Investigations and research

Staging of liver metastases with MRI in oncological treatment planning.

Metastatic disease in 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. The true prevalence of metastatic disease is unknown, but approximately 20%-25% of patients with colorectal cancer have liver metastases at the time of diagnosis. Studies based on autopsy results showed that up to 70% of colon cancer patients have liver metastases at autopsy [1]. Magnetic Resonance Imaging (MRI) is commonly used as the definitive imaging modality for the detection and characterization of liver lesions [2]. G. Morana et al. [3] have shown in cadaver studies of primary colorectal carcinoma that on average at least one liver metastasis of less than 10 mm in diameter is missed for each detected liver metastasis larger than 10 mm.

It is the task of radiological imaging to evaluate the liver in order to assess the presence or absence of metastases in surgical candidates and to evaluate the success of chemotherapy in others. Incomplete resection of colorectal hepatic metastases does not prolong survival [1], so knowledge of the exact extent of intrahepatic disease is crucially important in determining patient management and outcome. Almost all metastases larger than 10 mm are demonstrated with current imaging techniques, but the detection of smaller lesions is still relatively poor [4-8].

Data on the use of Diffusion-Weighted Imaging (DWI) MR for liver lesion detection are still limited. Variable image quality caused by motion artifacts and reduced signal-to-noise ratio have largely restricted applications to differentiating between benign and malignant lesions. Diffusion-weighted imaging using EchoPlanar Imaging (EPI) acquisition in the liver is useful for the detection of focal liver lesions, because of the black-blood effect when using low b-values.

The use of the black-blood effect for facilitating detection of liver lesions has been described previously by M. Nagayama et al. [9]. This black-blood effect has been shown to be useful in detecting focal liver lesions near the intrahepatic vessels [10]. Moreover, an axial fat-suppressed Black-Blood (b=10 s/mm²) Single-Shot Spin-Echo Echo-Planar Imaging (BB SS SE-EPI) sequence of the liver has been shown to be promising in the detection of small (<10 mm) focal liver lesions, especially - but not only - when lying in the vicinity of the intrahepatic vasculature [11,12].

Materials and methods

A previous study was performed on a 1.5 T MRI whole-body scanner (Intera (release 11), Philips Medical Systems, Best, the Netherlands) with a 4-element SENSitivity Encoding (SENSE) body phased-array coil. Gradients were used with a maximum gradient of 66 mT/m along x-, y-, and z-axis.

An axial fat-suppressed Black-Blood Single Shot Spin Echo-Echo Planar Imaging (BB SS SE-EPI) sequence with b-values of 0, 10, 150, and 400 s/mm² was used with the following parameters. TR: single shot technique, TE: 55.83 ms, flip angle: 90°, NSA: 4, FOV: 305 mm, rectangular FOV of 95%, matrix scan: 160 with 80% scan percentage, half scan factor 0.6, slice thickness 7 mm, slice gap 0 mm, foldover direction AP, EPI-factor 51, SENSE factor 2 along the in-plane phase-encoded direction. The measured voxel size was 1.91 mm x 2.42 mm x 7 mm.

Susceptibility artifacts from bowel loops were partially overcome by giving the patients 500 ml of water just before starting the BB SS SE-EPI. Respiratory triggering was applied using the belly-band system.

Discussion

The early detection of liver metastases is of the utmost importance in patients with cancer. In general, the presence of (relatively extended) liver metastases indicates non-resectability of the primary tumor for oncologic reasons [13], except for tumor palliation (i.e. to relieve obstruction of the gastrointestinal tract).
In these patients, chemotherapy is the method of choice. For a few malignancies, resection of liver metastases has been shown to improve the survival of the patients [14]. Colorectal cancer is one of a few malignant tumors in which the presence of limited synchronous liver metastases (i.e. occurring at the time of diagnosis of the primary tumor) or metachronous metastases (occurring after diagnosis of the primary tumor) warrants surgical resection [13]. Exact knowledge of the number, size, and regional distribution of liver metastases is essential to determine their resectability.

In patients with liver metastases from colorectal cancer, hepatic resection has proven survival benefits and is curative in a small proportion of cases. Patients whose metastases are small, few in number and metachronous have the best prognosis, but there is now good evidence that patients with more extensive disease can benefit from resection [15-18]. The number, size and distribution of lesions are no longer limiting factors, provided all lesions are removed with adequate tumor-free margins and there is sufficient normal liver to maintain liver function postoperatively.

Based on the number and localization of the liver metastases and considering all other clinical parameters of the patient, only about 30% of colorectal patients with liver metastases may undergo resection. However, the 5-year survival of these patients is between 30% and 48% in comparison to a survival of less than 5% of patients with liver metastases not amenable to liver surgery [14,19-21].

Figure 1. A 62 year old male patient with a medical history of colorectal carcinoma, treated by surgery.

Figure 1a. BB SS SE-EPI used as a road map sequence, b-value image (b = 10 s/mm²) clearly shows a focal hyperintensity (arrow) in the periphery of the right liver lobe.

Figure 1b. b-value image (b = 400 s/mm²). The lesion remains clearly hyperintense.

Figure 1c. T2w Turbo Spin Echo sequence. The lesion is barely visible. This illustrates the usefulness of the BB SS SE-EPI as a road map sequence.

Figure 1d. 3D T1w FatSuppressed GradientEcho sequence before injection of a contrast agent. Here again, the lesion is barely visible.

Figure 1e. 3D T1w FatSuppressed GradientEcho sequence in the arterial phase after injection of a SPIO-based contrast agent, showing discrete perfusion disturbances.

Figure 1f. In the portal-venous phase the lesion is clearly shown against a white background.

Figure 1g. 10 minutes delayed T2w Turbo Spin Echo sequence clearly shows the lesion as hyperintense. This lesion was surgically proven to be a metastasis (7 mm in diameter).
Transabdominal ultrasonography is widely used to assess the liver, but has some limitations: it needs considerable operator expertise and often reveals equivocal results in patients with (chemotherapy-induced) fatty infiltration of the liver. These problem cases are then often referred for a CT or MRI examination.

With the introduction of MultiDetector CT (MDCT) imaging, the use of CT in oncologic patients to “screen” for lung, liver, and lymph node metastases in the body has dramatically increased. MRI is still limited in the anatomic coverage, although the recent introduction of multi-channel MRI coils with wider coverage and the moving-table MRI technique has re-established the competitiveness of MRI with MDCT with regard to patient throughput. Additionally, one of the advantages of MRI in liver imaging is the better soft tissue contrast, which reveals better characterization of focal liver lesions in question. The development of liver-specific MRI contrast agents has further improved the diagnostic yield of MRI in lesion detection and characterization.

Although the primary modalities for liver imaging are ultrasound and CT, recent studies have suggested that contrast-enhanced MRI is the most sensitive method for detecting small metastases and MRI is now considered the preoperative standard [22-26]. Developments in MRI hardware and software and the availability of novel MRI contrast agents have improved small lesion detection [1]. During the last few years, MRI enhanced with SuperParamagnetic IronOxide (SPIO) contrast agent (ferucarbotran) has probably been considered to be the most sensitive method for detecting hepatic metastases [1].

In the few studies which have compared the different liver specific agents against each other, SPIO-enhanced MRI has demonstrated varying degrees of superiority, particularly for small lesions [27,28]. Furthermore, the importance using ferucarbotran by bolus injection and providing the opportunity to obtain dynamic T1w images has been described by J. Ward [1]. He found early T1 enhancement on 3D fat-suppressed T1w Gradient Echo images to be particularly valuable for depicting small tumors. The T1 effect is considerably less than occurs with extracellular fluid gadolinium-based contrast agents, but this is often beneficial in the context of metastatic disease. Liver and vessels often have a similar signal intensity which produces a virtual blank canvas against which small metastases are extremely conspicuous and reliably distinguished from vessels.

Figure 2. The same patient as Figure 1.

Figure 2a. BB SS SE-EPI used as a road map sequence, b-value image (b = 10 s/mm2) clearly shows two additional focal hyperintensities (arrows) in the periphery of the left liver lobe.

Figure 2b. T2w Turbo Spin Echo sequence before injection of contrast agent fails to show the lesions detected in Figure 2a.

Figure 2c. 3D T1w Fat-Suppressed Gradient-Echo sequence before injection of contrast agent. Here again, the lesions are not visualized.

Figure 2d. In the venous phase, the lesions can mainly be depicted under guidance of the BB SS SE-EPI sequence.

Figure 2e. 10 minutes delayed T2w Turbo Spin Echo sequence also shows the lesions. These lesions were surgically proven to be micrometastases (3 mm and 4 mm in diameter).
The combination of thin-slice 3D T1w and T2w imaging after SPIO increases diagnostic confidence and is more accurate for small lesion detection than delayed T2w imaging alone [1]. Since November 2004, the Department of Radiology at AZ St.-Jan AV, a general academic hospital in Bruges, Belgium, has been implementing the BB SS SE-EPI sequence described above to improve detection of focal liver lesions still further, to include lesions as small as 2-3 mm [12].

BB SS SE-EPI provides images depicting hyperintense focal liver lesions that stand out like beacons against dark-gray liver parenchyma (Figures 1-3).

The ability to isolate small lesions quickly – at the start of a liver protocol – makes BB SS SE-EPI a useful roadmap sequence. BB SS SE-EPI, is particularly valuable for staging metastatic disease. Initially, we included SPIO-enhanced sequences (pre- and post-contrast) as a quality control measure to check the accuracy of the black-blood technique, but the BB SS SE-EPI sequence has proved to be so robust that we no longer consider it necessary to perform the SPIO-enhanced sequences.

Realizing that the BB SS SE-EPI sequence was very good, we now use it instead of the SPIO-enhanced sequences as the new MRI gold standard for detection of focal liver lesions. As the BB SS SE-EPI sequence has a very good negative predictive value (during studies performed at our hospital using only BB SS SE-EPI, only one small liver metastasis of 4 mm diameter was missed out of more than 200 focal liver lesions (mean diameter 11 mm, range 2-89 mm) when compared with SPIO-enhanced imaging), this sequence is particularly useful for screening purposes.

A relatively higher b-value between 400 and 800 s/mm² provides more diffusion sensitivity and can therefore aid in lesion characterization.

With a higher b-value, cysts will appear more hypointense when compared with hemangiomas and solid lesions. For further characterization of small (<10 mm) non-cystic lesions more research is needed. Nonetheless, if an operation is planned, the surgeon has an accurate guidance during the operation to

Figure 3. 53-year-old male patient with a recent diagnosis of colorectal carcinoma.

Figure 3a. Using BB SS SE-EPI used as a road map sequence, b-value image (b = 0 s/mm²). Compare with Figure 3b.

Figure 3b. b-value image (b = 10 s/mm²). Comparison with Figure 3a clearly shows a black blood effect. Further a focal hyperintensity (arrow) stands out to the surrounding liver parenchyma.

Figure 3c. b-value image (b = 400 s/mm²). The lesion remains hyperintense.

Figure 3d, T2w Turbo Spin Echo sequence before injection of a contrast agent. The lesion could only be detected by using the BB SS SE-EPI as a road map sequence. The lesion could not be detected on either the dynamic 3D T1w FatSuppressed GradientEcho sequence or the delayed T2w Turbo Spin Echo sequence. The presence of an underlying micrometastasis (5 mm in diameter) was surgically proven.
perform Intra-Operative UltraSound (IOUS) for further characterization purposes in those areas where a focal liver lesion is detected using the BB SS SE-EPI sequence.

**Future**

Clearly, continuing improvements in imaging are allowing metastases to be identified at an earlier stage, but a different approach is still needed to improve the detection of metastases smaller than 2-3 mm. All liver metastases start out as microscopic seedlings which eventually grow to a size where they become visible on imaging. The literature on liver imaging is generally limited by inadequate methods for verifying findings, and in most studies false negative lesions are not assessed. This inevitably means that reported sensitivities are overestimated and that the true incidence of disease is underestimated. Moreover, in more recent studies investigators have attempted to judge their results against more rigorous reference standards so that there has been little if any improvement in the apparent sensitivities despite continuing improvements in imaging techniques. It is also likely that these results continue to underestimate the problem of metastases in the millimeter size range, so that the reported sensitivities remain falsely elevated.

Even when histological examination of the resected liver is used as the "gold standard", the verification of very small lesions is questionable since most specimens are sectioned at 1 cm intervals. Furthermore, recent follow-up studies have confirmed that a proportion of small metastases are undetected by preoperative imaging and surgery with IOUS.

Magnetic Resonance Elastography (MRE) has shown promise for the grading of liver fibrosis [29,30] and improved characterization of breast tumors [31]. Applying this novel MRE technique for the characterization of focal liver lesions could be promising.

Recently MRI has been used to measure Hepatic Perfusion Indices (HPI) [32,33], but the technique remains developmental and the best measurement method is still to be determined. Once the methodology is established, rigorous multi-observer studies will be required to validate the technique and determine its impact on patient management.

The use of molecular imaging techniques for the detection and characterization of liver metastases in clinical practice is even more futuristic.

**Conclusion**

Considering the economic aspects of the choice of imaging technique, it is often debated that MRI is too expensive to screen for liver metastases. However, in cases where no metastases are visualized but underlying metastases are likely (e.g. abnormal laboratory results) or a limited amount of liver metastases are found which are potentially resectable, a staging examination using MRI and BB SS SE-EPI seems essential [12]. The cost of this additional MRI examination is relatively low considering the more accurate pre-operative assessment and more accurate choice of expensive therapeutic modalities tailored to the patient’s pathologic assessment.

**References**


