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

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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 measurable, 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. 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. Likewise, studies have consistently shown that the single best predictor of residual tumor or local recurrence after thermal ablative treatment is initial tumor size. 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. 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. 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 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-
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, alpha1-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 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 ioxidanol (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-
tion window by using $\chi^2$ method. Lesion size between these 2 groups was also compared by using independent samples $t$ test. $P$ value less than .05 was taken to indicate statistical significance. Statistical calculations were performed by using Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA) and MedCalc v 8.2.1.0 (MedCalc Software, Mariakerke, Belgium). Receiver operating characteristic (ROC) analysis of AFP levels was performed by using an online tool (http://www.jrocfit.org; accessed December 27, 2008).

**Results**

**Distribution of Imaging Studies and Hepatocellular Carcinoma Lesions**

Summary of imaging studies performed in the 638 patients is shown in Table 1. Of the 638 explanted livers, 225 (35%) were diagnosed with HCC on explants pathology. Twenty-three of the 225 livers contained infiltrative or extensive multifocal HCC, for which the pathology report did not specify individual nodule locations and sizes, precluding a nodule-by-nodule correlation. Of these 23 cases of diffuse or infiltrative involvement, US had been performed in 12, demonstrating negative result (eg, nonspecific heterogeneous parenchyma) in 2 (17%), 3 or fewer nodules in 4 (33%), and suspicious multifocal or diffuse abnormality in 6 cases (50%). CT was performed in 12 of the 23 patients and showed 3 or fewer nodules in 3 (25%) and suspicious multifocal disease with description of size and location of discrete nodules numerated on explant pathologic report.

Table 1. Breakdown of Imaging Studies and Confirmed HCC Lesions in 638 Patients

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>430</td>
<td>385</td>
<td>216</td>
</tr>
<tr>
<td>+ HCC (%)</td>
<td>138 (32%)</td>
<td>149 (39%)</td>
<td>117 (54%)</td>
</tr>
<tr>
<td>Mean imaging/transplantation interval, mo</td>
<td>1.8</td>
<td>2.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Lesions/patient (total)$^a$ | 0.48 | 0.52 | 0.86 |
Lesions/patient (+ HCC)$^a$ | 1.59 | 1.42 | 1.68 |
Mean lesion diameter, cm$^a$ | 2.40 | 2.34 | 2.49 |

$^a$Excludes patients with infiltrative or multifocal disease without discrete nodules numerated on explant pathologic report.

Of the 225 patients with HCC, 202 contained unifocal or multifocal disease without discrete nodules on the pathologic report. A total of 337 nodules were found in this group (1.7 nodules/explant), with diameters ranging 0.2–9.0 cm (mean, 2.4; median, 2.1 cm). Locoregional therapy had been performed in 102 of the 337 nodules (30%) ranging 0.2–9.0 cm (mean, 2.4; median, 2.1 cm). Local ablative therapy was performed on 99 (30%) of the nodules without a pathologically specified diagnosis of HCC for which the pathology report did not specify the nodule correlation. Of these 23 cases of diffuse or infiltrative disease, 3 or fewer nodules were found in 9 (39%), 4 or more nodules in 13 (56%), and suspicious multifocal or diffuse disease in 3 (13%). Likewise, MRI was positive in all 13 who underwent imaging, with more than 3 nodules or infiltrative involvement suspected in 12 (92%).

Of the 225 patients with HCC, 202 contained unifocal or oligofocal disease with description of size and location of discrete nodules on the pathologic report. A total of 337 nodules were found in this group (1.7 nodules/explant), with diameters ranging 0.2–9.0 cm (mean, 2.4; median, 2.1 cm). Locoregional therapy had been performed in 102 of the 337 nodules (30%). Of the treated lesions, radiofrequency ablation was performed in 65 (64%), ethanol ablation in 4 (4%), TACE in 25 (25%), and combination therapy in 8 (8%).

**Sensitivity for Detection of Hepatocellular Carcinoma**

Lesion-based sensitivities of US, CT, and MRI for detection of HCC before transplantation were 46% (92/200), 65% (126/194), and 72% (126/175), respectively (Table 2). For each modality, sensitivity varied positively with lesion size. Sensitivity of US for small (<2 cm) nodules was 21%. Although enhanced CT and MRI were superior to US in this category, as in others, their sensitivities likewise remained below 50%. For the largest (≥4 cm) lesions, sensitivity of CT was 100% (32/30) and MRI 96% (27/28), 1 false negative on MRI was a 5.2-cm well-differentiated HCC that was evident on the explant specimen 5.6 months after the scan, which had demonstrated a corresponding 4.2-cm lesion deemed most consistent with a dysplastic nodule on the basis of characteristic signal intensities, size stability, and little or no arterial hypervascularity. Sensitivity of CT was slightly increased, 63% (78/125) vs 70% (48/69), with thinner collimation and slice reconstructions on advance-generation multidetector scanners (Table 3), mostly owing to the medium-size (2–4 cm) lesions. Per-patient sensitivity also showed an improving trend from US to CT and MRI (Table 2).

Because the radiologists were not blinded to other imaging results, we attempted to tease out a potential interpretive bias introduced by access to prior imaging results. The sensitivity of US was significantly increased by availability of comparison CT and/or MRI at the time of US interpretation, whereas neither CT nor MRI demonstrated such association (Table 4).

**Alpha-fetoprotein**

Serum AFP levels were available for 518 patients, including 195 patients with HCC. Sensitivity of AFP was 53% and 40% at 10 ng/dL and 20 ng/dL cutoff levels, respectively. Both

Table 2. Sensitivity of HCC Detection

<table>
<thead>
<tr>
<th>Size</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-nodule</td>
<td>92/200(46%)</td>
<td>126/194 (65%)</td>
<td>126/175 (72%)</td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>20/96 (21%)</td>
<td>35/88 (40%)</td>
<td>33/70 (47%)</td>
</tr>
<tr>
<td>2-4 cm</td>
<td>44/71 (62%)</td>
<td>59/74 (80%)</td>
<td>66/77 (86%)</td>
</tr>
<tr>
<td>≥4 cm</td>
<td>28/33 (85%)</td>
<td>32/32 (100%)</td>
<td>27/28 (96%)</td>
</tr>
<tr>
<td>Per-patient</td>
<td>88/138 (64%)</td>
<td>113/149 (76%)</td>
<td>99/117 (85%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 cm</td>
<td>2.41 (1.69)</td>
<td>3.16 (2.88)</td>
<td>2.39 (1.54)</td>
</tr>
<tr>
<td>2-4 cm</td>
<td>3.9 (1.54)</td>
<td>56/90 (62.2%)</td>
<td>66/106 (71.7%)</td>
</tr>
<tr>
<td>≥4 cm</td>
<td>2.46 (1.66)</td>
<td>50/69 (72.5%)</td>
<td>50/69 (72.5%)</td>
</tr>
</tbody>
</table>

Table 3. Scanner Collimation or Slice Thickness and CT Sensitivity

<table>
<thead>
<tr>
<th>Size</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 cm</td>
<td>46%</td>
<td>65%</td>
<td>72%</td>
</tr>
<tr>
<td>2-4 cm</td>
<td>65%</td>
<td>72%</td>
<td>72%</td>
</tr>
<tr>
<td>≥4 cm</td>
<td>88%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 4. Dependence of Sensitivity on Order of Imaging Studies

<table>
<thead>
<tr>
<th>Prior imaging</th>
<th>Mean size (SD)</th>
<th>$P$ value$^a$</th>
<th>Sensitivity</th>
<th>$P$ value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>2.41 (1.69)</td>
<td>.80</td>
<td>61/146 (41.8%)</td>
<td>.049</td>
</tr>
<tr>
<td>+</td>
<td>2.36 (2.88)</td>
<td>.31</td>
<td>54/154 (35.4%)</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>2.39 (1.54)</td>
<td>.65</td>
<td>70/104 (67.3%)</td>
<td>.46</td>
</tr>
<tr>
<td>+</td>
<td>2.29 (1.40)</td>
<td>.56</td>
<td>56/90 (62.2%)</td>
<td>.94</td>
</tr>
<tr>
<td>MRI</td>
<td>2.46 (1.66)</td>
<td>.86</td>
<td>76/106 (71.7%)</td>
<td>.94</td>
</tr>
<tr>
<td>+</td>
<td>2.50 (1.47)</td>
<td>.50</td>
<td>50/69 (72.5%)</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation.

$^a$t test.

$^b$Chi-squared method.
Table 5. HCC Patients With Both AFP and US Tests Within the Pretransplantation Window

<table>
<thead>
<tr>
<th>AFP</th>
<th>US N (94 total)</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>39 (41.5%)</td>
<td>21/23 (91.3%)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>19 (20.2%)</td>
<td>8/11 (72.7%)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>23 (24.5%)</td>
<td>12/12 (100%)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>13 (13.8%)</td>
<td>3/6 (50%)</td>
</tr>
</tbody>
</table>

NOTE. Concurrent per-patient CT and MRI sensitivity are shown for each combination of AFP and US results. CT and MRI were positive in a majority of patients with negative US results (last 2 rows).

*Positive test defined as ≥10 ng/dL.

AFP and US results were available at our institution for 94 of the 195 HCC patients (Table 5), and 13 (14%) of these had negative US and AFP level less than 10 ng/dL. In this US/AFP negative group, CT (n = 5), MRI (n = 5), or both (n = 1) revealed 9 nodules (mean diameter, 2.3 cm) in 8 patients. Patient-based specificities were 81.4% (263/323) and 88.2% (285/323) at 10 ng/dL and 20 ng/dL thresholds, respectively. ROC analysis of AFP levels yielded area under the fitted curve of 0.73.

False-positive Findings

Patient-based specificities and lesion-based positive predictive values are shown in Table 6. False-positive US findings were composed of 4 studies showing multifocal nodularity corresponding to diffuse benign macronodular cirrhotic parenchyma on explant and 12 numerable, dominant lesions represented by macroregenerative or dysplastic nodules (n = 6), hemangiomas (n = 2), nonhepatocellular neoplasms (n = 2), carcinoma, and cholangiocarcinoma, and no pathologic correlate (n = 4). False-positive CT findings included macroregenerative or dysplastic nodules (n = 6), hemangiomas (n = 2), carcinoma (n = 1), focal infarct (n = 1), or no pathologic correlate (n = 12). False-positive MRI findings included diffuse irregular abnormalities of necrosis with regenerative changes (n = 1), ill-defined or infiltrative parenchymal distortions of focal fibrosis (n = 2) or more discrete lesions consisting of macroregenerative or dysplastic nodules (n = 4), hemangiomas (n = 3), incidental carcinoma (n = 1), or no pathologic correlate (n = 10).

Discussion

Long-term survival after liver transplantation for HCC depends largely on tumor stage. Higher post-transplantation recurrence rates have been demonstrated in patients with single lesion larger than 5 cm or multiple nodules any of which exceed 3 cm, providing rationale for the Milan criteria adopted by the United Network for Organ Sharing. Even with the recent trend espousing greater liberality on tumor size criteria and persistent questions regarding accuracy of radiologic staging, imaging will continue to play a critical role in the organ allocation scheme. Early detection of malignant nodules is also an important requisite for amenability to a range of locoregional therapies including surgical resection, TACE, and chemical/thermal ablation that might be used in isolation or as neoadjuvant to transplantation. Dependence of therapeutic success on tumor size is perhaps most dramatically demonstrated for local ablative treatments in the nontransplantation setting in which size threshold as small as 2 cm might dictate significant difference in outcome.

Although the merit of routine imaging in patients with chronic liver disease continues to be debated, owing to paucity of randomized controlled trials, most physicians incorporate some form of imaging-based screening and surveillance at varying intervals. In the 1999 study by Chalasani et al, 84% of the 473 members of the American Association for the Study of Liver Diseases (AASLD) surveyed indicated use of some form of surveillance practice. Of these positive responders, the majority (69%) used US as the only imaging modality, whereas CT and MRI were used by only 24% and 9%, respectively, mostly as adjunct to US. A more recent survey of community practitioners in California demonstrated similar findings, with the vast majority using either semiannual or annual US. Indeed, this US-based testing reflects the current screening and surveillance recommendations of both the AASLD and the European Association for the Study of the Liver (EASL).

The reported sensitivities of unenhanced US for HCC detection are scattered broadly between 34% and 100%. This wide range undoubtedly reflects not only differing levels of sonographer skill and experience but also varying study methodologies. In a recent systematic meta-analysis of imaging accuracy in HCC diagnosis by Colli et al, 8 selected studies with acceptable methodological quality and using explant histology as reference standard demonstrated average unenhanced US sensitivity of 48% for all size lesions.

Published reports on accuracy of CT and MRI are likewise heterogeneous and varied in both methodology and results. Although the overall trend of these studies might indicate some improvement in performance over US, significant overlap exists in the range of sensitivities reported for the 3 modalities. Also, some of the more optimistic results with CT or MRI might arguably represent artifacts of prospective lesion-based screening and surveillance at varying intervals. In the 1999 study by Chalasani et al, the highest patient-based sensitivity (89%) with essentially no difference in lesion-based sensitivity. As might be expected with such rigidly controlled methodology, the study was limited to a small sample size of 25 patients. Indeed, a majority of the published investigations on the performance CT and MRI for HCC detection typically evaluate a cohort of less than 100 patients. In the largest series to date to our knowledge, prospective lesion-based CT sensitivity of mere 37% was reported in

Table 6. Specificity and Positive Predictive Value

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
</tr>
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<tbody>
<tr>
<td>Specificitya</td>
<td>281/292 (96%)</td>
<td>236/247 (96%)</td>
<td>86/99 (87%)</td>
</tr>
<tr>
<td>Positive predictive valueb</td>
<td>92/104 (89%)</td>
<td>126/148 (85%)</td>
<td>126/145 (87%)</td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>22/27 (82%)</td>
<td>42/57 (74%)</td>
<td>43/56 (77%)</td>
</tr>
<tr>
<td>≥2 cm</td>
<td>70/77 (91%)</td>
<td>84/91 (92%)</td>
<td>83/89 (93%)</td>
</tr>
</tbody>
</table>

aAll patients.
bLesion-based; excludes false-positive studies with nonmeasurable, indiscrete abnormalities.
430 patients undergoing transplantation at the University of Pittsburgh.\textsuperscript{14} Although an important contribution at the time, the earlier generation scanners used in this study that closed in 1998 render the results of limited contemporary relevance, and US and MRI were not concurrently evaluated. Robust technological advances in cross-sectional imaging, particularly for CT and MRI, during the last decade necessitate a balanced evaluation by using state-of-the-art equipment and protocols in the routine clinical setting.

We here provide, to our knowledge, the largest single-institution study on the performance of unenhanced US, multiphasic contrast-enhanced CT, and dynamic contrast MRI for HCC detection with the reference standard of explant pathology. We demonstrate that both contrast-enhanced CT and MRI are robust techniques for detection and characterization of the majority of HCC lesions as compared with unenhanced US. However, all 3 techniques proved suboptimal for detection of small (<2 cm) lesions. Our results, in accord with the meta-analysis by Colli et al,\textsuperscript{25} sound a note of caution on the current routine practice of US-based screening. The overall per-nodule US sensitivity of 46% becomes all the more sobering in light of the many larger HCCs among the missed lesions (sensitivities of 62% and 85% for 2–4 and ≥4 cm nodules, respectively). Furthermore, the statistically significant influence of prior CT and/or MRI on US sensitivity suggests that these rather modest values probably reflect an overestimation of true US performance in isolation, as would be expected in a screening and surveillance setting. This is not surprising because any suspicious lesion on a prior study would direct the sonographer or sonologist to perform a more targeted and meticulous search for the lesion of concern, and the sonologist would also be more inclined to diagnose sonographically subtle abnormalities as a possible lesion. The higher sensitivities of CT and MRI (65% and 72%, respectively) are also comparable to the pooled estimates of Colli et al (68% and 81%, respectively).

Of interest, thinner (0.60–0.75 mm) collimation acquisitions with 5 mm slice thickness reconstruction afforded by 16 and 64 detector CT scanners did not yield a notable improvement in sensitivity for small (<2 cm) nodules compared with older generation helical scanners with 7–8 mm collimation (41% vs 39%). The reason for a slightly more substantial gain in sensitivity for medium-sized 2–4 cm nodules (85% vs 76%) is open to speculation. If these findings bear out on larger studies adequately powered for such subanalysis, a reasonable explanation would be that gain in spatial resolution with thinner sections is unlikely to be of benefit when many of the smallest, therefore on average most differentiated, HCC tumors will be nearly isoattenuating.\textsuperscript{27,28} With medium-sized lesions more likely to demonstrate typical dynamic features of arterial hyperenhancement and portal phase de-enhancement, the faster multidetector scanners might prove beneficial as a result of improvement in temporal, rather than spatial, resolution. The fundamental advantage of MRI lies in its superior tissue contrast, as a result of not only increased sensitivity to contrast enhancement with gadolinium chelates compared with CT with iodine-based agents but also greater intrinsic signal differences between HCC and background liver (eg, T2 hyperintensity, and signal dropout on opposed-phase imaging indicating intratumoral fat).

The specificities of US, CT, and MRI (96%, 96%, and 87%, respectively) also approximate the trend reported in the above-cited meta-analysis (97%, 93%, and 81%, respectively). Many of the false-positive CT and MRI findings showed no correlating focal abnormality on explant, probably accounted for by foci of transient arterial hyperenhancement related to non-tumorous perfusion phenomenon such as arterial-portal shunting or possibly small lesions missed on explant sectioning. Slightly lower specificity of MRI overall is likely related to its exquisite sensitivity to enhancement of perfusion anomalies or benign nodules. Most of these false-positive findings were <2 cm (Table 6), and prior studies have shown that such small enhancing foci without visible explant correlate are not unusual in the cirrhotic liver.\textsuperscript{29}

This study focused on imaging detection, rather than on imaging diagnosis, of HCC. Indeed, for unenhanced US, such noninvasive diagnosis is typically not possible. Even for dynamic CT and MRI, AASLD criteria for noninvasive diagnosis of HCC do not allow for diagnosis of small (<2 cm) HCC based on any single imaging study. According to EASL criteria, even larger (>2 cm) suspicious tumors on CT or MRI require an additional dynamic imaging test or elevated AFP for confirmation. For the purpose of this study, we marked any suspicious lesion requiring deviation from routine surveillance as a positive imaging result. This inclusive definition, although compromising specificity and positive predictive value (for lesions <2 cm), offers the most clinically relevant evaluation of the utility of an isolated imaging study. In practice, we usually recommend short interval imaging follow-up or percutaneous biopsy of small but suspicious lesions.

Several limitations and caveats of this study bear mentioning. Most notably, it is not possible to directly extrapolate observed sensitivity differences in this study to a screening and surveillance population. That this study only included those receiving liver transplantation indicates a preponderance of advanced cirrhosis. US might be disadvantaged in this setting because markedly heterogeneous and distorted parenchymal pattern might obscure lesions on noncontrast US, which does not offer the benefit of dynamic enhancement visualization to facilitate detection. Also, in the pretransplantation setting, any gain in performance with MRI over CT in detection of smaller lesions might not justify the added cost when it might be questioned whether these early-stage tumors significantly contribute to post-transplantation recurrence, as indicated by proposals for expansion of the tumor size criteria.\textsuperscript{13,20} For patients eligible for locoregional therapies, however, there is a clear premium on detection of earliest-stage tumors because differences in complete ablation rates and long-term outcomes can be discriminated at much smaller size thresholds in this setting.\textsuperscript{5,7,8,22} In any case, the relatively low sensitivity of unenhanced US for infiltrative disease and even for medium-large nodules clearly raises concern. Contrast-enhanced US might provide increased accuracy and is used in Asia and Europe for targeted lesion characterization and post-treatment response, but its utility in screening for unknown lesions is technically limited.\textsuperscript{30,31}

US performance also suffers in obese patients, and the extent to which this influenced the results of our study is a point of worthwhile speculation. The population of United States patients evaluated in this study was probably marked by a higher average body mass index than those in most parts of Europe and Asia.\textsuperscript{32} Diverting overweight patients to CT or MRI surveillance might be a prudent strategy. A greater sense of urgency is
likely to surround this issue in the coming years, given the rising incidence of HCC associated with nonalcoholic fatty liver disease, for which obesity is a significant risk factor.\textsuperscript{53}

Also, our institutional practice of primary US scanning by a technologist, rather than by a board-certified radiologist, should be re-emphasized. Indeed, this remains the standard of practice in most centers in the United States. The significant operator-dependence of US raises the interesting question of how much performance gain might be achieved by imposing more rigorous operator standards. That the poor performance of US in this study does not owe fully to inherent limitations of the modality is suggested by improvement in sensitivity if prior CT or MRI was available, implying a significant component of human error during real-time scanning. The AASLD practice guideline touches on this important issue, if in a tone less than dogmatic: "Ideally, ultrasonographers performing HCC surveillance should receive special training, much as is done for mammographic surveillance in some jurisdictions."\textsuperscript{42} Realization of this ideal does not appear imminent, at least in the United States.

Another important limitation of our study owes to its retrospective nature, which, although providing an assessment of actual prospective performance in routine clinical practice without potential inflation of accuracies from research-oriented interpretations as discussed above and demonstrated previously,\textsuperscript{44} did not allow for a controlled imaging algorithm. Although patients awaiting transplantation at our institution routinely undergo some regimen of cross-sectional imaging, the modality and frequency would vary at the discretion of the clinicians and on the basis of several factors including presence of any known HCC, abnormalities on prior imaging studies or serum AFP analysis, and renal dysfunction. Patients undergoing MRI, used more frequently in cases of higher risk or with known abnormalities, had greater average size and number of lesions. Nevertheless, it should be reiterated that higher sensitivity of MRI was maintained across all size categories. Many patients had multiple imaging modalities within the 6-month pretransplantation window. However, interpretations of CT and MRI, unlike those of US, did not show significant bias from availability of recent comparison imaging results.

Explant pathology offers the most definitive reference standard but is not without limitations. Small subcentimeter HCC might be missed on 5–10 mm sectioning, potentially accounting for some of the supposed false-positive findings of CT and MRI. Also, the imaging pathology correlation might have been improved with less false positives if the pathologists had been prospectively informed of detailed imaging findings (ie, precise location of lesions), leading to more thorough sectioning and sampling in the suspected segments.

Last, there have been recent developments in MRI not evaluated in this study, including 3 Tesla imaging, 3-dimensional dynamic acquisition, and hepatocyte-specific contrast agents.\textsuperscript{34} Also, CT scanners used in the earlier patients of this study have become obsolete, with now routine use of 16–64 multidetector scanners in most centers. Although these refinements can be seen as more evolutionary than revolutionary, it is likely that both CT and MRI have further distanced themselves from unenhanced US, which has seen less substantial advances in recent years.

In conclusion, this retrospective evaluation of US, CT, and MRI in chronic liver disease with explant pathologic correlation demonstrates MRI as the most sensitive imaging study for HCC detection. However, detection rate of lesions <2 cm was suboptimal for all modalities. Relatively modest sensitivity of unenhanced US even for larger HCC lesions raises significant concern regarding its use alone as a screening tool in cirrhosis, at least in the current study population. A prospective study with a controlled imaging algorithm and with assessment of long-term outcomes and cost-benefit analysis is necessary.

References

17. Van Thiel DH, Yong S, Li SD, et al. The development of de novo


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Conflicts of interest
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