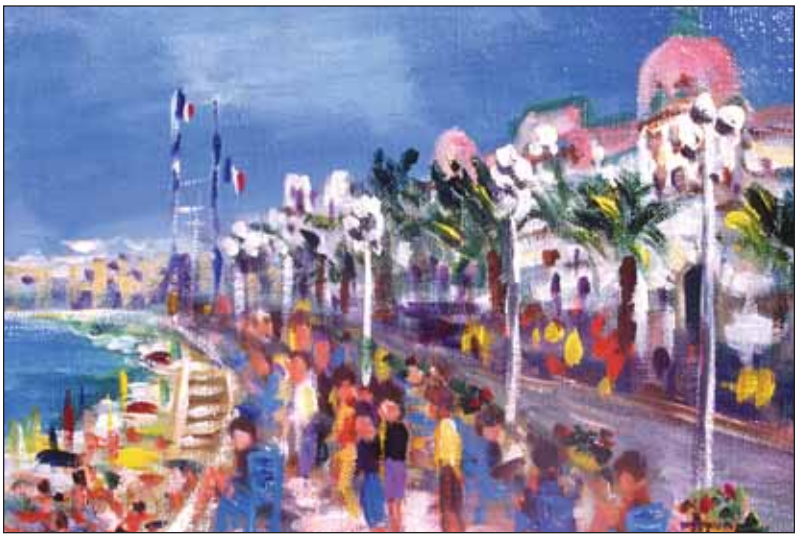

Annie Toja. *Nice, France, Promenade des Anglais.* Acrylic.

Imaging focal liver lesions is critical in the diagnosis, treatment, and follow-up of patients with hepatic metastases.

Imaging of Hepatic Metastases

Junsung Choi, MD

Background: *Imaging plays an important role not only in screening, evaluating, staging, and monitoriing disease, but also in surveillance following tumor ablation. Advances in imaging techniques have increased our ability to detect and characterize focal liver lesions, resulting in improvements in diagnostic capability and improved monitoring of liver metastases. This has led to increased interest in both hepatic imaging and image-guided hepatic interventions.*

Methods: *Several imaging options are reviewed according to their effective application, notably computed tomography (CT), CT during arterial portography, ultrasound, magnetic resonance imaging, positron emission tomography, and integrated PET/CT imaging.*

Results: *Although there are exceptions regarding imaging options based on patient selection and on institution preference and expertise, multidetector helical CT scanning remains the dominant modality in the evaluation of suspected hepatic metastases, and for preoperative planning, treatment monitoring, and posttreatment follow-up.*

Conclusions: *Ultimately, the choice of imaging modality must be based not only on the patient and the clinical situation, but also on the imaging expertise within each institution.*

Introduction

Metastatic disease involving the liver represents a common challenge in oncology. The liver is the most common site of metastases that arise from gastrointestinal malignancies; other primary sites of origin including breast, lung, pancreas, and melanoma.[1,2] Local therapy of liver metastases from primary locations such as breast, lung, gastric or pancreatic cancer may have little success due to the presence of extrahepatic disease. However, for colorectal cancer, hepatic resection in selected patients can result in 5-year survival rates of 20% to 45%.[3,4] Although the number of resectable candidates is limited compared with the number of

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Abbreviations used in this paper: CT = computed tomography, US = ultrasound, MRI = magnetic resonance imaging, PET = positron emission tomography, HCC = hepatocellular carcinoma.

patients demonstrating liver metastasis, preoperative imaging evaluation is important in proper patient selection to avoid unnecessary surgery. Advances in imaging techniques, notably computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), positron emission tomography (PET), and integrated PET/CT imaging, have increased our ability to detect and characterize focal liver lesions, resulting in improvements in diagnostic capability and improved monitoring of liver metastases. This has led to increased interest in both hepatic imaging and image-guided hepatic interventions.

Available Imaging Modalities of Hepatic Metastasis

Liver imaging has several roles in oncologic evaluation. One primary role is to screen for the presence of metastatic disease. The evaluation of suspected metastases is one of the most important indications for imaging. The second role applies to patients with known liver disease in whom further investigation is warranted. The workup of these patients may be for differentiation of metastasis vs benign masses (characterization) or for presurgical segmental localization for evaluation of resectability including visualization of vascular structures for tumor invasion and vascular anomalies. Successful outcome depends on the accurate determination of size and location of the tumor in relation to the liver segments, as well as vascular anatomy and vascular invasion. Volumetric data acquired from imaging can also be important in determining liver reserve for extended resections. Preoperative portal vein embolization for hypertrophy of the uninvolved portions of the liver has been used to increase liver reserve prior to major resections.[5] In these cases, volumetric evaluation of liver lobes and segments can add to the decision-making process for surgical resection.[6]

Imaging plays the principal role not only in staging, but also in monitoring treatment and surveillance following treatment. Advances in surgical and medical treatments are continually underway, and the number of local and systemic treatment options currently available is increasing. In addition liver resection, local or regional therapy includes a variety of ablation techniques. Chemoembolization and hepatic artery chemotherapy infusion are also available. Chemoembolization by catheterizing the hepatic artery branches and introducing chemoembolic agents has been used for the treatment of primary hepatocellular carcinoma (HCC) and hepatic metastases. Bland particulate embolization has also been performed for liver tumors including neuroendocrine carcinomas.

The challenge for diagnostic imaging is to provide a highly sensitive, specific, and noninvasive study that is readily available and well tolerated by the patient. The examination needs to be reproducible and consistent for accurate comparison. A new set of tumor response criteria for response assessment to treatment for research protocol patients, called response evaluation criteria in solid tumors (RECIST), presents new guidelines regarding the use of imaging modalities for the monitoring of response during therapy.[7] This had led to standardization in imaging techniques and target lesion measurement methods in an attempt to reduce misclassification of tumor response. Although many imaging modalities are available and there are exceptions based on institution preference and expertise, CT remains a common imaging modality for hepatic imaging in the evaluation of patients with or suspected hepatic metastases.

Computed Tomography

Since Godfrey Hounsfield invented CT in 1972, steady improvements in this modality have led to the current state-of-the-art multidetector helical CT (MDCT) scanners. In the mid 1980s, innovation of powered slip ring technology and advances in radiographic tube heat dissipation permitted continuous rotation of the gantry untethered by cables, allowing helical or spiral CT scanning (continuous scanning as the patient moves through the gantry at a constant velocity). Incorporation of multiple detectors has allowed several slices to be obtained with each rotation of the gantry. Current MDCT scanners can obtain 4 to 64 "slices" at a time, dramatically reducing overall scan acquisition times. A 64-slice MDCT scanner has decreased rotation time required for image acquisition to 0.33 of a second. Slice thickness as thin as 0.6 mm can be obtained and reconstructed at 0.5 mm increments, increasing the capability of high-resolution studies. The increase in speed of data acquisition allows for scans of the entire chest or abdomen during a single breath hold, thus eliminating respiratory misregistration. As a consequence of increase in speed, the use of rapid intravenous contrast administration with accurate timing of imaging is required for proper contrast enhancement.

With MDCT scanning, imaging of the liver can be timed more precisely to intravenous contrast administration in order to obtain different phases of tissue enhancement. Dual-phase evaluation with image acquisition during hepatic arterial and portal venous phases can improve lesion detection of hypervascular metastases. In addition, isotropic pixel size optimizes the data set for reformatted images in various planes that have as much detail as the axial images. Three-dimensional reconstructions of a range of tissue types and vascular structures also provide more detail. Kamel et al[8] have demonstrated the capability of multiplanar volume rendering and maximum intensity projection techniques to better delineate tumor and adjacent vascular

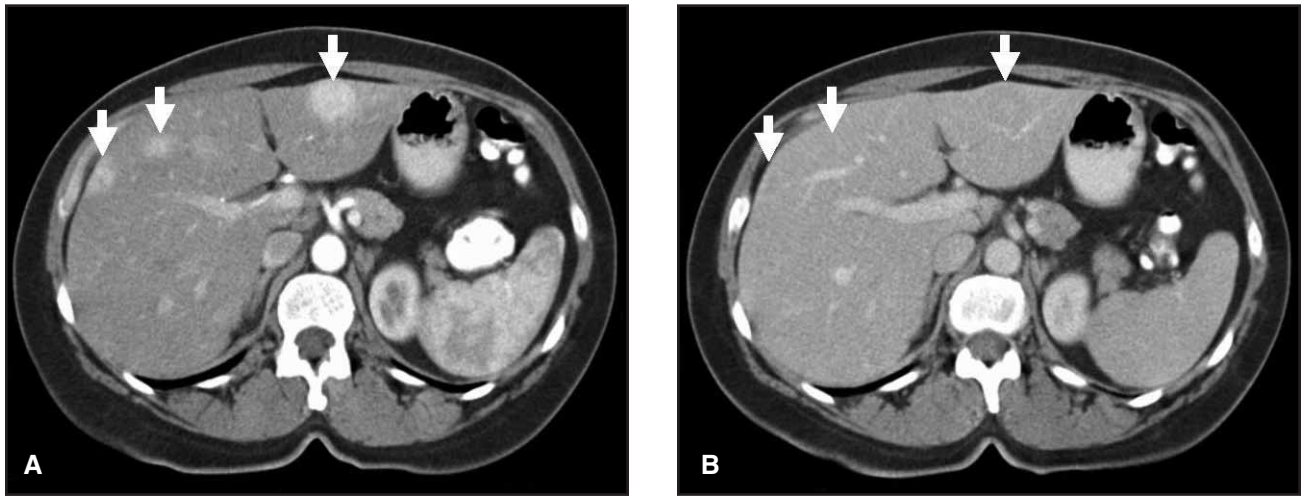

Fig 1A-B. — (A) Axial CT scan image shows hypervascular liver metastases (arrows) are well visualized during hepatic arterial phase of contrast administration in this patient with metastatic carcinoid tumor. (B) During portal venous phase there is wash out of contrast and poor visualization of the same lesions (arrows).

structures for accurate segmental localization of liver lesions. CT protocols that incorporate high-resolution liver imaging and vascular reconstructions have made it possible to evaluate the liver for preoperative planning without the need for additional testing such as conventional angiography. Accurate segmental localization of hepatic tumors as well as hepatic arterial and portal venous anatomy, which are important for surgical planning, can be provided.[9]

On CT scans, the appearance of metastatic disease of the liver depends on the vascularity of the tumor compared to the normal liver parenchyma. Larger tumors may have central low attenuation from necrosis or cystic degeneration, as well as calcifications. This can be seen with mucinous gastrointestinal metastases. Hypervascular metastases including neuroendocrine tumors, melanoma, sarcoma, and renal cell carcinoma enhance more rapidly than normal liver parenchyma, resulting in greater conspicuity better detected in the hepatic arterial phase (Fig 1).[10,11] Hypovascular lesions such as metastases from colorectal adenocarcinoma are best detected during the portal venous phase of liver enhancement, and a triple phase study may not be warranted.[12] Routinely, follow-up evaluation of these types of metastases are not performed using dual- or triple-phase scans. MDCT scanning provides the capability for thin-section scanning techniques, but Haider et al[13] reported that for routine evaluation of lesions with a diameter of 1.5 cm or less, collimation of less than 5 mm provided no improvement in detection.

In a meta-analysis of hepatic metastases from cancers of the gastrointestinal tract, Kinkel et al[14] reported a mean weighted sensitivity of 72% for CT based on 25 publications that included 1,747 patients. In another study with surgically proven liver lesions, a sensitivity of 69% to 71% and a specificity of 86% to 91% was shown using dual-phase helical CT.[8] For metastatic colorectal carcinoma, a sensitivity of 73% and specificity of 96.5% was reported.[15]

Computed Tomography During Arterial Portography

Computed tomography during arterial portography (CTAP) has been used primarily when considering hepatic resection.[16] Prior to the advances in helical CT and MRI, this method was considered the most sensitive for lesion detection in the liver preceding hepatic resection and was believed to play a complimentary role with intraoperative US.[17-19] However, CTAP is less routinely performed because it is an invasive, more costly procedure with less obvious superiority in lesion detection compared to current MDCT and MRI techniques. More recent comparisons of noninvasive imaging modalities, primarily MDCT and MRI, have shown equally accurate if not better lesion detection with lower false-positive rates.[15,20] Although current indications for CTAP have been significantly reduced, it remains an option if questions remain from noninvasive imaging studies.

Conventional catheter-directed angiography has been utilized for detection and preoperative planning of liver metastases and primary HCC.[21] With the improvements made in CT angiography and MR angiography, there is a developing trend toward using these modalities rather than conventional angiography for lesion detection and preoperative planning for HCC and liver metastases.[9]

Ultrasound

The mainstay of transabdominal US evaluation of the liver utilizes 3.5 to 5 MHz curved-array transducers. Real-time US evaluation with color-flow Doppler imaging offers a rapid noninvasive method for screening patients with suspected liver metastases. Most hepatic metastases are hypoechoic or hyperechoic, but addi-

tional sonographic patterns include cystic, calcific, mixed echogenic or diffuse. Findings suggestive of metastases include multiple solid lesions and presence of a hypoechoic halo surrounding a liver mass. Tumors of gastrointestinal origin, as well as more vascular tumors, are more likely to develop echogenic liver metastases. This can also be seen with primary HCC.

Transabdominal US has historically had low sensitivity with a false negative rate of greater than 50% and low specificity,[22] and therefore it has less utility in screening and surveillance for liver. Currently, it is not widely accepted, especially for primary diagnosis of liver lesions compared with other imaging modalities.

US evaluation can be more selectively applied to instances where other imaging studies discover an indeterminate lesion that requires further assessment for better characterization.[23] Several developments in US, including Power Doppler and harmonic imaging with contrast agents, have improved both detection and characterization of solid liver lesions. Power Doppler is another form of color Doppler imaging that uses a color map to show the distribution of the power of the Doppler signal without flow direction or velocity information. This reduces noise and provides more sensitive evaluation of flow.[24] The success of sonographic evaluation in obtaining accurate and reproducible results depends not only on these technical innovations, but also on skilled sonographers and highly experienced physicians dedicated to this subspecialty.

Harmonic imaging with microbubble contrast agents are used with phase inversion technology that filters out signal from the fundamental frequency and increases contrast signals arising from focal lesions and surrounding tissue. A second method is based on phase cancellation of the fundamental frequency with phase-inverted wideband pulses that result in high spatial and contrast resolution. Both methods cause destruction of the microbubbles in the field of view from insonation at high mechanical index. Contrast-enhanced US has been demonstrated to be useful for differentiating among hepatic tumors by their differing enhancement patterns.[25] Blood pool agents in the form of stabilized microbubbles that use a low mechanical index without microbubble destruction have also been studied. The nondestruction of the contrast agent allows for the real-time imaging in early and late phases after intravenous injection. Using CT and MRI as the reference, Albrecht et al[26] demonstrated that mean sensitivity for lesion detection increased from 69% to 90% when using SonoVue (Bracco International, Milan, Italy), a second-generation US contrast agent. Contrast also dramatically improved characterization of both malignant and benign liver lesions approaching that of CT and MRI. This demonstrates the potential of contrast-enhanced sonography for follow-up of known hepatic lesions by experienced sonographers.

Magnetic Resonance Imaging

Steady advancements in both MRI hardware and image acquisition techniques have had a major impact in abdominal imaging, particularly hepatic imaging. From the introduction of conventional spin-echo T1- and T2-weighted images, faster imaging sequences such as T1-weighted spoiled gradient echo and T2-weighted fast spin echo (turbo spin echo) have allowed for rapid imaging of the liver with breath hold to prevent motion artifact. The use of the phase-array surface coil provides higher signal-to-noise ratio over conventional body coils, allowing for smaller field of view, thinner slices, and higher resolution to improve lesion detection.

Contrast enhancement is routinely performed for the evaluation of liver metastases. Contrast agents specific to liver have been introduced in an effort to increase detection of liver lesions. Mangafodipir trisodium (MnDPDP, Teslascan) is a hepatocyte-selective contrast agent. After intravenous administration, the contrast agent is taken up by the hepatocytes, and normal liver parenchyma shows increased signal on T1-weighted images. Superparamagnetic iron oxide (SPIO) is specific for the reticuloendothelial system. This agent is captured by the reticuloendothelial system in the liver as well as in the spleen and bone marrow. The presence of iron particles causes signal loss in the liver on T2-weighted images, providing a darker background that is used to improve lesion detection. A limitation of SPIO use is long injection time, which prolongs the time for study completion.

In a prospective study comparing CT, CTAP, and MRI for staging colorectal cancer patients for liver resection, the sensitivity and specificity for MRI was 81.9% and 93.2%, respectively, which was not statistically different from contrast enhanced CT and CTAP.[15] When MRI was compared with and without SPIO and CT in patients with liver metastases from colorectal cancer, Vidiri et al[27] showed improved lesion detection with SPIO-enhanced MRI (with a sensitivity of 86.8% vs unenhanced MRI of 65%) compared with CTAP (with a sensitivity of 86.8% but a higher false-positive rate). At the present time, gadolinium is used more often as a non–liver-specific contrast agent for liver imaging. When compared to liver-specific contrast agents, the results appear to be slightly less superior.[28]

Positron Emission Tomography and PET/CT

The use of PET with the radiopharmaceutical 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG-PET) allows imaging of glucose metabolism. This functional imaging can lead to improvements in tumor detection by early detection of abnormal tumor metabolism prior to the appearance anatomic changes, and localization of tumor in unsuspected sites. Metabolic imaging using FDG-PET is useful in multiple indications in oncology.[29] A wide variety of malignant tumors accumulate FDG. This metabolic

information not obtainable by anatomic imaging techniques can be used to differentiate benign from malignant lesions, stage malignant lesions, detect tumor recurrence, and monitor therapy.[30] A limitation in the clinical value of PET imaging has been the inability to provide precise anatomic localization of the abnormal sites detected. The interpretation of PET has required visual comparison of abnormal uptake to current or recent CT scans for localization. Computer software has also been developed to coregister PET images to the anatomic detail found in CT images.

The direct integration of CT with PET is a more recent approach to improve localization. The integrated PET/CT scanner allows acquisition of CT and PET images in a single setting.[31] This leads to optimal coregistration of images. The fusion images have greater capability to be manipulated as they are interpreted on a dedicated workstation by viewing multiplanar images with the ability to change weighting of superimposed PET and CT data. By providing the ability to accurately fuse PET and CT data sets, PET/CT significantly reduces the magnitude of mislocalization of FDG uptake and improves the confidence levels of the interpreting physician in localizing potential lesions and improves the ability of the interpreting physician to localize potential lesions. This can also resolve potential misinterpretation of benign processes as malignant.

The utilization of the CT portion of the PET/CT scan can differ. It may be used as a low-dose scan for attenuation correction and anatomic correlation without the use of oral or intravenous contrast. This is not comparable to and does not replace a diagnostic CT scan, and it should be considered nondiagnostic. A diagnostic-quality CT scan can be performed with the administration of intravenous and oral contrast as normally done with standard CT imaging protocols. This would provide a full CT workup with the PET scan, obviating the need for additional CT imaging studies. Concerns have arisen regarding possible attenuation correction error leading to erroneously elevated FDG uptake with intravenous contrast and artifact induced with the use of oral contrast. However, they do not appear clinically significant in interpreting PET/CT scans.[32]

The evaluation of patients with known or suspected recurrent colorectal cancer is an accepted indication for FDG-PET. In addition to the usefulness of this modality for staging, Abdel-Nabi et al[33] have shown that it can be superior to CT for detecting liver metastasis. They reported sensitivity and specificity rates of 88% and 100%, respectively, with FDG-PET, compared with sensitivity and specificity rates of 38% and 97%, respectively, with CT. Other studies comparing the accuracy of FDG-PET and CT for detection of liver metastases demonstrated that PET was more accurate than CT.[34] As described previously, a meta-analysis of noninvasive imaging methods for detection of hepatic metastases from colorectal, gastric, and esophageal cancers reported equivalent specificity, with PET achieving the highest sensitivity.[14] Studies have also indicated that PET is most accurate for detection of hepatic metastases greater than 1 cm in diameter, but it is limited in detecting lesions smaller than 1 cm.[35,36]

The detection of extrahepatic disease is a critically important finding in patients who may otherwise be resectable candidates for liver metastases. Imaging of the entire body with PET permits the diagnosis of unsuspected metastases outside of the liver (Fig 2). The

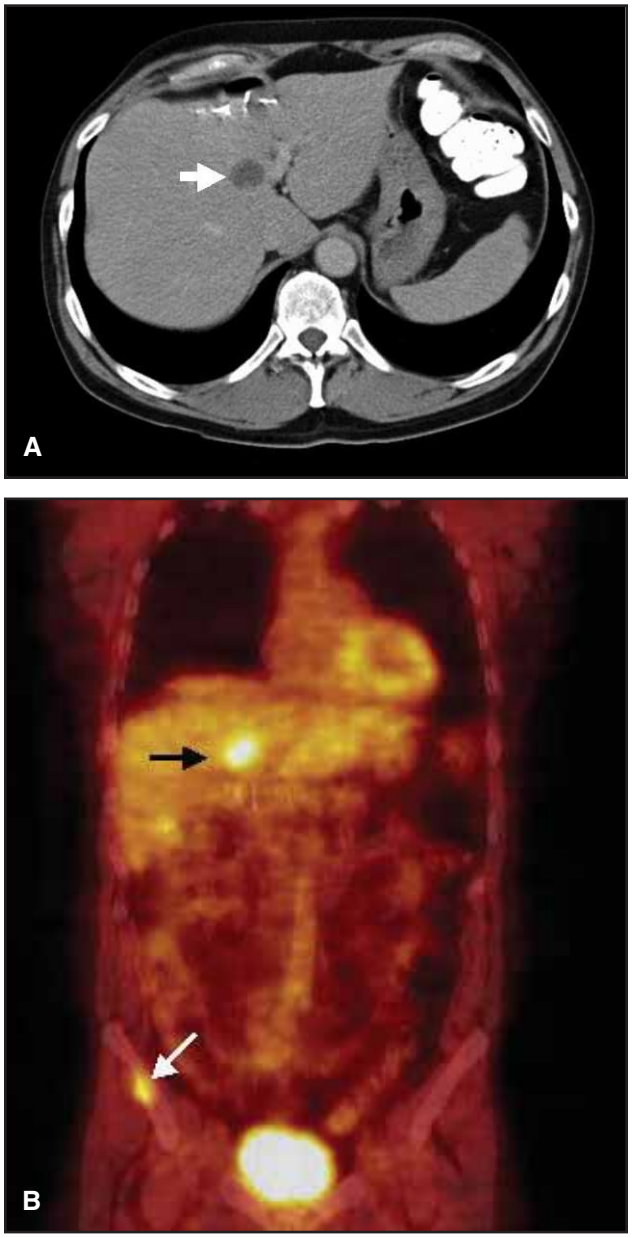

Fig 2A-B. — (A) Axial CT scan image demonstrates biopsy-proven local recurrence of liver metastasis following liver resection in the medial segment of the left lobe of the liver as a rounded low attenuation lesion (arrow) with no additional spread of disease. (B) Coronal image from a PET scan demonstrates the recurrent liver metastasis (black arrow) corresponding to the lesion seen on the CT scan as well as an unsuspected bone metastasis to the right iliac bone (white arrow)

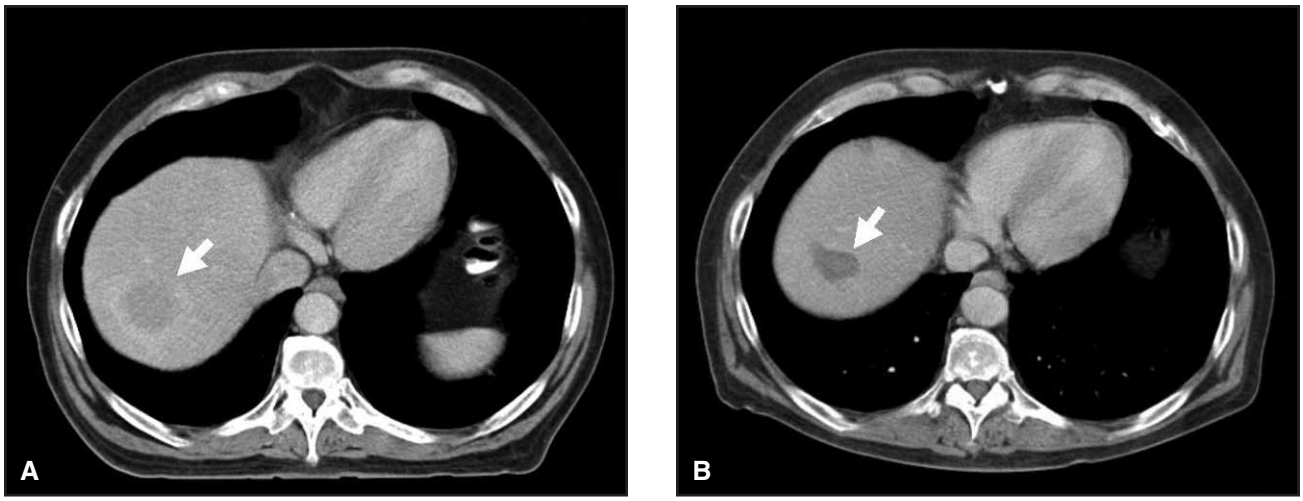

Fig 3A-B. — (A) Axial CT scan shows a peripherally enhancing low-attenuation mass in the superior aspect of the right lobe of the liver (arrow) prior to radiofrequency ablation. (B) Follow-up CT scan 1.5 years after ablation demonstrates satisfactory treatment with regression in size of the treated area (arrow) and no peripheral contrast enhancement to indicate recurrence or residual tumor.

detection of unsuspected metastases can range from 13% to 36% and has a major impact on clinical management and alters surgical management in 23% to 29% of patients.[35-37]

Imaging Methods Following Tumor Ablation

Radiofrequency ablation has become an increasingly utilized technique for treatment of unresectable liver tumors. This approach is one of a variety of techniques that are available for tumor ablation in the liver. Others include microwave and laser ablation, cryoablation, alcohol ablation, and intra-arterial hepatic chemoembolization for locoregional chemotherapy. The most commonly treated tumors are HCC and hepatic metastases from colorectal cancer. Ablation of metastatic neuroendocrine tumors has also been used to debulk tumors and provide symptomatic relief.[38]

Radiofrequency ablation can be performed percutaneously under CT, US, or MRI guidance. Most percutaneous ablations are currently performed under CT guidance. This is also performed laparoscopically and during open surgery using direct hepatic US guidance. The approach varies, depending on tumor size and location. Lesions located near the liver capsule or adjacent to other organs such as diaphragm or bowel may require an open surgical procedure.

CT is commonly used for the assessment of treatment response. The size of the treated lesion is usually larger than the size of the original lesion. This is the result of inclusion in the treatment of a rim of normal liver surrounding the lesion with possible hyperattenuation due to hemorrhage and coagulative necrosis on noncontrast CT.[39] Although occasional rim enhancement may be seen, no focal enhancement should be present along the margin of the treatment, which would indicate incomplete treatment. On subsequent follow-up, the nonenhancing lesion may remain stable or slowly decrease in size (Fig 3).

MRI demonstrates coagulation necrosis after radiofrequency ablation as intermediate to high signal-to-liver parenchyma on T1-weighted and low signal on T2-weighted images. A T2-hyperintense rim around the ablation area may be seen that may be due to edema from thermal injury. Heterogeneous signal on both T1- and T2-weighted images due to nonuniform evolution of inflammation and necrosis may make interpretation for residual or recurrent tumor difficult on unenhanced MRI scans. Following contrast administration, noncircumferential nodular area of enhancement is suggestive of tumor.[40] Both CT and MRI demonstrated a similar capability to detect local regrowth of tumors that were visualized within 4 months, with a possible slight advantage with MRI.[41] PET/CT imaging is also helpful to monitor for residual tumor or recurrence after ablation. Preliminary studies show the potential of PET/CT in detecting residual or recurrent tumor following ablation therapy.[42,43]

Conclusions

Advances in imaging technology have improved our ability to detect, characterize, and stage metastatic liver disease. Although every modality has benefited from advances in technology, MDCT scanning — with its speed and three-dimensional volume rendering that can provide detailed vascular anatomy — remains a dominant imaging modality not only for lesion detection and preoperative planning, but also for treatment monitoring and posttreatment surveillance. PET and integrated PET/CT show significant potential to alter

our approach to oncologic evaluation. High-resolution CT with contrast combined with PET may obviate the need for additional studies and may improve patient management. Ultimately, the modality used must be tailored not only to the patient and the clinical situation, but also to the imaging expertise within the institution.

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