# CT and MRI Improve Detection of Hepatocellular Carcinoma, Compared With Ultrasound Alone, in Patients With Cirrhosis

NAM C. YU,* VINIKA CHAUDHARI,* STEVEN S. RAMAN,* CHARLES LASSMAN,‡ MYRON J. TONG,§,‖ RONALD W. BUSUTTIL,¶ and DAVID S. K. LU*

*Department of Radiology, ‡Department of Pathology, and §Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles; ‖Huntington Medical Research Institutes, Pasadena; and ¶Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California

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**BACKGROUND & AIMS:** In patients with cirrhosis, hepatocellular carcinoma (HCC) is detected by ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI); US is recommended for screening and surveillance. We performed a retrospective analysis of the abilities of these cross-sectional imaging modalities to detect HCC. **METHODS:** We analyzed data from 638 consecutive adult patients with cirrhosis who received liver transplants within 6 months of imaging at a tertiary care institution. Imaging reports and serum alpha-fetoprotein levels were compared with results from pathology analysis of explants as the reference standard. Sensitivities of US, CT, and MRI were calculated overall and in defined size categories. False-positive imaging results and patient-based specificities were evaluated. **RESULTS:** Of the 638 patients, 225 (35%) had HCC, confirmed by pathology analysis of liver explants. In 23 cases, the lesions were infiltrative or extensively multifocal. In the remaining 202 explants (337 numerable, discrete nodules), respective lesion-based sensitivities of US, CT, and MRI were 46%, 65%, and 72% overall and 21%, 40%, and 47% for small (<2 cm) HCC. The sensitivity of US increased with the availability of CT or MRI data ($P = .049$); sensitivity values were 62% and 85% for lesions 2–4 and ≥4 cm, respectively. Patient-based specificities of US, CT, and MRI were 96%, 96%, and 87%, respectively. **CONCLUSIONS: US, CT, and MRI did not detect small HCC lesions with high levels of sensitivity, although CT and MRI provide substantial improvements over unenhanced US in patients with cirrhosis who received liver transplants.**

*Keywords:* Liver Disease; Transplantation; Liver Cancer.

Screening and surveillance for hepatocellular carcinoma (HCC) is advocated in high-risk patients with chronic liver disease.[1,2] Although of indeterminate morbidity and mortality benefit as a result of the lack of widely accepted randomized controlled trials, the adoption of this practice seems justified because treatment options and clinical outcomes in HCC patients depend primarily on tumor stage at diagnosis. For instance, the association between the number and size of HCC lesions and the rate of tumor recurrence and survival after liver transplantation has been well-documented.[3,4] Likewise, studies have consistently shown that the single best predictor of residual tumor or local recurrence after thermal ablative treatment is initial tumor size.[5–8]

The ideal imaging modality for detection of HCC is controversial. Unenhanced ultrasound (US) and serum alpha-fetoprotein (AFP) have been most widely used in screening, in part because of wide accessibility and low cost. Reported accuracies of US vary greatly, likely as a result of dependence on operator experience, attention to detail during scanning, and choice of transducer and equipment. However, poor sensitivity for small nodules is a uniformly recognized concern.[9–13] Advances in computed tomography (CT) and magnetic resonance imaging (MRI), including multidetector helical technology and fast breath-hold sequences, respectively, now allow dynamic multiphasic enhanced imaging of the liver with excellent spatial and temporal resolution, holding much promise for improved HCC detection.[9,11,13–18] Investigations prospectively comparing multiple imaging techniques with pathologic correlation are difficult to design and execute and, therefore, have been generally limited in scope.

This retrospective study provides a broad survey of the accuracy of US, CT, and MRI for HCC detection in a large population of cirrhotic patients undergoing liver transplantation in a single major United States transplantation center. Our main goal was to evaluate the performance of the 3 cross-sectional imaging modalities in the context of routine clinical interpretations by using explant pathology as the reference standard.

## Patients and Methods

### *Patient Population*

This study was conducted under the approval of our Institutional Review Board, with waiver of informed consent. Query of our database yielded 1097 adults receiving orthotopic liver transplantation at our institution from January 1999 to November 2006. Of these, 638 patients (407 men, 231 women; age 18–75 years, mean 53.2) with chronic liver disease who underwent unenhanced US, contrast-enhanced single or multi-

*Abbreviations used in this paper:* AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; CT, computed tomography; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; ROC, receiver operating characteristic; TACE, transarterial chemoembolization; US, ultrasound.


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detectorhelical CT, and/or dynamic contrast-enhanced MRI at our institution within 6 months of the transplantation comprised the study population. Patients with studies at outside imaging centers were not included in the study. Etiology of diffuse chronic liver disease included alcoholism (n = 54), hepatitis B virus (n = 66), hepatitis C virus (n = 277), some combination of the three (n = 54), or others (n = 188) including nonalcoholic steatohepatitis, hemochromatosis, autoimmune hepatitis, primary biliary cirrhosis, alpha$_1$-antitrypsin deficiency, and cryptogenic cirrhosis.

### *Serum Alpha-fetoprotein*

Serum AFP levels tested in our institution were retrospectively reviewed, and the last pretransplantation level not exceeding 6 months before transplantation was recorded. For patients with HCC who underwent neoadjuvant ablation or embolization treatment, the higher of either the pretransplantation or the pretreatment AFP levels was used.

### *Imaging Protocol*

Ultrasound was performed by using HDI 3000 (until 2002), HDI 5000 (2002–present), and iU22 (2004–present) units (Philips, Bothell, WA), equipped with latest generation 1–4 MHz and 2–5 MHz phased array transducers. Standard protocol at our institution involves primary scanning by an experienced sonographic technologist, with immediate review of the study on the PACS system (Centricity; GE Medical Systems, Milwaukee, WI) by a board-certified radiologist with expertise in abdominal imaging and US (sonologist). In selected cases, the sonologist requested or directly performed additional scanning to clarify findings on the initial images.

CT examinations were performed on single-slice (HighSpeed CT/i, GE Medical Systems; Picker PQ 6000, Picker International, Cleveland, OH), 4-slice multidetector (LightSpeed QX/I; GE Medical Systems), or 16 to 64-slice multidetector (Sensation 16, Sensation 64, or Definition 64; Siemens Medical Solutions, Erlangen, Germany) helical scanners with a multiphasic protocol consisting of unenhanced, hepatic arterial dominant, and portal venous dominant phases. Slice reconstruction thickness was 7–8 mm for the single or 4-slice scanners and 5 mm for the 16 to 64-slice scanners. Iohexol (Omnipaque) 350 or iodixanol (Visipaque) 320 (GE Healthcare) was administered via a power injector at 2–3 mL/s for total of 100–120 mL (rate and volume depending on intravenous access, patient weight and renal function) by using either a fixed time interval (until 2000) or a bolus tracking algorithm (2000–present: Care Bolus, Siemens or Smart Prep, GE).

MRI was performed on a variety of 1.5 Tesla scanners by using either 25 mT/m rise times (Signa Horizon LX, GE Medical Systems, and Magnetom Vision or Sonata, Siemens Medical Solutions, 1999–2006) or 40 mT/m rise time (Avanto, Siemens Medical Solutions, 2003–2006). Routine protocol included dynamic multiphasic imaging by using 2-dimensional spoiled gradient echo T1-weighted acquisitions before and during the arterial dominant, portal dominant, equilibrium, and delayed phases after power injection of 0.1 mmol/kg of gadodiamide (Omniscan; Nycomed-Amersham, Little Chalfont, UK). In addition, dual-echo (in-phase and out-of-phase) gradient echo and T2-weighted (fast or turbo spin-echo and partial Fourier fast or turbo spin-echo) sequences were obtained. All images were acquired with a phased array abdominal coil.

### *Imaging Interpretation*

Prospectively rendered interpretation reports of all imaging studies were reviewed retrospectively. A negative result (no HCC) was recorded when no lesion was detected or a visualized lesion was characterized as benign (eg, cyst, hemangioma, or macroregenerative nodule). Report of a suggestive or suspicious lesion warranting deviation from routine surveillance or management, including short-term follow-up imaging, additional imaging study, biopsy, or treatment, were recorded as a positive result (HCC). Lesions suspicious for HCC were typically characterized by 1 or more of the following features: (1) new or rapidly growing nodule, (2) nodule with arterial hypervascularity, especially when accompanied by venous phase washout, (3) dominant nodule containing fat, and (4) nodule with intermediate-high T2 signal. Previously detected lesions diagnosed as HCC that had undergone locoregional treatment, including thermal or chemical ablation and transarterial chemoembolization (TACE), before imaging were excluded from analysis unless a baseline imaging study of the same modality performed within 6 months before treatment was available to document either positive or negative result regarding the index lesion. Even in treated patients, however, the last available pretransplantation US, CT, or MRI, whether before or after treatment, was used for correlation of any concurrent untreated lesions.

### *Explant Pathology and Correlation*

All explanted liver specimens were processed by using routine protocol involving 5–10 mm sectioning through the entire liver. All lesions and suspicious areas on gross inspection of cut sections were taken for standard histologic examination, including hematoxylin-eosin and trichrome staining with microscopic examination. All specimens were reviewed by a group of experienced hepatopathologists who were generally aware of the clinical history (eg, clinically known etiology of liver disease and any suspected HCC), although not specifically provided with the imaging reports regarding number and locations of any suspected lesions. The dictated pathology reports were retrospectively reviewed, and the presence, size, and location of any HCC nodules were recorded. Correlation of nodules between imaging and pathology was based primarily on location and secondarily on size. For instance, if explant report indicated 2 lesions in the left lateral segment with no further specification of location (eg, subcapsular, anterior) and only 1 lesion was noted in this segment on imaging, the nodule with pathologic size closest to the imaging size was considered a true positive and the other a false negative. Concordant correlation was not designated if locations were conflicting, for instance, right versus left lobe, between imaging and pathology.

### *Statistical Analysis*

In addition to standard descriptive statistics, the sensitivities and positive predictive values of US, CT, and MRI were calculated on per-lesion basis, both overall and in defined size-based categories. Specificity was calculated on per-patient basis. Because the imaging results were obtained from routine interpretations during which the reader had access to prior imaging studies for comparison, the potential bias introduced by the order of imaging studies was investigated by comparison of sensitivities between cases with and without available prior imaging of another modality in the 6-month pretransplanta-