

Current Status in Imaging of Colorectal Liver Metastases

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Abstract

Colorectal cancer is a common malignancy that often metastasizes to the liver. Evaluation of the liver for metastases is important for staging and prognosis. Resection of limited hepatic metastases can result in prolonged survival. Imaging is vital to select appropriate patients to avoid unnecessary surgery. A variety of modern imaging tools can be used to detect and characterise hepatic lesions. These include contrast enhanced helical computed tomography (CT), CT arterial portography, magnetic resonance imaging (MRI) and intraoperative ultrasound (IOUS). Each has their advantages as well as disadvantages. Besides accuracy, availability, cost and presence of expertise determine the optimal modality or combination of modalities to use. The appearance of metastases on imaging can be correlated with histopathological abnormalities. Though metastases can often be distinguished from benign lesions, their appearances are by no means pathognomonic. Follow-up imaging for interval change and for assessment of response is often required.

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Introduction

Colorectal cancer is a common primary that metastasizes to the liver. About 20% of patients with colorectal cancer will have detectable metastases at the time of clinical presentation, with an additional 30% developing clinical evidence of hepatic disease within 24 months.¹ Imaging of the liver is thus necessary both for initial staging as well as to monitor the progress of therapy.

Detection of Hepatic Metastases

Detection of colorectal metastases forms an important aspect of cancer staging which greatly influences the treatment regime and prognosis. Studies have shown that resection of limited hepatic metastases in selected patients offers a 20% to 40% chance of 5-year survival. This is a significant improvement compared to 5% to 10% with non-surgical treatment.²⁻⁴ There is therefore a need to accurately determine the presence or absence, as well as the extent and distribution of hepatic metastases. This allows appropriate selection of surgical candidates, thereby avoiding unnecessary surgery with its potential complications. Conversely, it is equally important not to have false positives, which may exclude a patient with a potential chance of improved survival from surgery.

Optimal preoperative evaluation for liver metastases can be done by helical computed tomography (CT), magnetic resonance imaging (MRI) or CT arterial portography (CTAP). Intraoperative ultrasound (IOUS) can be performed at the time of surgery to detect metastases not seen during preoperative staging. The merits and disadvantages of the various modalities will now be discussed.

Helical Computed Tomography (CT)

Helical or spiral CT is the most commonly used modality in the preliminary staging of colorectal cancer. The main advantages are its ability to evaluate for both extrahepatic and intrahepatic disease. It is also widely available and less expensive compared to MRI, and is less invasive compared to CTAP.

The superior scanning speed of helical over conventional CT scanner allows images to be obtained at the optimal portal venous phase of enhancement to ensure optimal lesion detection. The blood supply of hepatic metastases is mainly via the hepatic arteries while that of normal liver parenchyma is via the portal venous route. Appropriate timing of the intravenous contrast injection and start of scanning allows images of the liver to be obtained during peak parenchymal enhancement, i.e. in the portal venous

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phase. During this phase of enhancement, liver metastases appear as hypodense lesions against the maximally enhanced background of the normal liver.

A recent article using optimal CT protocols, where helical CT findings were correlated with pathological and surgical findings on a lesion-by-lesion basis, showed a sensitivity of 85% with a 96% positive predictive value and false positive of 3.9%.⁵ Other studies with helical CT yielded sensitivities ranging from 72% to 81%.⁶⁻⁹ The slightly better results of the more recent study were attributed to finer collimation (5 mm) and higher contrast medium dose (170 mL) used.

With helical CT, it is possible to image the entire liver in both the arterial and portal venous phases. This is particularly advantageous for detection of hypervascular lesions such as primary hepatocellular carcinoma as well as hypervascular metastases. In the arterial phase, such lesions are seen as brightly enhancing against a less enhanced liver parenchyma. Use of dual (arterial and portal venous) phase scanning may marginally improve detection of liver metastases.¹⁰ However, other studies have shown that the addition of the arterial phase may not increase detection but only improve lesion conspicuity and diagnostic confidence.¹¹ It is probably less useful in the context of colorectal metastases which are typically hypovascular and therefore best appreciated in the portal venous phase.

CTAP

As mentioned above, the normal liver parenchyma derives most of its blood supply from the portal vein while blood supply to metastasis is largely arterial. If iodinated contrast medium is selectively delivered into the portal system, it is possible to greatly enhance the normal liver parenchyma, leading to greater lesion to background contrast and thus better detection of metastases. This can be achieved by direct injection of the superior mesenteric or splenic artery via an angiographic catheter.¹² This is an invasive procedure involving a femoral arterial puncture. There is a need for close coordination between the angiogram suite where the catheter is placed in the mesenteric artery and the CT scanner room where the injection of contrast medium and scanning is done. Reported sensitivity for metastasis was excellent and often exceeded 90%.^{12,13}

CTAP, however, has several drawbacks. It is invasive and time consuming and, in many centres, more expensive than helical CT or MRI. Interpretation can be difficult due to perfusion defects and there are more false positives.^{14,15} False positives are undesirable, as this would exclude patients that can potentially be cured by surgical resection of limited disease. Also, several recent papers using optimal MRI and helical CT techniques demonstrated similar sensitivities compared to CTAP.^{5,8,15} For these reasons,

CTAP is now less commonly performed in favour of helical CT or MRI. Figure 1 shows a CTAP scan of a patient suspected of colonic liver metastases. A follow-up contrast enhanced spiral CT (not shown) had reviewed a new lesion in segment IV. The CTAP demonstrates a hypodense lesion in segment IV (arrow) as well as another possible lesion in segment III (adjacent to asterisk). On MRI (Fig. 2), the segment IV lesion is well circumscribed, uniformly and markedly hyperintense on T2-weighted scans, which is suggestive of a cyst. No lesion was seen in segment III. These findings were confirmed on IOUS. The apparent abnormality in segment III on CTAP is probably due to perfusion abnormality, one of the causes of false positives in CTAP.

MRI

Optimal magnetic resonance techniques for detection of metastases are non-enhanced T2-weighted fat-suppressed spin-echo, gadolinium-enhanced spoiled gradient-echo breath-hold sequences or superparamagnetic iron oxide (SPIO) enhanced MRI. The latter is a reticuloendothelial agent that is used as a negative contrast, compared to gadolinium, which is an extra-cellular fluid space positive contrast agent. Sensitivity with current MR techniques approaches that of CTAP.¹⁵⁻¹⁷ Specificity of MRI is slightly better than CTAP. The T2-signal characteristic on MR is useful to distinguish metastasis from cyst or haemangioma.¹⁸

The main limitation of MR is cost and availability, especially when compared to helical CT. For satisfactory images, the patient also needs to maintain a breath-hold for at least 20 seconds. It is a useful alternative for patients allergic to iodinated contrast media and as a problem solving modality when there is difficulty distinguishing benign lesion from metastasis. Its multiplanar capability is also a bonus for surgical planning for lesions being considered for resection.

IOUS

Transabdominal ultrasound is not commonly used to stage colorectal cancer mainly due to its limited ability to detect extra-hepatic disease. It is also less sensitive for hepatic metastases when compared to CT or MRI, particularly for smaller lesions.^{13,19}

On the other hand, IOUS is considered the most sensitive technique for detection of liver metastases and is often the gold standard for evaluation of other imaging techniques when surgical specimen is not available.²⁰ Sensitivities reported are in the region of 95% to 99%.^{5,21,22} IOUS is far from ideal as it does not prevent unnecessary surgery and is time consuming to perform. It is, however, useful in preventing unnecessary liver resections by detecting additional lesions at the time of surgery. It also serves as a

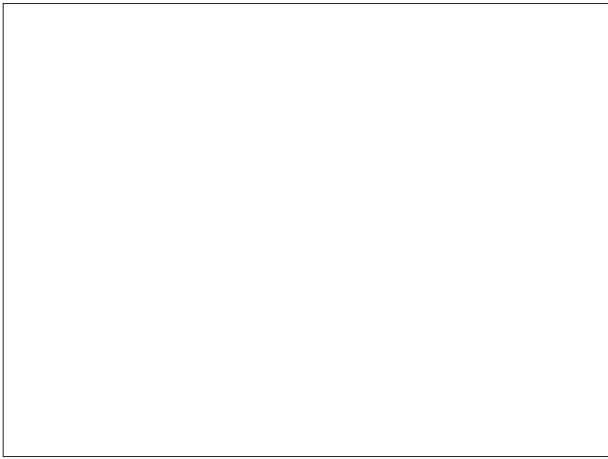


Fig. 1. Axial CT arterial portography liver scan of patient with suspected colonic liver metastases. It shows a lesion in segment IV (arrow) and another in segment III (adjacent to asterisk).

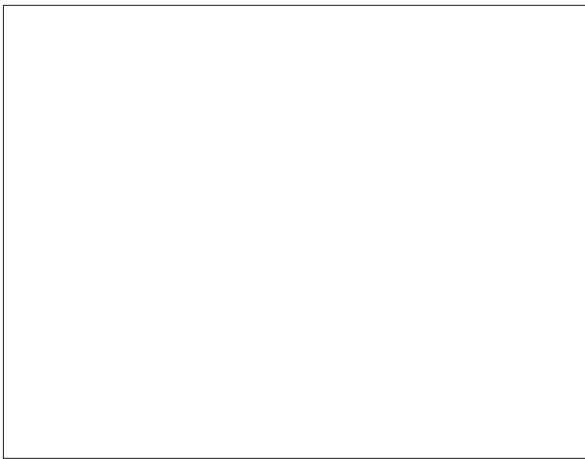


Fig. 2. T2-weighted inversion recovery image of the same patient. The segment IV lesion is markedly hyperintense, which is suggestive of a cyst. No lesion was seen in segment III. These findings were confirmed by intraoperative ultrasound.

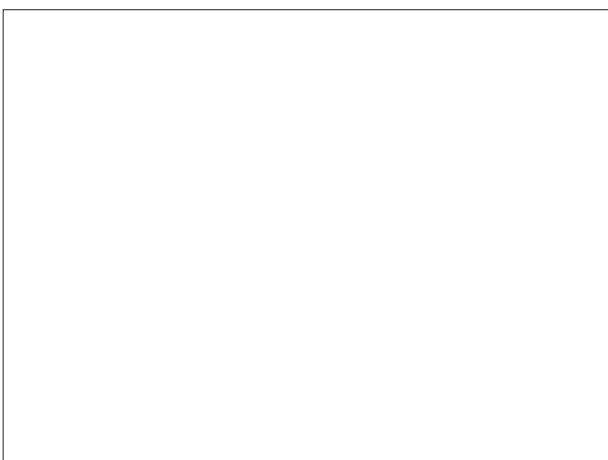


Fig. 3. Intraoperative ultrasound of the liver showing typical appearance of a cyst, which is anechoic, well circumscribed with no perceptible wall.

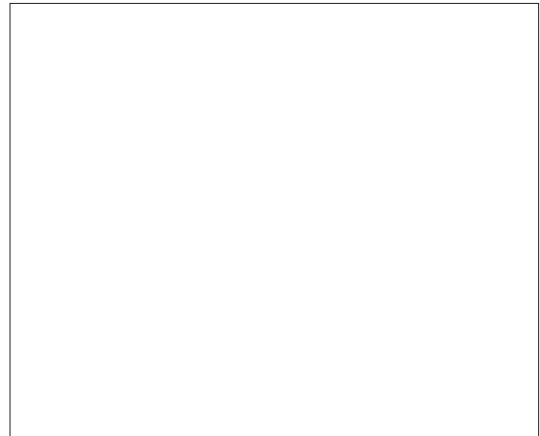


Fig. 4. T2-weighted spin-echo chemical selective fat-suppressed MRI showing 2 liver metastases with central low signal.

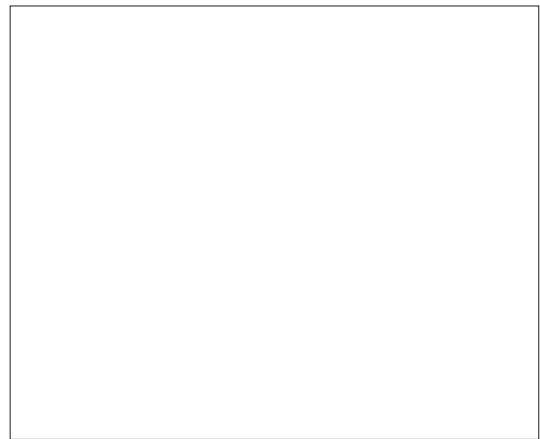


Fig. 5. T1-weighted gradient-echo-weighted scans after intravenous gadolinium, in the hepatic arterial phase showing a metastasis in segment II (arrow) with rim enhancement. The dark non-enhancing lesion lying close to it is a cyst.

guide for radiofrequency ablation or cryoablation where resection is not possible.²³ Some lesions suspected to be metastases on CTAP or MRI may turn out to be benign (cyst or haemangioma) on IOUS. Figure 3, for example, shows a typical IOUS appearance of a cyst. IOUS therefore forms a useful adjunct to preoperative imaging modalities.

Appearance of Liver Metastasis on CT and MRI with Histopathological Correlate

While it is important to detect as many metastases as possible, it is equally important to distinguish true metastases from incidental benign lesions, most commonly cysts and haemangiomas.

On helical CT, the distinction requires the use of intravenous iodinated contrast. Simple hepatic cysts typically show no perceptible wall, enhancement and have attenuation values close to water. Metastases on the other hand are more ill defined and demonstrate complete rim enhancement. A recent study studying the enhancement

pattern on multiphasic CT showed that a complete rim enhancement on arterial phase CT has a 82% positive predictive value (PPV) for metastases (sensitivity 75%, specificity 80%).²⁴ This contrasts with peripheral puddling seen in haemangiomas (86% PPV for haemangioma), which is followed by gradual and persistent filling in.

Definitive characterisation of some liver metastases remains difficult especially when the lesions are small (sub-centimetre). The imaging features of colorectal metastases are not pathognomonic and overlap with other benign lesions. In a prospective study by Valls et al⁵ using portovenous helical CT, false positive findings were found in 10 out of 257 lesions, including haemangioendothelioma, haemangioma, hepatic peliosis, biliary adenoma, centrilobular haemorrhage, biliary hamartoma, periportal fibrosis and normal liver parenchyma. False negatives were observed in 41 out of 290 lesions (14.1%), of which 36 small lesions were not even seen retrospectively. The criterion used for diagnosis of liver metastases in that study was “nodular low-attenuating lesions without characteristic findings of benign lesions (cyst and haemangioma)”.

On MRI, colorectal metastases are mildly hyperintense to the liver on T2-weighted scans while haemangiomas and most cysts are markedly hyperintense. Both are usually of low signal on T1-weighted scans. Larger hepatic metastases have central areas of coagulative necrosis and desmoplasia seen as areas of low signal intensity on T2-weighted scans. This finding was seen in 77 out of 154 lesions in Outwater et al's series.²⁵ Figure 4 is a T2-weighted fat-suppressed scan showing 2 such liver metastases with central low signal. On the post-gadolinium T1-weighted scan of the same patient (Fig. 5), an additional lesion is seen in segment II (arrow), which was not visible on her prior contrast-enhanced CT scan (not shown).

After gadolinium contrast administration, areas of perilesional enhancement can be seen which correspond to areas of peritumoral desmoplastic reaction, inflammatory cell infiltration and vascular proliferation.²⁶ The actual tumour tissue seen is thinner than the area of enhancement which corresponds to the areas of hepatic tissue reaction. In 1 patient of Semelka et al's series, pre- and post-chemotherapy MR scans show decrease in perilesional enhancement as a feature of response to therapy.²⁶ This suggests that the pathological change correlating to response to chemotherapy may be a decrease in peritumoral inflammation and vascular proliferation.

Outwater et al²⁵ found hypointense peripheral rims on T2-weighted scans in 25% of their series correlating to areas of compressed liver parenchyma, hepatocellular atrophy, fibrosis, inflammation and congested sinusoids. Lunevicius et al²⁷ found those fibrotic capsules around colorectal metastases in 20% of cases. The presence of

fibrotic capsule was associated with a lower rate of initial recurrence in the remnant liver. Further radiological-pathological correlation of this capsule is required to determine if imaging can identify a subgroup of colorectal metastases with good surgical prognosis.

Follow-up of Treated Colorectal Metastases

Much imaging of the liver for colorectal metastasis is performed for the assessment of response to therapeutic regimes. This is done by comparing serial scans of the same patient, looking for interval change in size and number of lesions.

Measurement of colorectal liver metastases is an important task faced by radiologists working in an oncologic setting. Treatment decisions are often based on whether there is response to therapy. The definition of response has traditionally been based on the WHO criteria²⁸ where bidimensional products are used. This is the longest diameter multiplied by the greatest perpendicular diameter. Complete response is defined as resolution of the lesion. A decrease of 50% of the bidimensional product constitutes a partial response and an increase of 25% constitutes progression.

Recently, a consensus meeting of several important cancer groups named “Response Evaluation Criteria in Solid Tumors” (RECIST) published new guidelines. These new criteria are based on changes in unidimensional measurement. A 30% change in tumour diameter constitutes partial response and a 20% increase constitutes progression.²⁹ The appropriate criteria to use depends on the criteria adopted by the practising oncologist. However, as the bidimensional product is still commonly used as a criterion for assessment of response, it is wise for radiologists to continue to supply the bidimensional measurements.

Nazarian et al³⁰ studied the measurement of the bidimensional product by 3 radiologists on precontrast and postcontrast studies and found that the metastases were significantly smaller after contrast administration. However, Park et al³¹ found that there was no consistent pattern to demonstrate over or underestimation of disease progression on unenhanced or contrast-enhanced spiral CT of the liver. It is important to make comparisons on comparable scans and not to compare lesion size on contrast-enhanced scans with those of unenhanced scans. A consistent scan protocol for each follow-up scan also makes direct comparison an easier task.

Conclusion

With the different methods of imaging available for the detection and diagnosis of colorectal metastasis, the obvious question would be “Which is the optimal method?”. The answer lies in the question. The optimal method is not necessarily the best in terms of sensitivity or specificity, but

what is optimal has to take into consideration cost, availability and expertise.

Contrast-enhanced helical CT remains the most widely available modality for the evaluation of hepatic metastases and is likely to remain so for some time. It is the modality of choice for follow-up of treated lesions. While transabdominal ultrasound is also widely available and even more affordable, its low sensitivity, as well as a lack of ability to evaluate extrahepatic disease, limits its use in evaluation of colorectal liver metastases or for follow-up. With optimal helical CT scan protocols, it is possible for sensitivity of CT to approach that of the more invasive CTAP. Current MRI techniques are also comparable with CTAP, but usage is limited mainly by cost as well as limited availability. It is, however, an invaluable problem-solving modality.

IOUS is time-consuming and appropriate training is required as ultrasound is operator dependant. If used correctly, it can prevent unnecessary liver resections though it does not prevent surgery itself. Also, it can be used to guide intraoperative radiofrequency ablation or cryotherapy of lesions that cannot be resected.

Each of these techniques has their own unique advantages and is often complementary. Thus, evaluation of patients with suspected colorectal liver metastasis would often require more than one of these techniques. For example, a patient being considered for resection of limited hepatic metastasis after an optimal helical CT scan would still benefit from IOUS, as this may detect more lesions and provide additional useful information to the surgeon. Additional MRI scan may also be done prior to surgery if the helical CT findings were inconclusive.

While this review has mainly concentrated on cross-sectional imaging techniques, there is a rapidly emerging role of positron emission tomography (PET) in the whole body evaluation of patients with colorectal malignancy, including hepatic metastasis. Detection of disease depends on the increase uptake of a glucose analogue, [fluorine-18] 2-deoxy-2-fluoro-D-glucose (FDG), by metabolically active cancer cells. A recent meta-analysis³² concluded that FDG-PET is the most sensitive non-invasive imaging modality for diagnosis of hepatic metastasis from gastrointestinal tract cancers, with a mean weighted sensitivity of 90% when papers with greater than 85% specificity were considered. However, the main advantage of PET over the other techniques could be the increased ability to detect extrahepatic disease, which is equally important in the selection of patients for resection of hepatic metastasis.³³

Finally, it must be understood that whatever the imaging modality, it is never possible to exclude metastases in the liver. Even a portion of patients with negative IOUS, the current gold standard, will develop metastases eventually.

The reason for this is that metastasis usually begins at microscopic level and imaging only detects them when they are more than 3 to 5 mm in size.

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