Foreword: *Radiology* Select Volume 7—Imaging the Liver

Dear *Radiology* Select Reader:

Imaging the Liver is the seventh volume in our *Radiology* Select series. We chose this topic because of the large amount of research in hepatic imaging and the importance of surveillance for and treatment of hepatocellular carcinoma in populations with increased incidence of cirrhosis and of new therapies to prevent disease progression. We are very excited about offering a compilation of articles on a theme that is relevant to many different practice settings in radiology—including modalities of compted tomography, magnetic resonance (MR), ultrasonography, positron emission tomography, and interventional radiology. Given the variety of hepatic imaging techniques and interventions, the liver has been the basis of a large amount of research.

We are delighted that Valérie Vilgrain, MD, PhD, and Maxime Ronot, MD, PhD, have agreed to serve as the guest editors of this volume, given their expertise in liver imaging and intervention and the breadth and depth of their knowledge of research in the field. Dr Vilgrain completed her radiology residency at University of Paris (France) and a fellowship in radiology at Beaujon University Hospital, Clichy, France. She is currently chair of the Department of Radiology at the Beaujon University Hospital and full professor of radiology at the Paris Diderot University and Sorbonne Paris Cité (France). Her colleague, Dr Ronot, associate professor of radiology, is an internationally recognized leading researcher in imaging of liver diseases and interventions.

Drs Vilgrain and Ronot had the difficult task of reviewing original research and reviews recently published in *Radiology* and selecting articles for inclusion in this compilation. They chose to focus on five major areas: *(a)* imaging of hepatocellular tumors, *(b)* diffusion-weighted MR imaging, *(c)* quantitative imaging, *(d)* hepatobiliary MR contrast agents; and *(e)* vascular and interventional imaging. Because we are limited in the number of articles we can include in the volume, the final list of articles is, of necessity, subjective. The contents reflect a somewhat personal view of which are the key articles—not the result of a quantitative determination. In this compilation we also include one RadioGraphics article since it so nicely describes the American College of Radiology's Liver Imaging Reporting and Data System, the structured reporting system for liver tumors. We, of course, recognize that *Radiology* has published many more fine articles on the subject area than can be condensed into this 31-article volume. Many excellent and clinically important articles therefore are of necessity not included.

Continuing medical education (CME), in the form of CME credits as well as self-assessment CME (SA-CME) is an important aspect of clinical practice in radiology. Recent American Board of Radiology diplomates, in addition to needing CME, also need SA-CME for recertification. We believe that *Radiology* Select offers a perfect vehicle to provide up-to-date SA-CME for our readers and will help them better understand how research evolves and translates into clinical practice. Therefore, the corresponding authors of selected articles were contacted and asked to supply questions for CME and SA-CME activities. We are proud to offer up to 13 *AMA PRA Category 1 Credits*™ with this volume.

The online era provides multimedia opportunities for publications. We exploit this capability by providing audio and video conversations with authors to explore their views on the effect of their work and the work of others in the field. These conversations also allow experts to share their thoughts on future developments and the effects of their work on these.

In keeping with the trend of increasing reliance on electronic publishing, we are offering *Radiology* Select in two formats: HTML on the Internet and print on demand. Print on demand is a bound printed edition containing the articles for those who prefer reading hard copy. The online edition is an HTML version for viewing with a Web browser. Individual PDFs can be downloaded, and readers can listen to and view the audio and video conversations with authors and editors. The CME and SA-CME activities are available only through the online version.

We thank Drs Vilgrain and Ronot for reviewing and selecting the articles collected in this volume. We are especially grateful to the authors of the articles, without whom *Radiology* Select would not be possible.

Sincerely,

Deborah Levine, MD, Series Editor, *Radiology* Select
Herbert Y. Kressel, MD, Editor, *Radiology*

Video
Online Educational Edition of *Radiology* Select includes a video with series editor Deborah Levine.

Introducing *Radiology* Select: Imaging the Liver

Valérie Vilgrain, MD, PhD
Maxime Ronot, MD, PhD

In 1976, Taylor et al published an article in *Radiology* entitled "Gray Scale Ultrasound Imaging: The Anatomy and Pathology of the Liver" (1). Before the development of ultrasonography (US) of the liver, imaging of this organ was limited to radionuclide imaging or was based on an invasive vascular or biliary approach. Indeed, hepatologists and abdominal radiologists extensively used hepatic angiography to help diagnose liver tumors, splenoportography for assessing portal hypertension, and hepatic venous catheterization to help determine the hepatic venous pressure gradient. Percutaneous cholangiography was also indicated for the diagnosis and treatment of biliary tumors. On one hand, it is possible to measure the giant steps that have been made since that time. On the other hand, it is interesting to note that the major advances in liver surgery and liver anatomy were achieved before the era of modern liver imaging: The first right hepatectomy was performed by Jean-Louis Lortat-Jacob in 1952, Claude Couinaud described the segmental anatomy and the role of major vascular landmarks in 1954, and Thomas Starzl performed the first liver transplantation in 1963 in a 3-year-old boy with biliary atresia.

Liver imaging really began to evolve in the 1980s and 1990s with three imaging modalities: US, computed tomography (CT) and magnetic resonance (MR) imaging. US rapidly became the primary imaging modality for liver diseases and is still important today because screening for chronic liver diseases is mostly performed with this technique. US was improved by combining it with other tools such as duplex and color Doppler, contrast agent enhancement, and, more recently, US elastography. Thus, US has progressively become the first-line all-in-one imaging modality for the liver.

CT has become increasingly popular for imaging of the liver thanks to two major technical advances: With multiphase acquisitions and helical technology, rapid acquisitions can be performed at key phases, allowing visualization of the unique vascularity of the liver with its dual arterial and portal venous inflow and enhancement of liver tumors. More recently, spectral imaging has been introduced as a new field in tissue characterization.

MR imaging created a true revolution in liver imaging. In 1983, Stark et al published an article in *Radiology* entitled "Nuclear Magnetic Resonance Imaging of Experimentally Induced Liver Disease" (2), which prefigured the role of MR imaging in tissue characterization. These authors developed and evaluated experimental animal models of hepatitis, fatty liver, and hepatic iron overload and showed changes in T1 and T2 relaxation times in 0.35-T MR acquisitions. Interestingly, these topics are still key areas of research in this field.

Meanwhile, a shift has occurred from diagnostics to treatment in the field of vascular and interventional radiology. A new medical specialty has emerged called interventional oncology. It is now recognized as one of the four pillars in the treatment of cancer and cancer-related disorders, along with medical oncology, surgical oncology, and radiation oncology. The liver has become a central organ in interventional oncology with various endovascular and transhepatic approaches.

Video
Online Educational Edition of *Radiology* Select includes videos with guest editor Valérie Vilgrain, MD, PhD.

This *Radiology* Select collection covers research relevant to liver imaging between 2007 and 2014 and includes 30 articles published in *Radiology* and one review from *RadioGraphics*. The articles were chosen to represent the most important advances and reviews in liver imaging and the ongoing contribution of scientific publications. For instance, concepts that were developed in earlier studies and thagt have recently been confirmed have been chosen, emphasizing the role of preliminary or experimental study results in recent research. Unfortunately, many outstanding articles could not be included, and our selection was necessarily subjective. Nevertheless, originality, clinical influence, and scientific value of the articles were taken into consideration. The collection is presented in five main themes: Diagnostic Performance of Imaging Hepatocellular Tumors, Diffusion-weighted MR Imaging, Quantitative Imaging, Hepatobiliary MR Contrast Agents, and Vascular and Interventional Imaging.

Hepatocellular tumors include benign tumors that are mainly seen in healthy livers, such as focal nodular hyperplasia and hepatocellular adenomas, as well as malignant tumors that mainly develop in patients with a chronic liver disease, mainly cirrhosis. The latter tumors are classified as regenerative nodules, dysplastic nodules, and hepatocellular carcinomas (HCCs). This differentiation is important because regenerative nodules are benign, while dysplastic and neoplastic nodules are premalignant and malignant, respectively. Both MR and CT are used for characterization of focal liver lesions. Besides changes in cellular architecture, nodule vascularity also changes during multistep hepatocarcinogenesis, from mainly portal inflow to exclusively arterial inflow.

In a study with CT during arterial portography and hepatic arteriography, Kitao et al (3) have also shown changes in venous drainage during multistep hepatocarcinogenesis from hepatic veins to hepatic sinusoids then to portal veins, explaining corona enhancement in HCC. Recent research on genetic abnormalities and genotype-phenotype correlations in hepatocellular tumors has improved understanding of tumoral features on images.

Shanbhogue et al (4) provide an interesting review of the cytogenetics and molecular biology of hepatocellular tumors, showing the association of gene expression with tumor differentiation in HCC and with imaging features in different subgroups of hepatocellular adenoma. Unlike most malignant tumors, the diagnosis of HCC can be achieved noninvasively in patients with chronic liver disease. First-line diagnostic criteria are similar in Western and Eastern guidelines and are based on a combination of hypervascularity on arterial phase images and hypoattenuation or hypointensity on portal venous or delayed phase images when using contrast agent–enhanced CT or MR imaging. The strength of these combined criteria is their very high specificity, although they are less sensitive, especially for small lesions.

Di Martino et al (5) compared the diagnostic accuracy and sensitivity of gadoxetic acid–enhanced MR imaging with multidetector CT and showed that the diagnostic accuracy and sensitivity of MR imaging is better in all cases of HCC, including lesions smaller than 2 cm. It is important to assess the variability of diagnostic criteria, as well as the sensitivity, accuracy, and specificity. Davenport et al (6) found that the interreader agreement for MR imaging was substantial for hypervascularity on arterial phase images but only moderate for hypointensity on portal venous or delayed phase images, as well as for the presence of a pseudocapsule.

The Liver Imaging Reporting and Data System (LI-RADS), which standardizes report content and structure, has been developed by the American College of Radiology to help reduce the variability and inconsistency of the interpretation and reporting of liver images. Purysko et al (7) provide d an excellent review of version 1.0 of the LI-RADS and discuss the major and ancillary imaging features used to categorize the probability of having a HCC. Slight modifications have been made in LI-RADS since publication of the article by Purysko et al, but the key concepts remain unchanged (LI-RADS v2014, *http://www.acr.org/quality-safety/resources/LIRADS*).

Our second liver imaging theme includes articles on diffusion-weighted imaging (DWI) with MR. DWI has become an element of routine MR protocols for both the detection and the characterization of liver lesions. Parikh et al (8) showed that the detection rate of focal liver lesions is higher with DWI than with standard MR sequences. The improved detection rate for DWI compared with that for T2-weighted imaging was also observed in malignant tumors alone, including those smaller than 3 cm in diameter. These results have been confirmed by many others, which suggests that the interpretation of MR images in patients with malignant lesions should include careful analysis of the DWI results.

DWI has also been shown to help differentiate benign from malignant tumors and to improve diagnosis of HCC. Kim et al (9) evaluated hypovascular nodules and reported hypointensity during the hepatobiliary phase on gadoxetic acid–enhanced MR images in patients with cirrhosis. These are the most difficult lesions to characterize because they do not have the typical findings of HCC but are suspicious on hepatobiliary phase images. Interestingly, this study showed that in these lesions hyperintensity on

images obtained with DWI is strongly associated with progression to hypervascular HCC.

DWI provides both qualitative and quantitative results. Several parameters can be extracted depending on the model used. With at least two *b* values, the apparent diffusion coefficient (ADC) of tissue can be quantified. When a wide range of multiple *b* values (including high and low *b* values) is used, the intravoxel incoherent motion phenomenon enables separation of pure diffusion from perfusion-related diffusion. The ADC values of the liver parenchyma are known to be reduced in patients with cirrhosis, compared with those in healthy patients. Luciani et al (10) calculated ADC, *D,* and *D**, with the latter two representing pure molecular diffusion and perfusion-related diffusion, respectively. This study showed that the reduced ADC in cirrhosis is related to reduced perfusion (*D**) rather than to changes in pure diffusion.

It is important to understand the factors associated with increased variability when dealing with quantitative imaging. Chen et al (11) measured normal liver ADC by using different respiratory motion compensation techniques and different anatomic positions. They confirmed that the reproducibility for the left liver lobe is inferior to that for the right and recommend the free-breathing technique.

Finally, the outstanding state of the art review on DWI by Taouli and Koh (12) covers qualitative and quantitative aspects of this sequence and explains the importance of acquisition parameters and postprocessing.

Our third theme covers quantitative imaging of the liver, which represents an increasing portion of the medical literature on liver imaging. Articles discuss the quantification of liver steatosis, liver iron content, perfusion parameters, and the measurement of liver stiffness. Liver steatosis is related to several factors and is mainly classified as alcohol-related steatosis or nonalcoholic fatty liver diseases (NAFLDs). The diagnosis and quantification of steatosis is of importance because this condition is associated with increased morbidity and increased mortality after major liver surgery. More recently, NAFLD has been the focus of particular attention because it is now the leading cause of liver disease in Western countries and its prevalence has doubled in the past 20 years. NAFLD is defined as excessive fat accumulation in the liver (> 5% of hepatocytes, histologically).

A subgroup of NAFLD patients has liver cell injury and inflammation (nonalcoholic steatohepatitis, [NASH]), which may progress to cirrhosis and HCC. Therefore, an accurate noninvasive assessment of liver fat content is important. van Werven et al (13) prospectively compared the diagnostic accuracy of US, CT, dual-echo MR imaging, and MR spectroscopy in patients who underwent liver resection and show that unlike US and CT, MR imaging and MR spectroscopy findings are strongly correlated with histopathologic results. Nevertheless, dual-echo MR techniques to quantify liver fat content may be altered in the presence of liver iron. In 2008, O'Regan et al (14) evaluated breath-hold multiecho gradient-echo MR imaging for simultaneous lipid quantification and T2* measurement. The fat fraction was highly correlated with spectroscopic measurements. Multiecho gradient-echo MR sequences were also validated in a prospective study by Yokoo et al. (15). The authors confirmed that the results of multiecho MR are better than those of dual- or triple-echo methods and that the multi-interference method (which takes into account the three main fat peaks) is the most accurate technique.

Perfusion imaging, either CT perfusion or dynamic contrast-enhanced MR imaging, is used to assess changes in diffuse liver diseases or in liver tumors, especially in patients undergoing drug treatments that target angiogenesis. Perfusion parameters may also be associated with tumor differentiation and, thus, prognosis. In a study on advanced HCC by Sahani et al (16), higher perfusion values were found in well-differentiated HCCs than in other grades. This type of imaging must be standardized, however, and Goh et al (17) showed that measurements from commercial software packages are not interchangeable, which can make cross-study comparisons difficult. These discrepancies may be due to the different modeling techniques used.

The assessment of liver fibrosis by measuring liver stiffness began in the early 1980s with the introduction of transient elastography. This technique is based on the transmission of vibrations with an external transducer, inducing an elastic shear wave that propagates through underlying tissue. US is used to monitor the propagation and measure the velocity of shear waves, which are directly related to tissue stiffness. MR imaging can also be used to assess tissue stiffness by measuring the displacement induced by shear wave propagation with motion-sensitized sequences. MR elastography has the advantage of providing three-dimenstional data. Huwart et al (18) prospectively assessed MR elastography and showed that it is accurate and better than biochemical testing for estimating the degree of liver fibrosis. More recently, liver stiffness has been used to identify the presence of inflammation in NAFLD patients: Chen et al (19) showed that liver stiffness is higher in patients with NASH than in those with simple steatosis, even in the absence of fibrosis. If confirmed in

large prospective trials, MR elastography could play a major role in the evaluation of these patients. In this case, standardization is essential; as reported by Bohte et al (20) and like any quantitative method, thresholds for clinically important degrees of change must be defined. Meanwhile, US elastography has been integrated into conventional US systems. Both methods have been compared with transient elastography, and diagnostic accuracy has been shown to be comparable or higher for assessing liver fibrosis (21,22).

Our fourth theme is hepatobiliary MR contrast agents. These agents combine the properties of extracellular gadolinium chelates for multiphasic examination of the liver at the arterial and portal venous phases, as well as at a specific phase during hepatocyte uptake and biliary excretion. During the hepatobiliary phase, functional hepatocytes take up the contrast agent and appear iso- to hyperintense, and nonhepatocellular lesions and impaired hepatocytes appear hypointense. Thus, these contrast agents were first evaluated for tumor detection and characterization, in particular for hepatocellular tumors. Ahn et al (23) showed that combined reading hepatobiliary phase routine MR images with gadoxetic acid improves diagnostic accuracy for HCC. More recently, Park et al (24) compared images from gadoxetic acid–enhanced MR with those from DWI in patients with HCC and showed that the combination of these sequences is more sensitive and accurate than each MR sequence separately.

Although most HCCs are hypointense on the hepatobiliary phase images owing to altered hepatocytes, some are iso- or hyperintense. Tsuboyama et al (25) showed that the degree of expression and the localization of transporters (OATP1B1, OATP1B3, and MRP2) affect hepatocyte-selective enhancement of HCC. Interestingly, liver enhancement on gadoxetic acid–enhanced MR images at the hepatobiliary phase can be reduced in healthy subjects due to genetic OATP1B1 polymorphisms (26). In addition to the detection and characterization of lesions, gadoxetic acid has also been used in the evaluation of liver function. The best correlation with indocyanine green clearance takes into consideration hepatocellular uptake combined with liver and spleen volumes (27).

Our fifth and final theme discusses vascular and interventional imaging of the liver. The selections highlight how interventional studies have improved, moving well beyond case studies and short-term results. Transarterial chemoembolization (TACE) is the standard of care for intermediate-stage HCC. In a large series of patients treated with TACE for HCC, Lewandowski et al (28) evaluated the role of tumor biology and the severity of liver disease in tumor progression and survival.

Assessing tumor response is another key issue in patients with TACE, because retreatment is based on imaging. Shim et al (29) compared traditional criteria for solid tumors (WHO, RECIST) with more recent criteria such as EASL or mRECIST, which have been developed to help visualize viable tumor components. They reported that prediction of long-term survival is improved with the latter, therefore providing interesting prognostic biomarkers. Lee et al (30) showed that tumor biology and severity of liver disease influence overall survival in patients with HCC treated with percutaneous radiofrequency ablation, similar to the case with TACE. Moreover, the high survival rate associated with this treatment confirms the role of tumor ablation as the first-line treatment of small HCCs.

Little is known about the long-term survival of patients with small liver colorectal metastases treated with percutaneous radiofrequency ablation and systemic chemotherapy. In a study by Solbiati et al (31), most patients with colorectal metastases of the liver were ineligible for surgery, and the long-term survival was equivalent to that in surgical reports.

In HCC, it is difficult to compare treatments because the choice of therapy is based on multiple factors, such as tumor size and number, liver function, presence of portal hypertension, general status, and comorbidity. When possible, curative treatment is preferable to palliative care. Takuma et al (32) used propensity score matching to compare combined TACE and radiofrequency ablation with surgical resection. Following score adjustment, overall survival rates were comparable between the two groups. Their results showed how statistical methods can minimize the limitations of noncontrolled studies and control-confounding variables. Other intra-arterial treatments besides TACE such as radioembolization (or selective internal radiation therapy) have become popular in recent years. Radioembolization is a liver-directed therapy that delivers yttrium 90 microspheres, resulting in internal radiation therapy. The two main indications are liver metastases and HCC. In 2008, Sato et al (33) confirmed the efficacy of this treatment in unresectable chemorefractory liver metastases. Since then, several studies have confirmed the excellent tolerance of radioembolization, and results of controlled trials in liver metastases and HCC will soon be released to better define the indications for this approach.

The increased prevalence of diffuse liver diseases and HCC is a major cause of morbidity and mortality worldwide. The purpose of this *Radiology* Select volume is to highlight the recent improvements in liver imaging and to increase medical knowledge.

We hope that these articles will help radiologists provide better clinical care to patients with liver diseases.

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Maxime Ronot, MD, PhD, graduated from Paris Diderot University (France), where he received his MD and PhD degrees. He completed his residency and fellowship training in diagnostic and interventional imaging at the University Hospitals of Paris and Geneva. He now serves as associate professor in the Department of Medical Imaging at the Beaujon University Hospital (Clichy, France). His main foci of research have been liver diseases and tumors, interventional abdominal oncology, functional imaging of the liver, and elastography.

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