller than 1 cm, using surgery with intra-operative ultrasound as a reference standard. The availability of multi-detector CT with thinner slices, and the development of 3D breath-hold T1 acquisitions with gadolinium MRI, also using thin slices, both offer the possibility of further improvements in the detection of small lesions, but results from these techniques are yet to be validated.

Microscopic metastases

All metastases start out as microscopic clumps of tumour cells. When they grow to a size of 100–200 microns, humoral factors stimulate the growth of new and abnormal blood vessels around the periphery of the lesion. At this size the lesions are not visible on conventional imaging, but might possibly be detected by dynamic radionuclide or ultrasound techniques as a result of the disturbance in hepatic arterial/portal flow ratios which is caused by the tumour angiogenesis. Radionuclide studies in the 1980s and doppler ultrasound studies in the 1990s both demonstrated an ability to predict which patients with apparently normal livers at imaging and surgery would subsequently develop overt colorectal metastases in the liver. These techniques have not been widely applied as other users have found their results difficult to reproduce and clinical colleagues have so far been reluctant to offer speculative chemotherapy on the basis of these tests. Similar approaches are now being tried using CT and MRI.

Conclusions and key points

Detecting metastases larger than 1–2 cm should be achieved in 90–95% of cases with CT and 95–100% of

cases with SPIO enhanced MRI.

Optimum CT and MRI methods are currently only moderately successful in detecting lesions in the 2–15 mm size-range. SPIO enhanced MRI appears superior to CT at present, but improvements may be expected with the use of multi-slice technology in CT, and also with T1w 3D acquisitions in gadolinium enhanced MRI.

Detecting lesions smaller than 2 mm is rarely possible with imaging, but might be achievable using radionuclide or doppler based perfusion techniques.

Further Reading

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