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Magnetic Resonance Imaging of Liver Metastasis

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Liver magnetic resonance imaging (MRI) is becoming the gold standard in liver metastasis detection and treatment response assessment. The most sensitive magnetic resonance sequences are diffusion-weighted images and hepatobiliary phase images after Gd-EOB-DTPA. Peripheral ring enhancement, diffusion restriction, and hypointensity on hepatobiliary phase images are hallmarks of liver metastases. In patients with normal ultrasonography, computed tomography (CT), and positron emission tomography (PET)-CT findings and high clinical suspicion of metastasis, MRI should be performed for diagnosis of unseen metastasis. In melanoma, colon cancer, and neuroendocrine tumor metastases, MRI allows confident diagnosis of treatment-related changes in liver and enables differential diagnosis from primary liver tumors. Focal nodular hyperplasia–like nodules in patients who received platinum-based chemotherapy, hypersteatosis, and focal fat can mimic metastasis. In cancer patients with fatty liver, MRI should be preferred to CT. Although the first-line imaging for metastases is CT, MRI can be used as a problem-solving method. MRI may be used as the first-line method in patients who would undergo curative surgery or metastatectomy. Current limitation of MRI is low sensitivity for metastasis smaller than 3 mm. MRI fingerprinting, glucoCEST MRI, and PET-MRI may allow simpler and more sensitive diagnosis of liver metastasis.
Semin Ultrasound CT MRI 37:533-548

Introduction

Liver metastasis, by definition, is a malignant lesion originating in an organ distant from the liver, which would secondarily disseminate and grow in the liver. Liver is a very common site of metastasis. Gastrointestinal tumors such as neuroendocrine tumors, colorectal cancers, esophageal and gastric tumors, and pancreatic cancers are among the most common sources for metastatic disease to the liver. Colorectal cancers (CRCs) are especially very common, with approximately 50% of the patients would have metastatic liver disease either at the time of diagnosis or in the follow-up period after surgical resection.[1] Despite advances in surgery, targeted biologic therapies, and chemotherapy, the survival rates of patients with liver metastasis are still dismal, with a significant portion of these patients dying owing to their metastatic liver disease.

Disseminations through the portal venous and arterial systems are the most common routes for metastasis. Once the tumor cells detach from their original site, they travel into the vascular system and extravasate into the target organ parenchyma and proliferate. They are frequently found as multiple lesions of different sizes in both liver lobes, and several cancers often incite desmoplastic reaction when they metastasize, which gives them their hard consistency.[2] Often times, internal necrotic changes give rise to their pseudocystic appearance. Central fibrous scar formation and capsular retraction (when they are located close to the liver capsule) may also be detected.[3,4]

Clinical Presentation

Most liver metastases are clinically silent and detected with cross-sectional imaging. When they are symptomatic, the disease is most often at an advanced stage and the prognosis is poor. Metastasis from hormonally active tumors may present

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http://dx.doi.org/10.1053/j.sult.2016.08.005
0887-2171/

with symptoms related to the hormonally active metabolites secreted by the metastatic cells.

Role of Cross-Sectional Imaging in the Evaluation of Metastatic Liver Disease

Imaging plays a crucial and integral role in the diagnosis and monitoring of metastatic liver disease. Several imaging modalities including ultrasonography (US), computed tomography (CT), positron emission tomography (PET), and PET-CT scans can be used for this purpose. In this article, we are going to focus on the role of MRI, which is becoming the gold standard modality in the diagnosis of hepatic metastases.

MRI for Liver Metastases

MRI offers superior soft tissue resolution, providing several advantages over other cross-sectional imaging modalities for the detection and characterization of the focal liver lesions. This superiority becomes more prominent when it comes to detection of small-sized metastases. The reported sensitivity of contrast-enhanced MRI (CE-MRI) is 91%-97% compared with 71%-73.5% for CT.[5-7] The sensitivity of MRI increases, especially, in the characterization of the lesions deemed to be "too small to characterize" on multidetector CT studies[8] (Fig. 1).

Advanced MRI Techniques

Several new MRI techniques have entered clinical practice in the past few years, and they have now become essential components of standard liver MRI protocols.[9] Diffusion-weighted imaging (DWI), hepatocyte-specific magnetic resonance (MR) contrast agents (HSMRCA), MR elastography, and MR perfusion may be counted among them. For the sake of brevity, we focus on DWI and HSMRCA. MR elastography and MR perfusion are less commonly used in clinical practice, and both are currently in the research realm awaiting translation into bedside clinical practice. It is highly possible that they would become part of the routine liver protocols in the coming years.

DWI of the Liver

DWI is a technique that can provide tissue contrast based on the measurement of diffusion properties of the water molecules within tissue.[10] It is mainly based on the intravoxel incoherent motion and provides quantification of the water diffusion and microcapillary blood perfusion within the tissue in a noninvasive manner.[11]

DWI was mainly a tool for neuroimaging; however, it has become an indispensible part of the liver MRI studies. It is not only used in the detection of liver lesions but also commonly used for focal liver lesion characterization and assessment of treatment response. The technique does not require any IV contrast use, and its use may be even more helpful in patients with renal dysfunction. It is quick to perform, with no significant increase in the overall examination time, and the image quality is getting better with new refinements in the technique. Although it is mainly used as a qualitative method, it also allows quantification, which may provide an objective parameter, especially in assessing tumor response. Ultimately, with the use of DWI, one can obtain highly relevant data regarding the structural tissue changes at cellular level in a noninvasive manner. DWI may be also helpful for the evaluation of the response of malignant liver lesions to new antineoplastic agents, which mainly target the tumor vascularity.[9] With these agents, the overall hepatic metastasis size may not change despite highly successfull devascularization and necrosis of the tumor cells within the metastatic focus. The addition of hepatocyte-specific agent gadoxetate disodium to DWI was reported to be superior to DWI alone for detecting liver metastases from colorectal cancer metastases ≤ 1 cm in diameter.[12]

When it was first introduced, DWI was performed by adding a symmetric pair of diffusion-sensitizing gradients around the 180° refocusing pulse of a T2-weighted sequence.[13] In densely packed environments, water molecules would not demonstrate any appreciable change in their phases between the 2 gradients and would, therefore, generate little difference in the rephasing. In this situation, there would be

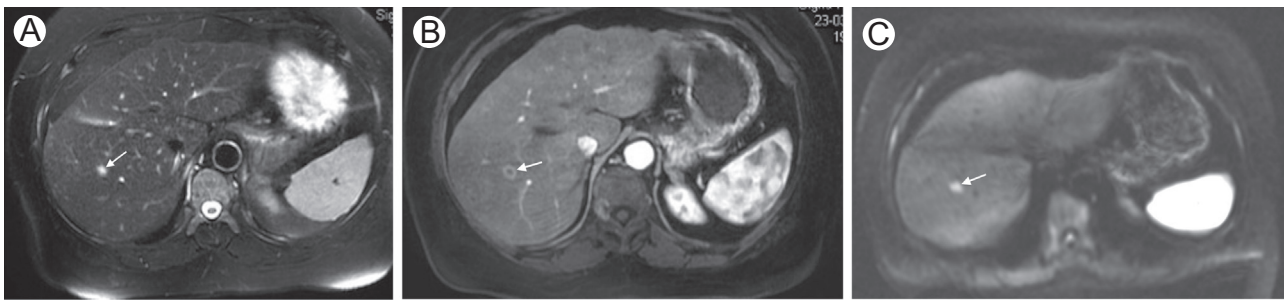

Figure 1 A 45-year-old male patient with newly diagnosed pancreatic cancer with subcentimeter liver metastasis. (A) Axial fat-suppressed T2-weighted image demonstrates 5-mm hyperintense focus in the right liver lobe (arrow). (B) Arterial phase T1-weighted axial contrast-enhanced MR image shows typical ring enhancement (arrow) with (C) subsequent diffusion restriction (arrow) on DWI sequence ($b = 500$).

minor difference in the underlying T2 signal, resulting in high-signal intensity in the diffusion-weighted (DW) images.[14-16] The sensitivity of the sequence to water diffusion can be modified by changing the *b* factor. By increasing the *b* value, the sequence is more sensitized to the diffusion effects, and DWI is performed by using at least 2 different *b* values. The quantitative data from the DWI are reflected in a diffusion coefficient, also called as apparent diffusion coefficient (ADC, expressed in mm^2/s). Low ADC values represent diffusion restriction, whereas high ADC values represent areas with low cellularity and less diffusion restriction.[10,17] With the use of ADC, quantifying the differentiation of cystic lesions from the solid lesions can become a possibility, allowing noninvasive diagnosis.[18-20]

DWI can be performed using breath-hold and free breathing approaches, and it is generally performed before the injection of IV gadolinium chelates. However, it has also been reported that administration of MRI contrast agent before the DWI sequence may not significantly alter the ADC values.[11]

Despite all the promising data related to DWI, the imaging specialists should be aware of its potential limitations and pitfalls. In its current role, DWI should be mainly used as an ancillary source of information in addition to data from other conventional MR sequences.[21]

Hepatocyte-Specific Contrast Agents

Gadolinium chelates used as IV contrast media in MRI studies are crucial for increasing the sensitivity and specificity of the liver MRI examinations. With increasing use of MRI for the liver examinations, several HSMRCAs have been used in the past. Currently, there are 2 HSMRCAs available for clinical use, and both are gadolinium-based agents, which overcome the other shortcomings related to former HSMRCAs. These 2 agents currently used in clinical practice are gadobenate dimeglumine (Gd-BOPTA, MultiHance; Bracco Diagnostics) and gadoxetate disodium (Gd-EOB-DTPA, Primovist in Europe and Eovist in the United States; Bayer Healthcare Pharmaceuticals). We would mainly focus our discussion on the use of gadoxetate disodium, as it is more commonly used for liver-specific MRI examinations and is more hepatocyte specific when compared with gadobenate dimeglumine. With the introduction of gadoxetate disodium, the use of MRI has greatly expanded.

Pharmacokinetics of the Gadoxetate Disodium

Owing to its unique properties, a brief discussion of the pharmacokinetics of gadoxetate disodium is warranted. It first distributes to the extracellular space after IV administration, and once in the extracellular space, it can either be excreted from the kidneys through glomerular filtration or taken up by the hepatocytes and excreted into the intrahepatic biliary canalicules.[22] This dual-elimination pathway gives gadoxetate disodium its hepatocyte-specific aspect. In subjects with preserved renal and hepatic function, it can be expected that 50% of the injected contrast is eliminated by the liver, whereas the remaining 50% is by the kidneys.[23] This unique elimination from the liver can provide valuable information, both structural and functional. The internalization of the gadoxetate by the hepatocytes is made possible with the use of a specific molecule called organic anion transporting polypeptide 1 (OATP-1). After taken up by the hepatocyte, gadoxetate is then actively transported into the biliary canalicular system, and this is accomplished via the help of the canalicular multispecific organic anion transport molecule.[23,24] This same molecule is also used for the transport of the bilirubin molecule from the hepatocytes to the biliary canalicules.[25] Biliary transit time is not related to sex, age, body mass index, gastric filling, and technical variations (1.5 vs 3 T) but to liver function.[25] As both gadoxetate and bilirubin use the same transport protein (OATP-1) for active transport into the hepatocyte, they both compete for this transporter molecule. Therefore, in cases of hyperbilirubinemia, hepatic parenchymal enhancement and

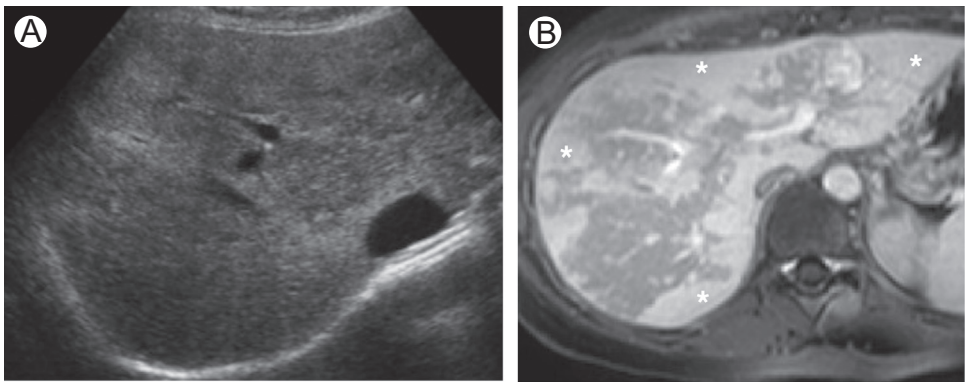

Figure 2 A 45-year-old female patient with known breast cancer in clinical remission referred to radiology for abnormal liver function test results. (A) US study demonstrated parenchymal heterogeneity owing to hypoechoic and hyperechoic areas with no discernible focal mass. (B) Axial postcontrast venous phase T1-weighted image shows homogenously enhancing subcapsular areas (asterisks) throughout the liver, and there was also diffusion restriction matching these areas. Biopsy revealed breast cancer metastasis in the subcapsular areas.

biliary secretion of the gadoxetate would both decrease.[26] It should also be mentioned that given the dual elimination of the molecule, studies have shown compensation by the remaining normally functioning elimination route.[27,28] This physiological compensation may have a role in decreasing the risk of nephrogenic systemic sclerosis and that administering gadoxetate in patients with decreased renal function may be safer than administering extracellular gadolinium chelates.[29]

Use of Gadoxetate Disodium

Gadoxetate disodium was approved for clinical use in Europe in 2004, followed by United States in 2008 and Canada in 2010; there has been a massive flush of the literature regarding its clinical value and use. Several different specialties including radiology, hepatology, and surgery have contributed to the accumulation of this massive body of information.

Different studies have demonstrated the superiority of MRI with hepatocyte-specific contrast agents, in particular gadoxetic acid, relative to dynamic CT (Fig. 2). This superiority becomes even more important particularly for the detection and characterization of small lesions. This particular advantage of MRI, performed with gadoxetate disodium, is particularly important in patients who are candidates for curative liver surgery.[30-33] In a meta-analysis published in 2012, summarizing the diagnostic performance of gadoxetic acid, reported a very high sensitivity and specificity, 93% and 95%, respectively, for detection of colorectal liver metastases.[34] For the reasons provided, the expert panel concluded that gadoxetate disodium–enhanced liver MRI is superior to US, PET, and CT and, therefore, recommended the use of gadoxetate disodium in patients who are candidates for surgical resection owing to liver metastasis[35] (Fig. 3).

Gadoxetate disodium–enhanced liver MRI may also have a role in the follow-up assessment of hepatic metastases. CT may be particularly difficult for the follow-up evaluation of the metastatic liver disease owing to generalized parenchymal hypodensity and heterogeneity in patients who developed steatosis and sinusoidal obstruction, both are particularly common after irinotecan- and oxaliplatin-based regimens.

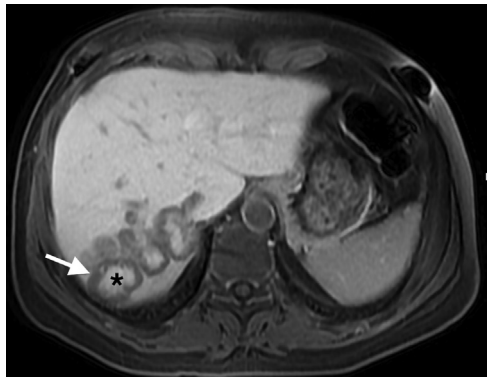

Figure 4 A 56-year-old woman patient with known breast cancer, referred for MR imaging for heterogeneity in right lobe on US. Hepatobiliary phase image shows a few lesions with peripheral washout (arrow) and central contrast filling (asterisk) most likely because of central fibrosis within the metastases.

In these patients, the detection and characterization may be particularly challenging to detect hypoattenuating liver metastases. MRI performed with gadoxetate disodium may be helpful for resolving this diagnostic conundrum. A meta-analysis comparing the diagnostic performance of MRI, CT, PET, and hybrid PET-CT in the preoperative setting revealed that MRI was the most sensitive modality for the detection of metastatic liver lesions in patients who have undergone chemotherapy.[36] Another prospective analysis revealed the superiority of gadoxetate disodium–enhanced MRI relative to CT in the detection of colorectal liver metastases with a diameter of less than 1 cm in patients with background hepatosteatosis.[37] For all these reasons provided in the literature, the expert panel stated that gadoxetate disodium–enhanced liver MRI may be of particular benefit in the preoperative assessment of these patients.[35]

Hepatic metastases typically demonstrate a ring enhancement on early postcontrast phases, with incomplete centripetal progression on portal venous and delayed phases.[38] Peripheral low-signal-intensity zone or washout on the portal venous or delayed phases is also considered to be highly specific for malignancy.[39] On hepatobiliary phase, they appear as

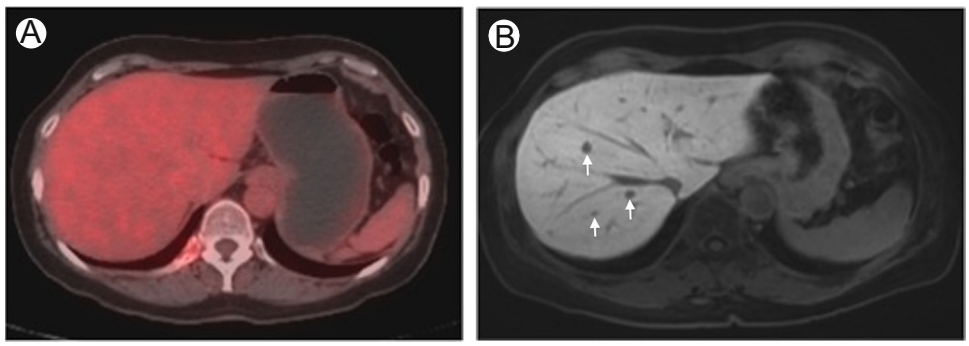

Figure 3 A 46-year old female patient with newly diagnosed breast cancer undergoing imaging for initial staging. (A) Axial fused FDG(18)-PET-CT image demonstrates no evidence of metastatic foci within the liver parenchyma. (B) Axial T1-weighted hepatobiliary phase MR image (performed 6 days after the initial PET-CT scan) shows several small metastatic foci (arrows) in the liver parenchyma that was invisible on PET-CT. (Color version of figure is available online.)

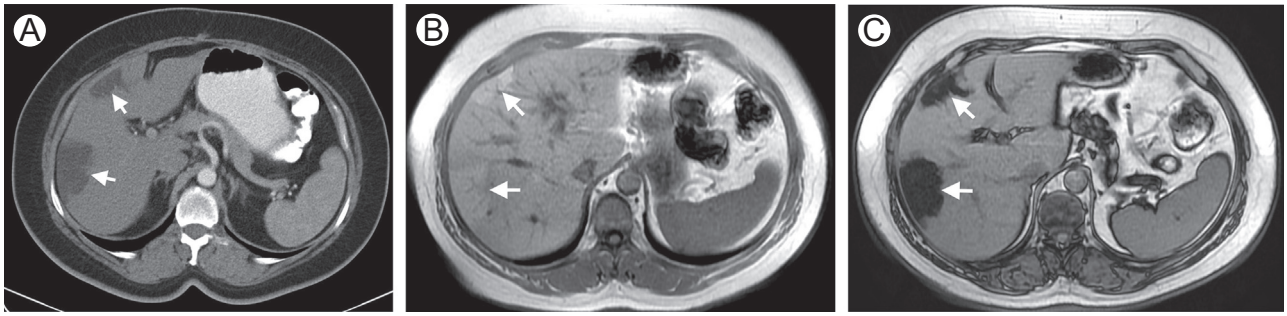

Figure 5 A 55-year-old female patient with colon cancer presented with elevated liver enzymes after chemotherapy. (A) Axial contrast-enhanced CT shows 7 hypodense subcapsular areas (arrows) in the right lobe, suspicious for metastases. (B and C) There was a signal drop in these areas (arrows) on out-phase T1-weighted axial MR image compared with in-phase images (B), consistent with multinodular steatosis.

hypointense as they do not contain functional hepatocytes. A hypointense rim with a central round hyperintense portion was reported to be a highly suggestive finding for metastatic liver lesion on the hepatobiliary phase (Fig. 4).[40-42]

In addition to its use as the single contrast agent for liver imaging, gadoxetate disodium can also be combined with gadofosveset trisodium (Ablavar, Lantheus Medical Imaging). Gadofosveset trisodium is an intravascular contrast agent that binds transiently to serum albumin, resulting in a steady-state blood pool for approximately 1 hour.[43] The combined use of gadoxetate disodium and gadofosveset trisodium was reported to significantly improve the detection of liver metastases and their differentiation from hemangiomas.[44]

In liver imaging, 3-T MR scanners are now being commonly used, and gadoxetate disodium may also be used with high success in these scanners for detection of liver neoplasms.[45]

Evaluation of Common Liver Metastases

Colorectal Cancer Metastases

CRC is a very common cause of morbidity and mortality, and liver is a very common site for tumor metastasis. Approximately 30% of the cases have metastatic liver disease at initial presentation, with almost 14.5% of the cases showing development of liver involvement during chemotherapy.[46,47] Early detection and characterization of liver metastases are of crucial importance for optimal triage of patients who may benefit from hepatic resection from those who need chemotherapy, to improve 5-year survival.[48]

Gadoxetate disodium–enhanced MRI is the preferred modality for the evaluation of liver metastases and was reported to be more accurate than CT[12] (Figs. 5-8). The superiority of MRI, with incorporation of hepatobiliary phase and DW images, in detecting hepatic CRC metastasis becomes more apparent in the setting of hepatic steatosis.[49] Lower recurrence rates in the liver after resection for CRC metastasis have been reported when hepatobiliary phase MRI was incorporated into the MRI protocol (48% vs 65%, $P = 0.04$, $n = 92$ hepatobiliary MRI, and $n = 150$ without).[50] In a recently published trial, it was reported that the use of gadoxetate disodium may be beneficial for patients with hepatic CRC metastases. In this study, the use of gadoxetate disodium did not change the diagnostic workup costs significantly compared with MRI studies performed with extracellular MR contrast agents and CE multidetector CT studies. However, patients assessed with gadoxetate disodium needed less additional imaging, and based on these results, the authors suggested that the gadoxetate sodium should be preferred as initial imaging study to evaluate surgical resectability in

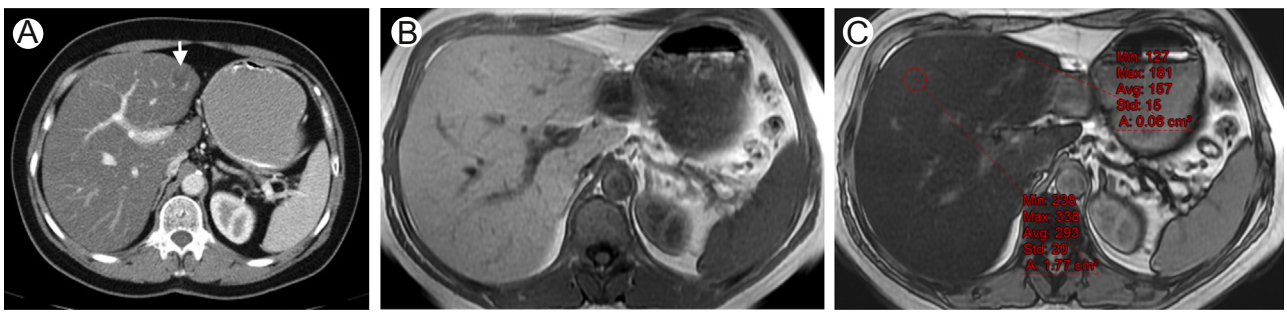

Figure 6 A 74-year-old male patient with colon cancer who underwent posttreatment staging evaluation. The patient has no known metastatic disease at the time of imaging. (A) Axial contrast-enhanced CT scan demonstrates diffuse fatty liver and a hypodense lesion (arrow) in the left liver lobe. (B) In-phase axial MR image shows no evident left liver lobe mass. (B) Out-of-phase MR image shows more signal dropout within the lesionlike area compared with background fatty liver consistent with hypersteatosis. (Color version of figure is available online.)

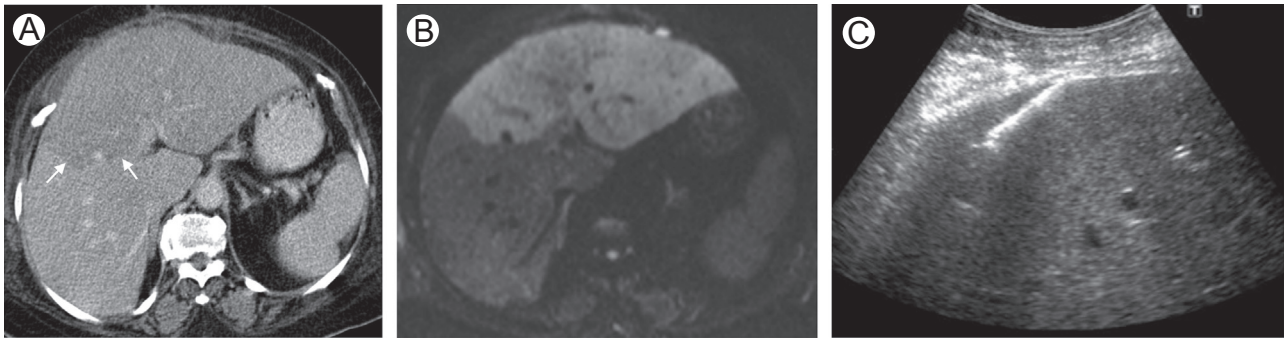

Figure 7 A 55-year old male patient with known colon cancer referred for increased liver enzymes and newly developed epigastric pain. (A) Axial contrast-enhanced CT image shows mild hypodense demarcation line (arrows) and mild parenchymal heterogeneity in left liver lobe (asterisk). (B) Corresponding DW image demonstrates widespread diffusion restriction in the left liver lobe (arrows). (C) Subsequent US-guided biopsy confirmed diffuse parenchymal metastatic tumor infiltration. Initially, biopsy was refused (after CT examination) owing to normal appearance of left lobe on US; based on MRI findings, biopsy was performed.

patients with hepatic metastases from CRC.[51] Another recently published research article and consensus report also supported and recommended, based on the current evidence and experience, the use of gadoxetate disodium-enhanced liver MRI as the most accurate imaging modality for preoperative diagnosis of liver metastases from CRC.[52,53] The addition of DWI to the hepatobiliary phase may also improve lesion detection, especially the ones smaller than 1 cm; however, the difference was not reported to be statistically significant.[12]

Surgical resection is the only potentially definitive treatment for liver metastases owing to CRC, and with surgery, 5-year survival rates may increase to 25%-50%.[54,55] The criteria for surgical resection of hepatic metastases are still an evolving process, with the aim of achieving complete resection (R0 resection) and leave adequate amount of residual liver parenchyma behind.[56] Perioperative chemotherapy may be beneficial to patients with resectable and potentially resectable liver disease. Neoadjuvant chemotherapy may offer eradicating the micrometastases and assessing chemotherapy responsiveness. It also allows time to evaluate whether more metastatic disease would develop in the extrahepatic areas.[57] The risk of hepatic dysfunction owing to chemotherapy-induced steatosis and sinusoidal obstruction syndrome and loss of the surgical window should be considered as the potential drawbacks of this approach. The major determinants of resectability are the size, number, and distribution of the liver metastases. Therefore, accurate detection and characterization is of crucial importance to guide the optimal surgical approach. Information regarding the vascular and biliary system is also important for proper surgical planning. Disappearing metastasis (radiologic) may pose diagnostic difficulties as pathologic analysis of resected liver parenchyma often showed viable tumor cells, especially at the tumor-liver interface.[57] The incidence of this phenomenon was reported to be between 7% and 24% depending on the quality and type of preoperative imaging.[58] As they are a site of recurrence after resection, accurate mapping of these lesions is crucially important.

The role of liver MRI in patients with newly diagnosed colorectal cancer is a question remained to be answered. A report by Han et al. showed that the role of liver MRI in patients with negative liver findings on CT and patients with subcentimeter liver lesions that are deemed to be "too-small-to-characterize" may be limited. In their study, the authors did not recommend the routine use of liver MRI in this patient group.[59]

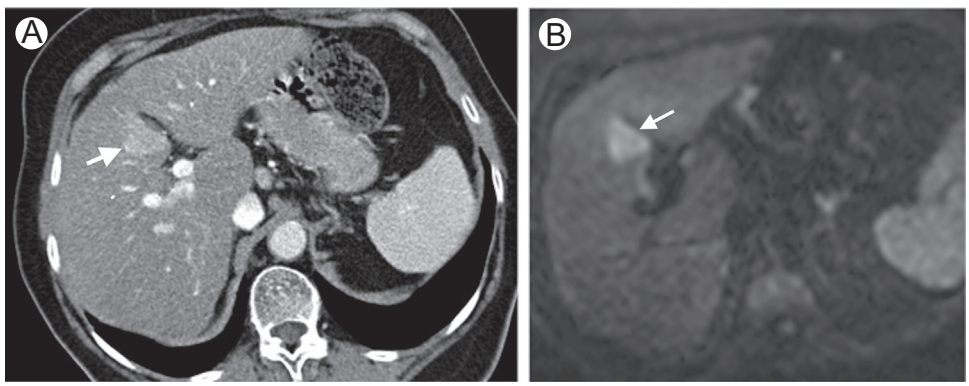

Figure 8 A 60-year-old woman patient with known colon cancer who underwent several cycles of chemotherapy with no known liver metastasis. (A) Axial contrast-enhanced CT image showed hyperdense wedge-shaped area anterior to the main portal vein (arrow) in fatty liver suggestive of focal fat sparing. (B) DWI showed focal diffusion restriction (arrow), not characteristic for focal fatty sparing. Image-guided biopsy revealed metastatic breast cancer.

Breast Cancer Metastases

Breast cancer is the most common cancer among women, with an estimation of 1 in 8 women developing breast cancer during her lifetime.[60] Distant metastases are not uncommon, with 50% of the patients having metastatic disease during the course of the illness.[61,62] Metastatic breast cancer portends a poor prognosis, with a median survival of 2-3 years, with very few (2%) surviving 20 years after the diagnosis of the metastasis.[60,63]

Liver is a common site for metastatic disease in patients with breast cancer, ranking third after bones and the lungs. Liver metastasis is generally a part of systemic tumor dissemination; however, isolated hepatic metastasis is also not unexpected; rare finding is detected in only 4%-5% of the cases.[64] Although systemic chemotherapy, with no curative intent, is the goal for systemically disseminated disease, the treatment approach to isolated liver metastasis is different. Liver resection may be a feasible approach in these patients. Several studies demonstrated benefit from liver resection in these patients, with a 3-year survival rates of 50%-75% and a 5-year survival of approximately 18%-61%.[65-67] Resection of the chemotherapy-resistant clones and necrotic tumor, poorly accessible to chemotherapy, may improve the efficacy of the sytemic therapy.[68,69] Conversion of hormonal (positive for expressing progesterone and estrogen receptors) or human epidermal growth factor receptor 2 (HER2) test results in metastatic breast cancer in the liver, mostly from positive to negative, is also not uncommon and may also negatively affect the results of systemic chemotherapy.[70] Surgical therapy for metastatic liver disease from the breast cancer is emerging as a viable and safe approach in a subgroup of carefully selected cases, providing a substantial period of disease-free time which systemic therapy, and its potential negative consequences can be avoided.[70] Overall, HER2-expressing breast cancers show greater tendency to metastasize to the liver than the hormone-expressing breast cancers.[71]

Unusual forms are common, and new lesions that have benign features such as very high T2 signal or steatosislike areas should be evaluated carefully, and follow up should be recommended (Fig. 9).

Pretreatment imaging characteristics of liver metastasis from the breast cancer may provide clues for predicting the tumor response. It was reported that hypervascularity detected on dynamic MR imaging may be suggestive of poor treatment response when compared with hypovascular metastases.

Steatosis, hepatic contour, and signal intensity changes after chemotherapy may be detected in patients with breast cancer with liver metastasis (Fig. 10). Diffuse nodularity of the liver, mimicking cirrhosis, (commonly referred to as "pseudocirrhosis") is not unusual after chemotherapy in hepatic breast cancer metastases[72] (Fig. 11). Multifocal capsular retractions and enlargement of the caudate lobe, mimicking macronodular cirrhosis, may be seen. The development of portal hypertension and ascites may be seen in these cases. This phenomenon is predominantly visualized in cases of breast cancer metastases and rarely visualized in other hepatic metastases.[73] The parenchymal heterogeneity seen in these patients may pose diagnostic difficulty for detection of residual or newly developed metastatic disease.

Hepatic Neuroendocrine Tumor Metastases

Neuroendocrine tumors (NETs), mostly (70%) originating from the gastrointestinal tract, are slow-growing tumors with a strong propensity to metastasize to the liver.[74] As most patients with liver metastasis die of liver failure, accurate imaging and assessment of the hepatic metastatic load are mandatory for optimal treatment approach.

Liver metastases are typically hypovascular and appear hypointense when compared with liver parenchyma on portal venous phase images. Breast, lung, colon, and gastric carcinomas typicall fall in this category. The enhancement pattern of hepatic metastases from NETs is characteristically different from these tumors as they demonstrate earlier enhancement on arterial phase images with decreased conspicuity on later phases[75] (Fig. 12). Hepatic metastases from renal cell carcinoma, melanoma, thyroid, choriocarcinoma, and occasionally, breast cancer may be detected as hypervascular lesions mimicking NET metastases. NET metastases smaller than

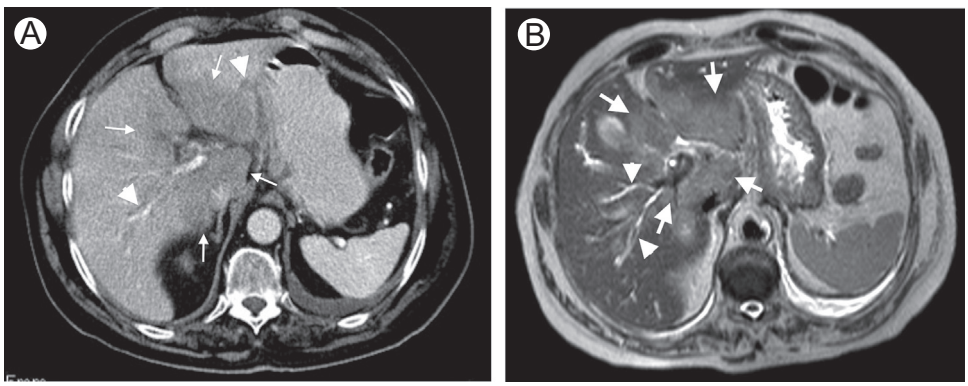

Figure 9 A 70-year-old female patient with known breast cancer presented to emergency room with acute jaundice and right upper quadrant pain. (A) Contrast-enhanced axial CT scan demonstrates hypoattenuating areas in the liver hilum including segments 2-3, left and caudate lobes as well as parts of segment 5 (arrows). Also note associating mild biliary dilation in both liver lobes (arrowheads). (B) Axial T2-weighted MR image demonstrates infiltrative lesion in the liver hilum (arrows) causing biliary dilation (arrowheads). US-guided biopsy revealed metastatic liver disease owing to breast cancer.

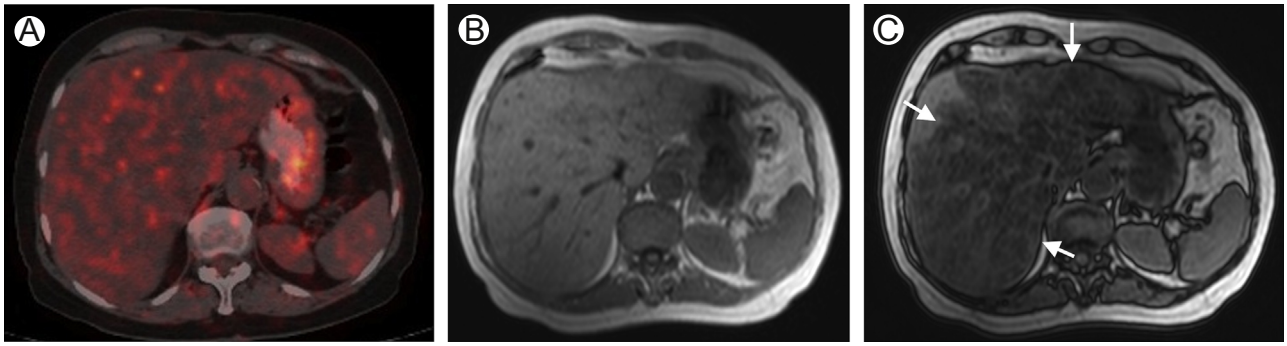

Figure 10 A 62-year-old female patient with known breast cancer, treated with surgery and several cycles of chemotherapy regimens, was asymptomatic at the time of follow-up imaging. (A) PET-CT showed abnormal FDG-uptake areas in the central liver areas without any discrete focal lesion. The findings were interpreted to be concerning for infiltrative metastatic liver disease in the left lobe. (B) In-phase T1-weighted axial MR image demonstrated no focal parenchymal abnormality in the corresponding area, so was the DWI sequence (not shown). (C) Out-of-phase T1-weighted axial MR image demonstrates widespread fatty infiltration in central liver (arrows) confirming chemotherapy-associated steatohepatitis (CASH). (Color version of figure is available online.)

1.5 cm may mimick flash-filling hemangiomas as they both demonstrate arterial phase hyperenhancement with increased T2 signal.[38] One helpful diagnostic clue is the retention of contrast in the flash-filling hemangiomas as opposed to washout tendency of hypervascular metastases.[76,77] "Peripheral washout" is another useful sign that refers to contrast washout from the lesion periphery on delayed CE images with a resultant target appearance. The rim appears hypointense relative to the center in these phases. This sign has been reported to be fairly specific for hypervascular carcinoid or NET metastases over other pathologic abnormalities.[75]

In addition to its role in diagnosis and posttreatment follow up, MRI may also act as an imaging parameter for prognostic stratification of patients with liver NET metastases. In a study published by Sommer at al., it was reported that arterial phase hypervascularization on preradioembolization MR imaging is a strong predictor of favorable treatment response in addition to neuron-specific enolase level below the median and a Ki-67 proliferation index ≤ 2 %.[78]

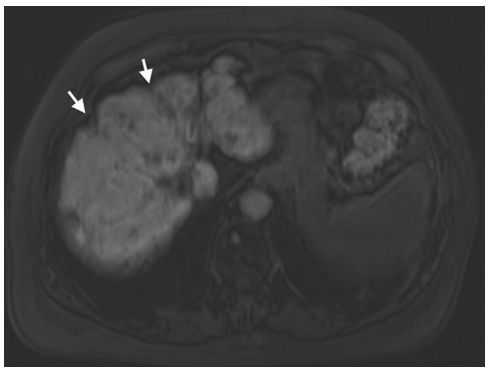

Figure 11 A 69-year-old female patient presented with elevated liver enzymes after several cycles of chemotherapy. Hepatobiliary phase T1-weighted image after Gd-EOB-DTPA administration shows decreased function (hypointense appearance) and capsular retractions (arrows) consistent with posttreatment pseudocirrhosis.

Hepatic Malignant Melanoma Metastases

Malignant melanoma (MM) is a relatively common and biologically aggressive tumor. MM frequently metastasize to the liver and is detected in 14%-20% of patients in clinical series,[79] even after long latency.[80] The early and timely diagnosis of melanoma is important for predicting the prognosis in patients with liver metastasis owing to MM, and 1-year survival in these patients is estimated at 10%.[81]

MRI is commonly used in the diagnosis of hepatic MM metastases and was reported to be more sensitive in detection than CT and PET,[77,82] and even noncontrast MR images appear successful for liver screening in patients with MM.[82,83]

On precontrast T1-weighted MR imaging, the lesions appear characteristically hyperintense, because of their melanin content, and hypointense on T2-weighted images[77] (Fig. 13). Diffuse melanoma infiltration without any identifiable focal liver mass and subsequent death owing to fulminant hepatic failure has also been reported.[84]

Imaging After Locoregional Therapy for Liver Metastases

Locoregional treatments with ablative technologies and intraarterial chemoembolization or radioembolization are commonly used methods in the treatment of liver metastases. Cross-sectional imaging is the main tool for the evaluation of early-stage assessment of procedural success and follow up. US, CT, PET-CT, and MRI may all be used for this purpose. As other modalities except for MRI is out of the scope of this article, we focus on the role of MRI. Subtraction images may be helpful, especially after percutaneous ablation, to differentiate true enhancement (suggesting residual or recurrent disease) from postablative changes.[75]

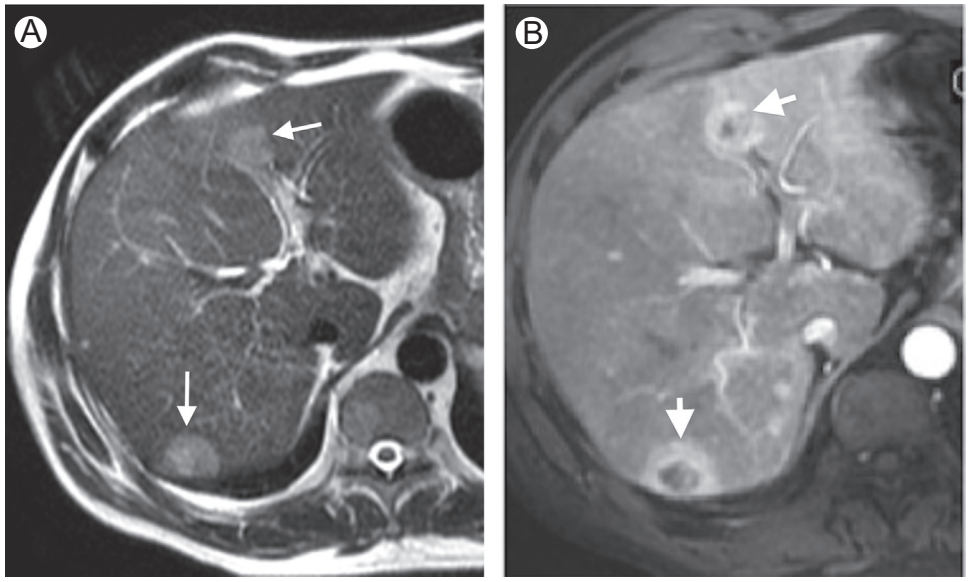

Figure 12 A 55-year-old male patient with known pancreatic neuroendocrine tumor. (A) T2-weighted image demonstrates metastatic lesions with high-signal intensity (arrows). (B) Arterial phase axial T1-weighted MR image shows the hypervascular nature of both metastatic lesions (arrows).

Imaging Findings After Ablative Locoregional Liver Therapy

The imaging specialist should be familiar with the postprocedural imaging findings to prevent the potential diagnostic confusion. Radiofrequency ablation and microwave ablation are the 2 most commonly used local ablative technologies.

The term "ablation zone" refers to the area undergoing coagulative necrosis after ablative therapy. This encompassess the actual tumor zone as well as the 5-10 mm around the tumor, which is akin to disease-free resection margin aimed after conventional surgical resection.[85]

Heterogenous or peripheral T1 hyperintensity is very common after ablation, representing hemorrhagic products and debris, whereas heterogenous hyperintensity is common in T2-weighted images (Fig. 14). Assessment of contrast enhancement in the dynamic phase is crucial as this finding is highly suggestive of local residual disease or recurrence, depending on the clinical context. Periablation edema and contrast enhancement is extremely common, especially in the early postprocedure period, and these findings represent the granulation and inflammatory changes. Typically, a concentric, thin rim enhancement, more conspicious on the arterial phase, is common and is not suspicious for recurrence. This edema typically persists for 4-9 months.[86,87] Any asymmetric thickening or nodularity in this peripheral rim is highly suspicious for local recurrence, and comparison with prior images may be helpful for the diagnosis.

Figure 13 A 75-year-old male patient with melanoma. Axial fat-saturated precontrast T1-weighted image demonstrates multiple subcentimeter hyperintense lesions (arrowheads) consistent with melanoma metastases.

Transient and persistent biliary dilation, periablation zone transient perfusion changes, and mild perihepatic hemorrhage are other common expected findings after ablation.

DWI may be helpful in detecting the local tumor recurrence. The recurrent viable tumor typically appears as hyperintense on DW images in contrast to hypointense necrotic dead tissue. The findings in DWI sequences should be carefully correlated with the morphologic findings on dynamic CE scans. ADC maps may also be extremely helpful to differentiate T2 shine-through effect from true diffusion restriction. Low ADC values in hyperintense areas on T2-weighted image may represent viable neoplastic tissue.[88-90]

Transient biliary dilation because of edema and early inflammatory changes are common after percutaneous ablation; however, persistent dilation over long term is a sign of procedural biliary system injury and permanent stricture formation. Injuries to larger biliary channels are fortunately rare because of the cooling effects (heat-sink) of the adjacent arteries and veins. Biloma formation may also be seen and appears as fluid density cystic structure either at the ablation zone and distant from the original kill zone. Fistulization between adjacent vascular structures and anatomical third spaces as well as gallbladder injuries is rare.

Tract seeding during ablation is also very rare. In case of seeding, the tumor appears similar to the original tumor

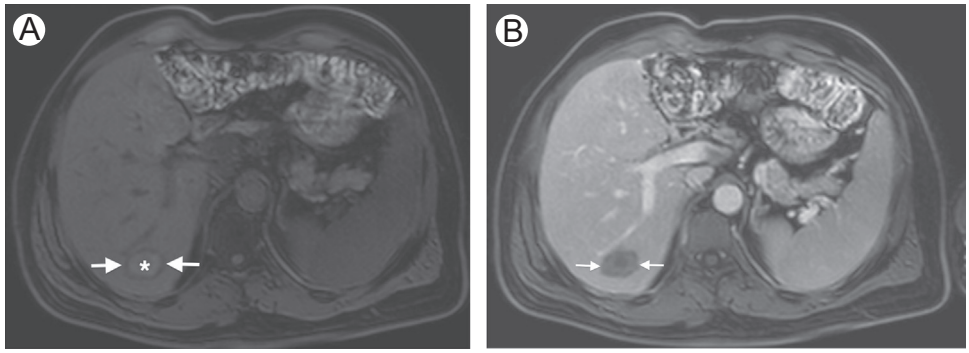

Figure 14 A 55-year-old man with known colon cancer with biopsy-proven liver metastases who underwent follow-up imaging 2 months after radiofrequency ablation. (A) Precontrast axial T1-weighted image demonstrates central hyperintensitry (asterisk) consistent with early-phase post-RFA changes within the treated area (arrows). (B) Postcontrast axial T1-weighted image demonstrates no abnormal enhancement at the ablation area (arrows). RFA, radiofrequency ablation.

and is located along the needle tract. The development of the tumor seeding may be catastrophic and may be difficult to treat. Tumor seeding should be differentiated from postinflammatory changes and, in relevant clinical situations, biopsy or follow-up imaging should be recommended. Agressive tumor biology, subcapsular location, large size electrodes, and multiple repositionings and punctures are all risk factors.[91-93] Nodular contrast enhancement on dynamic imaging and diffusion restriction, along the needle path, are both helpful clues for the diagnosis.

Vascular complications are rare and occur because of either direct mechanical or indirect thermal injury. Vascular injuries may manifest as massive hemorrhage or in the form of vascular fistulization or pseudoaneurysms.

Imaging Findings After Transarterial Chemotherapy or Radiotherapy

Intraarterial treatments take advantage of the dual vascular supply of the liver. As the metastatic foci in the liver mostly derive their blood supply from hepatic artery and the rest of the liver from the portal vein, theoretically, by using the transarterial way, the metastases may be selectively treated by sparing the liver parenchyma. Metastatic liver disease from several different malignant neoplasms may be treated by transarterial approaches, but most of the information accumulated is on the treatment of colorectal and neuroendocrine tumor metastases (Fig. 15). For the technique and procedural details, the interested readers can refer to the article by Kalva et al.[94]

The comparison of the lesion size was used as the main determinant. However, it is now well known that size alone cannot be used as the sole criterion for assessing the tumor response. Given vascular embolization as the underlying mechanism used in these methods, regression in the vascularization of the target lesions and subsequent lack of enhancement on dynamic T1-weighted MR imaging in addition to edema and necrosis may also be helpful parameters for response assessment. Initial enlargement of the target tumor may also be seen, and this finding may not always represent tumor progression.[95]

DWI may also provide helpful information on top of the morhologic data provided by the conventional MR sequences.

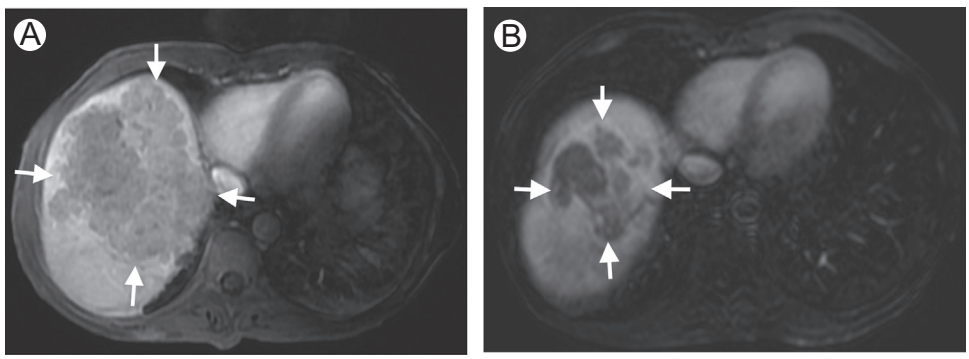

Figure 15 A 53-year-old male patient with biopsy-proven large liver metastasis at the liver dome. (A) Preradiombolization axial T1-weighted MR image demonstrates predominantly solid large metastatic mass (arrows). (B) Postradioembolization image shows significant reduction in size and solid-enhancing component of the same lesion (arrows) consistent with treatment response to Y-90 radioembolization.

Significant interval increase in the ADC values, representing decreased cellularity, after treatment may also be used as an ancillary finding as a parameter of positive treatment response.

Atypical Presentations of Liver Metastases and Challenging Findings

Typical imaging findings in metastatic liver disease may not be challenging to the imagers, and diagnosis is relatively straightforward. However, it is well known that liver metastases may mimick other benign and malignant clinical conditions, and awareness to these findings is crucial for the right diagnosis.

Diffuse infiltrative metastatic disease may be highly challenging to recognize in some patients. This pattern is less common, and hematologic malignancies are known to metastasize in this pattern.[96-99] Fatal liver failure may develop in these patients, and the diagnosis of the underlying pathology may be difficult. US and CT findings may be subtle and difficult to diagnose, and MRI may be helpful as the problem-solving technique in problematic cases (Fig. 16). DWI sequence may be especially helpful and has the potential to guide the higher yield biopsy by pointing the infiltrated area.

Chemotherapy regimens have diverse effects on the liver, and some may appear years after therapy. The development of focal nodular hyperplasia–like lesions and regenerative nodules after chemotherapy (particularly platin containing regimens) and hematopoietic stem cell transplantation is well known[100] (Fig. 17). Incidental detection of these lesions on follow-up imaging studies may be confusing and has a potential to misguide the clinical decision-making process. These lesions typically appear as arterially hyperenhancing lesions with no definite contrast material washout on dynamic MRI studies. Delayed-phase central scar enhancement, typical for focal nodular hyperplasia, may also be seen.

Metastatic liver disease may also mimic primary liver cholangiocarcinoma clinically when they lodge close to the liver hilum (Fig. 9). These patients may present with epigastric and right upper quadrant pain with or without associated jaundice, and differential diagnosis of metastatic liver disease from primary cholangiocarcinoma may be difficult without histopathologic confirmation.

Hepatic steatosis frequently develops after chemotherapy cycles and is similar to nonalcoholoic steatoshepatitis (also known as chemotherapy-associated steatohepatitis)[101] (Fig. 10). The liver, macroscopically, appears yellow owing to fatty infiltration of the hepatocytes. In these patients, MRI may be more helpful for lesion detection and characterization, as the sensitivity of CT studies may become lower in these patients.[37,102] In addition to lesion detection, MRI may also be used to quantify fat deposition in the liver parenchyma and may help assessing the hepatic insult secondary to chemotherapy. Focal or diffuse parenchymal fatty infiltration in these patients may not only morphologically simulate metastatic liver disease but may also show focal fluorodeoxyglucose (FDG) uptake[103] (Fig. 3). On the contrary, metastatic liver lesions may also mimic focal parenchymal fatty infiltration or sparing, which may be easily overlooked (Fig. 8).

Fat may be frequently seen within the liver parenchyma, and MRI is highly successful for detecting its presence.[104,105] However, the presence of fat within the metastatic liver lesions is not very common, and fat-containing primary tumors including Wilms tumor, liposarcoma, and renal cell carcinoma may give rise to fat-containing metastases within the liver parenchyma (Fig. 16).[106]

Role of MRI in Prognosis and Predicting Response of Liver Metastases to Chemotherapy

In addition to its high sensitivity in diagnosing liver metastases, MRI may also have a role, by using DWI and other sequences, in predicting prognosis and tumor response to chemotherapy. Koh et al[107] have demonstrated in their study that the detection of high ADC values in pretreatment metastatic liver foci secondary to CRCs may be an indicator of poor prognosis. The authors postulated that the presence of necrosis and loss of cell membrane integrity, causing high ADC values, in the

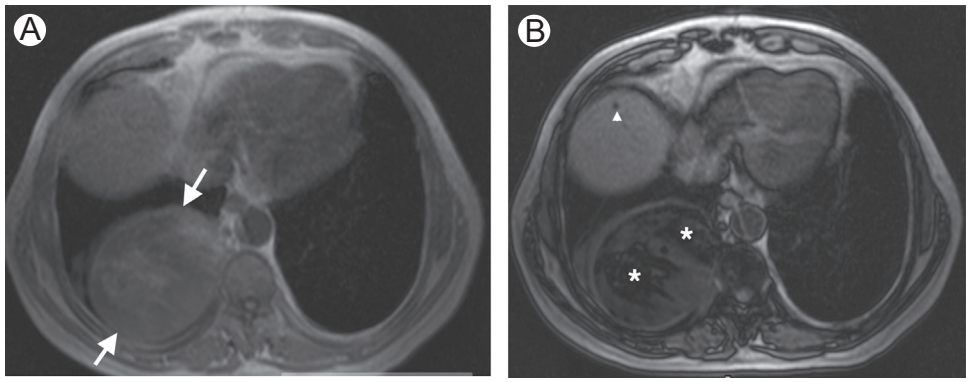

Figure 16 A 46-year-old female patient with biopsy-proven liposarcoma with a subcentimeter hypodense liver lesions detected on CT. (A) In-phase axial T1-weighted MR image shows patchy hyperintense areas in the mass (arrows). (B) Out-of-of phase axial MR image shows signal drop within the mass (asterisk) and the subcentimeter lesion (arrowhead) confirming presence of fat. Liver lesion was consistent with metastasis of liposarcoma.

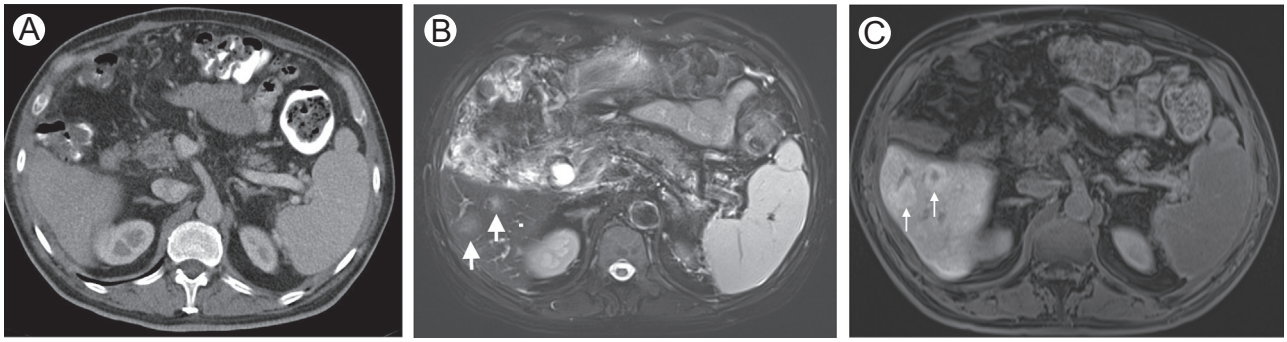

Figure 17 A 67-year-old female patient with known colon cancer under clinical remission, underwent several cycles of chemotherapy, was referred for newly detected multiple liver lesions on US. (A) Axial contrast-enhanced CT revealed no visible lesion in the liver parenchyma. (B) Axial fat-suppressed T2-weighted images showed 2 centrally hyperintense nodular lesions (arrows) in segment 6. (C) Hepatobiliary phase images show retention of gadoxetate disodium at the periphery of lesions (arrows) consistent with focal nodular hyperplasia–like lesions owing to oxaliplatin chemotherapy.

pretreatment phase of these metastases may indicate aggressive biologic behavior (Fig. 18). Poor perfusion, causing necrosis within the metastatic masses, was also proposed to be responsible for tumor hypoxia and acidic environment, further attenuating the tumoricidal effect of the chemotherapy.[108] Contrast-enhanced MRI demonstrates response to systemic chemotherapy with size and contrast enhancement changes (Fig. 19).

Future Directions

Several new state-of-art developments in MRI have a potential of opening new horizons for imaging specialists including more quantitative approaches in MRI (MR fingerprinting), the combination of MRI with PET (PET-MRI), and metabolic approaches such as glucose chemical exchange saturation transfer (glucoCEST) assessing the glucose metabolism with MRI.

In MR fingerprinting, the quantitative assessment of the tissue T1 and T2 relaxivity has a great potential, in addition to conventional qualitative approaches in MRI assessment. In this approach,the use of new technique may not only improve the success rate of detection of liver metastases but also has a great potential to provide information regarding response to treatment.[109]

PET-MRI offers exciting clinical and research opportunities by combining the superior soft tissue resolution of MRI with metabolic assessment of the tissues with PET using several different tracers for molecular targets.[110] Compared with conventional [18F] FDG-PET-CT, PET-MRI was shown to be more sensitive for the detection of liver metastases.[111] This higher accuracy of PET-MRI over PET-CT may have significant implications on therapeutic approaches. PET-MRI may also be helpful for assessing the response to treatment in addition to its diagnostic capabilities.[112]

GlucoCEST technique depends on the greater tendency of the tumor cells to use anaerobic glycolysis for production of energy than healthy tissues, a phenomenon known as the Warburg effect.[113] This effect is used in conventional PET-CT with the use of [18F] FDG molecule. In glucoCEST technique, MRI is used to to probe the glucose uptake by the tumor cells without the use of radioactive tracers, by a technique known as chemical exchange saturation transfer.[114] This technique has a great potential by offering significant cost reductions by eliminating the use of radiotracers and logistical hurdles related

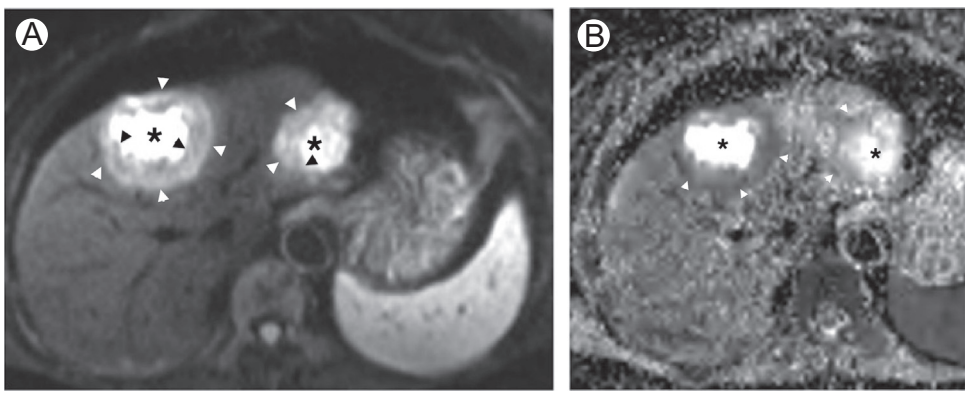

Figure 18 A 65-year-old male patient with known colorectal cancer metastases to liver. (A) DWI (b = 500) shows hyperintense rim (arrowheads) of the metastatic lesions with even more hyperintense central areas (asterisks). (B) Corresponding ADC map confirms true diffusion restriction in the lesion rims (arrowheads) with central T2 shine-through effect (asterisks) confirming central necrosis in the metastases.

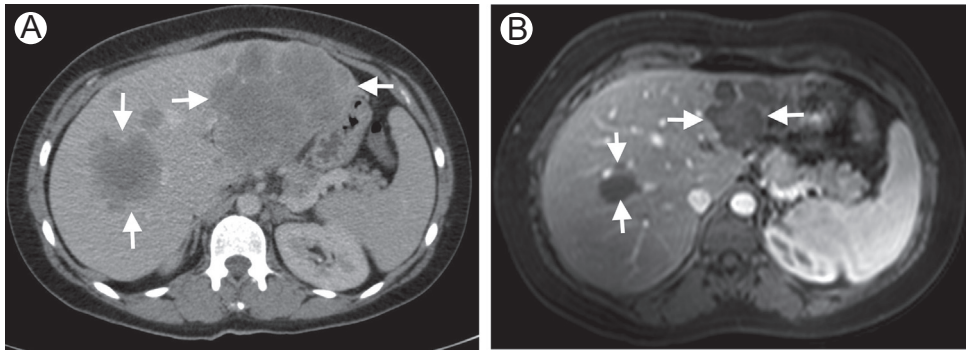

Figure 19 A 38-year-old male patient with metastatic colon cancer who underwent bevacizumab treatment. (A) Pretreatment axial portal venous phase CT image demonstrates large lesions (arrows) with internal vascularity. (B) Posttreatment axial portal venous phase contrast-enhanced MR image shows significant devascularization of the lesions consistent with treatment response (arrows).

to them. GlucoCEST also has a great potential by eliminating radiation exposure to oncologic patients who need frequent imaging in their follow-up.

Conclusion

Metastatic liver disease is very common in the course of cancer. The presence of hepatic metastatic disease is commonly a sign of advanced stage malignancy, and early detection and proper follow up is mandatory for optimal management. Although all cross-sectional imaging modalities including US, CT, and PET-CT may be used, MRI appears to be most successful modality with its superior soft tissue resolution. This advantage of MRI became even more pronounced with the advances in hepatocyte-specific contrast agents and new developments in MRI software and hardware technology.

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