World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i42.4654

*World J Gastroenterol* 2011 November 14; 17(42):4654-4659
ISSN 1007-9327 (print) ISSN 2219-2840 (online)


TOPIC HIGHLIGHT

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# Imaging diagnosis of colorectal liver metastases

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Received: March 31, 2011 Revised: June 15, 2011
Accepted: June 22, 2011
Published online: November 14, 2011

## Abstract

Rapid advances in imaging technology have improved the detection, characterization and staging of colorectal liver metastases. Multi-modality imaging approach is usually the more useful in diagnosis colorectal liver metastases. It is well established that hepatic resection improves the long-term prognosis of many patients with liver metastases. However, incomplete resection does not prolong survival, so knowledge of the exact extent of intra-hepatic disease is crucially important in determining patient management and outcome. The diagnosis of liver metastases relies first and totally on imaging to decide which patients may be surgical candidates. This review will discuss the imaging options and their appropriate indications. Imaging and evaluating of colorectal liver metastases (CRLM) have been performed with contrast-enhanced ultrasound, multidetector computed tomography, magnetic resonance imaging (MRI) with extra-cellular contrast media and liver-specific contrast media MRI, and positron emission tomography/computed tomography. This review will concentrate on the imaging approach of CRLM, and also discuss certain characteristics of some liver lesions. We aim to highlight the advantages of each imaging technique, as well as underscoring potential pitfalls and limitations.



**Key words:** Liver metastasis; Colorectal cancer; Imaging-modality; Diagnosis

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Xu LH, Cai SJ, Cai GX, Peng WJ. Imaging diagnosis of colorectal liver metastases. *World J Gastroenterol* 2011; 17(42): 4654-4659 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i42/4654.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i42.4654

## INTRODUCTION

Metastatic disease to the liver is a very common clinical situation in oncology. The liver is one of the most common sites of metastatic spread of epithelial cancers, second only to regional lymph nodes. Colorectal cancer is one of a few malignant tumors in which the presence of limited synchronous liver metastases or metachronous metastases need surgical resection[1]. Colorectal liver metastases (CRLMs) develop during the course of colorectal cancer in up to 50%-70% of patients[1-3]. Metastases are confined to the liver in 30%-40% of patients at the time of detection and are potentially resectable in about 20%-30% of the cases[4,5]. Hepatic resection is the only potentially curative treatment for these colorectal liver metastases and in selected groups, the 5-year median survival has been reported to be up to 30% (range 15%-67%)[5]. Patients with untreated but potentially resectable metastases show a median survival of 8 mo and the 5-year survival rate

of these patients is less than 5%[6,7]. Eligibility for surgical treatment requires strict criteria. Besides an adequate clinical condition, all liver lesions have to be completely resectable. The diagnosis of liver metastases relies first and totally on imaging to decide which patients may be surgical candidates. Thus, the imaging technique able to demonstrate the exact number, regional distribution, size of metastases and the volume of the remaining liver is crucial to determine resectability.

In many centers, imaging and evaluating of CRLM have been performed with contrast-enhanced ultrasound (CEUS), multi-detector computed tomography (MDCT), magnetic resonance imaging (MRI) with extra-cellular contrast media and liver-specific contrast media MRI, and positron emission tomography/computed tomography (PET/CT). This review will concentrate on the imaging approach of CRLM, and also discuss certain characteristics of some liver lesions. We aim to highlight the advantages of each imaging technique, as well as underscoring potential pitfalls and limitations.

## IMAGING MODALITY PERFORMANCE

### CEUS

The development of CEUS has dramatically increased the potential of sonography in the assessment of focal liver lesions. The use of contrast agents allows perfusion mapping of focal lesions, thus enabling characterization of focal lesions. Bernatik *et al*[8] investigated the diagnostic yield of CEUS *vs* helical CT in the detection of liver metastases (no histological diagnosis), CEUS showed 97% of lesions seen by CT.

Although CEUS is widely used to assess the liver, it has some limitations: it needs considerable operator expertise and often reveals equivocal results in patients with (chemotherapy-induced) fatty infiltration of the liver. Due to the limitations in the visualization of segmental distribution and 3D-shape of metastases, it is limited in the preoperative assessment of patients with colorectal liver metastases.

### MDCT

Nowadays MDCT is the mainstay of staging and follow-up of these patients, because it provides good coverage of the liver and the complete abdomen and the chest in one session. MDCT scanner has the capability for high-resolution studies with sub-millimetre slice thickness resulting in isotropic pixel sizes, which enable images to be reformatted in various planes that still have the same resolution as the axial images. This may improve detection of small lesions. High-resolution scans with maximum intensity technique and volumetric three-dimensional rendering enable accurate segmental localization and delineation of tumour[9]. Vascular reconstruction enables the demonstration of the hepatic arterial and portal venous anatomy obviating the need for conventional angiography in surgical planning of tumour resection[10]. Volumetric measurement of tumour size and normal liver is also more accurate[11].

How many scans are necessary for a CT examination of the liver? In patients with colorectal cancer, liver metastases are calcified in 11% at initial presentation[12]. These lesions with calcification are much better seen on unenhanced scans than on portal-venous phase scans. Small CRLM often are hyperattenuating during the hepatic arterial phase whereas larger lesions will often show a hyperattenuating rim during the hepatic arterial phase and a hypoattenuating centre representing diminished vascularity and/or tumour necrosis[13], and larger lesions usually are detected as hypoattenuating lesions during the portal venous phase[14]. However the vascularity and therefore enhancement characteristics can be widely variable for reasons that are poorly understood[15-17].

Meijerink *et al*[18] concluded 50 patients suspected of CRLM, they found adding rigid-body co-registered subtraction CT images to a conventional 4-phase CT protocol for pre-operative detection and characterization of CRLM seems of no value. Wicherts *et al*[19] found Arterial and equilibrium phase have no incremental value compared to hepatic venous phase CT in the detection of CRLM. Venous phase is still the most significant timing to detect liver metastases.

Several studies have assessed the value of using thin slices to improve detection of small metastases. Two point five mm or 3.75 mm thick slices were significantly superior to 5, 7.5 and 10 mm thick slices[20,21]. When the slice thickness is decreased to 1 mm, no further improvement in lesion detection is seen, but there is a considerable increase in image noise with subsequent degradation of image quality[22].Therefore a slice thickness of 2-4 mm is recommended for axial viewing.

Although MDCT is the modality of choice for staging colorectal cancer, up to 25% of liver metastases may still be missed[23,24]. Extra care has to be taken for patients with contrast allergies or with renal impairment.

### CT with arterioportography

In CT with arterioportography (CTAP), CT scanning of the liver is performed during contrast agent injection into either the superior mesenteric artery or splenic artery *via* a percutaneously placed catheter. It provides maximum tumor-to-liver contrast by enhancing the liver parenchyma alone as in the portal phase and depicts tumor deposits as areas of perfusion defects. This is based on the fact that metastases are almost exclusively fed *via* the hepatic artery. CTAP was usually reserved for imaging candidates prior to surgical hepatic resection as it provided an accurate segmental localization of liver metastases and excellent depiction of liver vasculature. This invasive technique is less routinely performed with the advent of MDCT and MRI with liver-specific contrast agents, which are as accurate in lesion detection but with much lower false positive rates[25].

### MRI

The standard MRI protocol should always include un-

enhanced T1- and T2-weighted and contrast-enhanced pulse sequences. In liver MR imaging a set of T1-weighted in-phase and opposed-phase gradient-recalled echo gradient-recalled echo images is acquired to assess the parenchyma for the presence of fatty infiltration or focal sparing of diffuse fatty infiltration. For T2-weighted imaging, the turbo-spin echo (TSE) or the fast spin echo with fat suppression are preferred over the single-shot TSE pulse sequences. In addition, heavily T2-weighted pulse sequences with a time of echo of approximately 160-180 ms may help in differentiation between solid [metastasis, hepatocellular carcinoma (HCC), *etc.*] and non-solid lesions (e.g., haemangioma, cyst)[26,27].

After the acquisition of unenhanced pulse sequences, contrast-enhanced pulse sequences are always obtained. Nowadays, two different groups of MR contrast agents for liver imaging are available: first, the non-specific gadolinium chelates and second the liver-specific MR contrast agents. The latter group can be divided into two subgroups, the hepato-biliary contrast agents, and the reticulo-endothelial (or Kupffer cell) contrast agents.

## NON-SPECIFIC GADOLINIUM CHELATES

The liver and liver-lesion enhancement patterns obtained with non-specific gadolinium chelates (extracellular contrast agents) are similar to those obtained with iodinated contrast agents used in CT. Several agents with similar properties are on the market, including gadopentetate dimeglumine (Schering, Berlin, Germany), Gd-DTPA-BMA (GE Healthcare, Oslo, Norway), Gd-DOTA (Guerbet, Aulnay-sous-Bois, France), and Gado-teridol (Bracco, Milan, Italy).

Extracellular gadolinium chelates are used extensively for liver MRI. Following intravenous injection of a gadolinium-based agent, typically three phases of contrast enhancement are imaged: the arterial, portal venous phase and the equilibrium phase. During the arterial phase, most of the liver does not enhance as the majority of the liver's blood supply is *via* the portal vein. Enhancement patterns of liver lesions are similar to those demonstrated on CEUS and contrast-enhanced CT. The equilibrium phase or delayed phase is useful for helping with lesion differentiation (e.g., haemangioma *vs* metastasis). In addition, washout of contrast from HCC and peripheral or heterogeneous washout from liver metastases are characteristic findings on delayed imaging[28,29].

## LIVER-SPECIFIC CONTRAST AGENTS

### *Hepatobiliary agents*

Hepatobiliary agents represent a heterogeneous group of paramagnetic molecules of which a fraction is taken up by hepatocytes and excreted into the bile. Mangafodipir trisodium (Teslascan®, GE Healthcare) is taken up by hepatocytes and results in signal intensity increase on T1-weighted images (a so-called "T1 enhancer")[30], and a fraction is also taken up by the pancreas, which has been used for pancreatic MR imaging[31,32]. Focal non-hepatocellular lesions (i.e., metastases) do not enhance post-contrast, resulting in improved lesion conspicuity Mangafodipir-enhanced MRI has been show to be superior to unenhanced MRI and helical CT for detection of liver metastases[1,32,33].

Gd-BOPTA (Multihance®, Bracco) is a liver-targeted paramagnetic contrast agent and unlike conventional Gadolinium chelates, has almost two-fold greater T1 relaxivity which improves image contrast and detection of liver lesions, due to its high T1-relaxing effect and hepatocyte binding capability[34].

Gd-EOB-DTPA (Primovist®, Schering) and Gd-BOPTA are hybrid contrast agents, which carry a lipophilic ligand[35]. After intravenous bolus injection these agents show biphasic liver enhancement with a rapid T1 enhancement of the liver similar to that seen with non-specific extracellular gadolinium agents. Then hepatic signal intensity continues to rise for 20-40 min (Gd-EOB-DTPA) and 60-90 min (Gd-BOPTA), reaching a plateau after about 2 h because of hepatocytic uptake. This results in increasing contrast between liver and non-hepatocellular tumors[36].

### *Reticuloendothelial agents*

All reticuloendothelial system (RES) agents are superparamagnetic iron oxide-based contrast agents (SPIO). SPIO particles are taken up by RES cells (so-called Kupffer cells) of normal liver parenchyma, as also by macrophages of the spleen and lymph nodes. They shorten T2 and T2* relaxation times in the liver tissue, and resulting in a loss of signal intensity in normal liver parenchyma. Despite of this, malignant liver lesions do not have a substantial number of RES cells and appear as hyperintense lesions with distinct borders in contrast to the hypointense liver parenchyma after application of SPIO on T2-weighted MR images[37,38] .

There are some published studies comparing some methods reporting varying sensitivity. Some have reported that SPIO-enhanced MRI has better diagnostic efficacy for liver lesions over that of Gadolinium-enhanced MRI, Gd-BOPTA-enhanced MRI and dynamic CT imaging with high sensitivity values[39-41]. Another study has claimed equal sensitivity between SPIO-enhanced MRI and Gd-BOPTA-enhanced MRI in the delayed hepatocyte phase for the detection of LMs[42,43]. Mainenti *et al*[44] found Gd- and SPIO-enhanced MRI had equal performance and were shown to perform significantly better than the other modalities on a per lesion basis. These data were similar to previous studies comparing Gd- and SPIO-enhanced MRI each other[4,39] or with MDCT[39,45] or PET/CT[46]. Based on Zech *et al*[47] experience and the existing literature, imaging using Gd-EOB-DTPA-enhanced MR can be expected to be superior to the using standard gadolinium chelates or to spiral CT, especially for the differential diagnosis of hypervascular lesions.

Blyth *et al*[48] suggest that MRI is a highly sensitive method of pre-operative imaging of colorectal liver me-

tastases and should be considered the "gold standard". Except contraindications to MRI include pacemakers, implantable cardiac defibrillators, cochlear implants and metallic orbital foreign bodies, MR imaging is still limited in the anatomic coverage, although the recent introduction of multi-channel MR coils with wider coverage and the moving-table MR technique has re-established the "competitiveness" of MR with MDCT with regard to patient throughput. One of the advantages of MR in liver imaging is the better soft tissue contrast, which reveals better characterization of focal liver lesions in question. The development of a liver-specific MR contrast agent has further improved the diagnostic yield of MRI in lesion detection and characterization.

### PET/CT

The recent introduction of PET/CT hybrid scanners enables seamless and accurate fusion of the high resolution anatomic localisation of CT with the functional data of FDG-PET. A combination of FDG-PET and CT scanning characteristics seems promising, and integrated PET/CT is becoming more widely available, although the exact clinical value and efficacy is not yet fully established. Due to restricted availability, high cost and an additional radiation exposure, PET/CT should be used in selected patients where the diagnosis is not clear following conventional diagnostic modalities.

## TRUE ACCURACY OF IMAGING AND FUTURE DEVELOPMENTS

Twenty to twenty-five percent of patients with known solid malignant tumors have hepatic metastases at the time of diagnosis. The incidence of solid benign liver tumors is around 20%[49], thus in patients with known malignancy, 20%-25% of lesions under 2 cm are benign[50]. The most frequent benign lesion is hemangioma with a prevalence of 7%-21%, followed by focal nodular hyperplasia with a prevalence of up to 3%; other benign lesions are far rarer[28,49].

In two studies showed that 24%[39] and 18%[51] of lesions 1 cm or smaller were not detected by any imaging technique. Which imaging modality is the best model in detection of CRLM? The issue of when to use which imaging method is still not solved. The answer likely depends on local equipment, availability, and operator expertise.

Contrast-enhanced intra-operative US (CE-IOUS) is considered the gold standard thereby achieving universal usage and should arguably be considered the final diagnostic procedure[52-55]. Several studies have shown that IOUS still has a higher sensitivity and specificity than the noninvasive techniques, such as helical CT and MRI[54,56-58]. However, there have been few studies on CE-IOUS in literature and CE-IOUS is not widely used among hepatic surgeons.

CT liver imaging offers increased sensitivity and may also able to assess extrahepatic disease but is inferior to MRI scanning in direct comparisons[59-62].

CTAP is considered by many to be the "gold standard" for hepatic imaging but it is an invasive technique with a high (up to 15%) false-positive rate[60].

Hekimoglu *et al*[37] could detect lesions CRLM over 1 cm by all the 3 imaging modalities including SPIO-enhanced MRI, GbD-enhanced dynamic MRI and dynamic CT imaging also with a high sensitivity. However, only SPIO-enhanced MRI detected LMs less than 1 cm with 100% sensitivity which has not been reported until today. So, He therefore, recommend SPIO-enhanced MRI for patients with colorectal carcinoma with suspected small sized LMs. MRI provides a sensitive, non-invasive method of assessing liver lesions and direct comparison between CTAP and MRI shows that MRI is better at identifying and characterising liver lesions[63-65].

Kinkel *et al*[66] performed a meta-analysis including papers published between 1985 and 2000 and concluded that, at equivalent specificity, PET/CT is more sensitive than US, CT and MRI for the detection of hepatic metastases from gastro-esophageal and colo-rectal cancers. Subsequently Bipat *et al*[4] performed a meta analysis including papers published between 1990 and 2003 and concluded that PET/CT is the most sensitive diagnostic tool for the detection of hepatic metastases from colo-rectal cancer on a per patient basis, but not on a per lesion basis. Mainenti *et al*[44] found PET/CT shows a trend to perform better than the other modalities in the identification of patients with CRLM.

The combination of PET and CT is a perfect solution. On theoretical grounds, it is preferable to combine PET with (functional) MRI, for better soft tissue evaluation with a relatively low radiation burden. An excellent example of the application of PET/MRI fusion is accurate delineation of malignant lesions in the liver, to allow optimally guided locoregional therapeutic intervention[67]. It is expected that integrated PET/MRI scanners will become clinically available in the next few years.

Clearly, continuing improvements in imaging are allowing metastases to be identified at an earlier stage but a different approach is needed to improve the detection of metastases smaller. A multi-modality strategy is recommended since no single modality can accurately detect all colorectal liver metastases[68].

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