A panel of experts recently completed updating the European Guidelines for the use of Ultrasound Contrast Agents. It is due to be published in early 2008 and updates and extends the 2004 Guidelines, which covered only the liver. The new liver section, which includes the use of USCM in interstitial ablation, incorporates the recent Barcelona guidelines for management of focal lesions discovered during ultrasound surveillance in cirrhotic patients. Though focussed on SonoVue, it forms a useful framework for a general discussion of this topic. It also covers clinically established uses in the kidneys and pancreas, in abdominal trauma, in vesico-ureteric reflux and in transcranial studies.

The liver section of the guidelines opens with a rationale for beginning with characterisation of focal lesions rather than their detection, as may seem logical. This points up a fundamental awkwardness of the way USCM work in the liver: the initial arterial phase is particularly useful for differentiating between various focal lesions, while the late (sinusoidal) phase is critical for determining the malignant nature of solid liver lesions.

Benign lesions such as haemangiomas and focal nodular hyperplasia have a rich arterial supply and often enhance early in the arterial phase. In haemangiomas, the blood enters the lakes that constitute the abnormality at the periphery of the lesion, giving rise to peripheral nodular enhancement. From here, it percolates towards the centre of the haemangioma, usually fairly slowly, taking up to five minutes to fill completely. At this stage, the lesion disappears as it matches the intensity of the enhanced liver parenchyma, though the process is incomplete in haemangiomas that contain thrombus, usually larger lesions. Thus, delayed scanning is required to confirm that the lesion has disappeared or at least become smaller.

FNHs also have an arterial supply via one or several tortuous feeding vessels. However, the flow pattern is distinctive, arriving first at the centre of the lesion and filing it in a centrifugal fashion, often forming a spoke wheel pattern. The enhancement is often intense and very rapid (the "light bulb sign") and so the early images after arrival of the contrast are critical; the study should be recorded so that these early frames can be reviewed, if necessary in slow motion, to allow the characteristic pattern to be recognised. In the late phase, FNHs disappear as the liver enhancement matches the enhancement in the lesion. In around a quarter of cases, the central scar becomes visible in this phase as a stellate central filling defect.

For both lesions, these features carry the same confidence as the equivalent CT or MR haemodynamic findings and do not require further investigation when they are typical, as is the case in around 75% of cases. Atypical cases, which amount to 5 or 10%, require further investigation.

Other lesions with diagnostic haemodynamic patterns are focal fatty sparing and change as well as regenerating nodules: they have normal haemodynamics and so behave in exactly the same way as the surrounding liver, disappearing in the late phase. Hepatic adenomas seem to have a variety of patterns, but experience with them is still limited, as it is for other uncommon focal lesions such as granulomas and peliosis.

For detection, the demonstration of filling defects in the late (sinusoidal) phase is critical; among solid lesions, only those that are malignant lesions show this behaviour. It is based on the fact that malignancies lack the normal sinusoidal structure, in which the microbubbles are retained after they have been largely cleared from the blood stream. For some microbubbles, this is a specific targeting effect, based on phagocytosis, as has been demonstrated for Sonazoid. For others,
the degree of phagocytosis is minimal (SonoVue being an example) and the retention seems to relate to the large volume of slowly flowing blood in the liver. Regardless of the mechanism, the effect is similar, malignancies appearing as progressively obvious filling defects as the late phase develops around one minute after injection. The rule is a simple one: “black is bad” meaning that solid liver lesions that do not retain contrast in the late phase (i.e. wash out early) are deemed to be malignant. Thus far, no exceptions have been described among metastases or cholangiocarcinomas, allowing for scanty moving microbubbles that may be seen within hypervascular lesions such as neuroendocrine metastases. HCCs have a range of behaviour that matches their histological spectrum. Most behave in the same way as metastases and form late phase defects, but those that are well differentiated (some 20%) may be exceptions to this rule and do retain contrast in the late phase so that they simulate benign lesions. The majority of HCCs are hypervascular in the arterial phase with branches that penetrate into the lesion from its edges and observing this is important in detecting HCCs in cirrhotic livers. This may require repeated injections.

To detect late phase defects, the entire volume of the liver must be scanned using the cine loop to review suspect regions and store relevant still images. This may require two doses of an agent such as SonoVue with a relatively short life. The most difficult parts of the liver to cover are the deep segment 7 and the subdiaphragmatic segment 8: in both cases, scanning with the patient in the left decubitus and/or with the head of the couch tipped up may bring these parts of the liver into range and access.

The only other lesions that appear as late phase defects are non-perfused tissue such as cysts and the devitalised tissue of trauma. Abscesses often have a characteristic appearance as filling defects (often larger than suspected on B-mode) with flow in internal septae that divide the lesion into locules. Devitalised tissue in trauma in the liver (as well as in the spleen and kidneys) is well seen on contrast-enhanced ultrasound. This application is recommended in the guidelines in selected patients whose trauma is limited to the abdomen. It may also be useful where repeated studies are required to assess progress, especially in children.

There is a kinship between the avascularity of such devitalised portions of the liver and the use of contrast agents in monitoring interstitial ablation. The clarity with which ablated tissue can be distinguished from the surrounding tissue allows an accurate assessment of the extent of the ablated region at the end of the session. If necessary, extending the ablation can be carried out in the same session rather than having to send the patient to CT and then possibly back to the interventional suite for further ablation. Not only is this approach more efficient but it also produces financial savings. It could be argued that liver ablation therapy should not be carried out without ultrasound contrast monitoring.
**Contrast Enhanced Ultrasound of Focal Liver Masses**

Stephanie R Wilson  
University of Calgary

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**Contrast Enhanced Ultrasound (CEUS)**

- Real-time dynamic examination
- Intravascular microbubble contrast agents
- Shows lesional enhancement analogous to CECT and CEMR

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**Algorithm for Characterization**

- Step one  
  - PVP enhancement  
  - "Washout"..............malignant
  - "Sustained enhancement" ....benign

Wilson and Burns  
Algorithm  
AJR 2006

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Generally high agreement of CEUS with  
CECT especially in AP  
Burns and Wilson  
Radiology 2006
HEMANGIOMAS – ALWAYS SHOW PNE AND CP

Peripheral Nodular
Enhancement
concordance 93% (88-99%,
p<.0001, n=76)

Centripetal Progression
concordance 93% (87-99%,
p<.0001, n=76)

Unique to CEUS

• Ability to show vascularity
• More akin to angiography
• Directional filling

Real time capability of CEUS

• Shows enhancement regardless of its
timing
duration
intensity

Stellate vessels  FNH

Metastases
Cirrhotic Liver

- Detection and characterization of nodules is very difficult
- CEUS easily performed at detection
- Resolves indeterminate CT and MR scans

Enhancement Patterns of Hepatocellular Carcinoma on Contrast-enhanced Ultrasound: Correlation with Pathologic Differentiation

Jang HJ
Kim TK
Burns PN
Wilson SR
Radiology 2007

Classic Description of HCC

Methodology

- 120 HCC
- Pathology confirmation
  - 23 well differentiated
  - 84 moderately differentiated
  - 13 poorly differentiated

  - Differentiation correlated with enhancement features on CEUS

RESULTS

- AP
  - Hypervascularity 104/120 (87%)
    - MD (95%, 80/84)
      compared to
    - WD (61%, 14/23) (p<0.0001)
    - PD HCC (77%, 10/13) (p=0.002)

- PVP
  - “washout” negative enhancement

  - BUT – does not always happen
RESULTS

- AP ATYPICAL
- Isovascularity in 9/120 (8%)
- Hypovascular in 7/120 (6%)

“Washout”

- NO washout to 300 seconds. in 9/104 (9%)
- mostly well-differentiated HCCs 7/9 (78%)

“Washout”

- Of 104 hypervascular tumors, only 42\% (44/104) showed **typical washout** by 90 seconds.
“Washout”

- Of 104 hypervascular tumors, only 42% (44/104) showed typical washout by 90 seconds.

“Washout”

- Late washout
  - between 91-180 seconds
  - 27/104 (26%) HCC
  - between 181-300 seconds in 24/104 (23%)

“Washout”

- NO washout to 300 seconds.
  - in 9/104 (9%)
  - mostly well-differentiated HCCs 7/9 (78%)

Atypical variation

- In absence of hypervascularity
- See only increasing “washout”
- Suspect HCC

Learning Points

- Moderately-differentiated HCC
- Accounts for the majority

  - shows classic enhancement
    - AP hypervascularity (95%, 80/84)
    - PVP washout (97%, 78/80)

Learning Points

- Well-differentiated and Poorly-differentiated HCC
- The minority of tumors
- Account for the so called atypical variations of enhancement
Learning Points

- Of 104 hypervascular HCCs
- absence of PVP washout
  - rarely seen in moderately-differentiated HCC (2/80, 3%)
  - no poorly-differentiated tumors (0/10, 0%)

Learning Points

- late washout (>than 90 sec)
  - (60/104, 58%)
  - occurs more frequently than

- “washout” in the conventionally defined PVP (< 90 seconds, 44/104, 42%)

Learning Points

- Well-differentiated tumors, more closely aligned to normal liver
  - fails to show “washout” in 7/14 (50%)

Learning Points

- Increasing hypoechogenicity in the PVP
  - Mimicking “washout”
  - In the absence of prior AP hypervascularity (10 of 16 HCC without hypervascularity)

Learning Points

- Extended observation of HCC in the portal phase of contrast-enhanced ultrasound is important as

Learning Points

- May occur in infrequent HCC
  - Recognition is essential to avoid missing atypical HCC

Thank you!!
S2-3 Early Diagnosis of Hepatic Carcinoma Using Contrast Enhanced Ultrasound: Primary Hepatic Clear Cell Carcinoma

CHEN Min-hua  FAN Zhi-hui  DAI Ying  WU Wei  YANG Wei  YAN Kun  LI Ji-you

Peking University School of Oncology, Beijing Cancer Hospital & Institute

**Background**: The common pathological features of small early well-differentiated hepatocellular carcinomas (HCCs) are large number of fat or glycogen in cells and the tumors could be called primary hepatic clear cell carcinoma (PHCCC). PHCCC accounts for about 37% of minute early stage HCC, so early diagnosis is very important. Because its different pathological characteristic with HCC and untypical image, there are few reports regarding the image manifestation of PHCCC.

**Objective** The perfusion patterns on contrast enhanced ultrasound (CEUS) of 26 patients with 32 PHCCCs were reviewed and were analyzed according to the echo on fundamental sonography and degrees of pathological differentiation. The value of CEUS to enhance the diagnostic rate was investigated.

**Material and Methods** Among the 618 cases performed CEUS using SonoVue (Bracco), 26 patients with 32 PHCCCs were confirmed by biopsy using 21-18G needles under the instruction of CEUS. Twenty-five patients (92%) had cirrhosis. Five cases (19%) were detected during the follow-up period after the treatment of HCCs. Two cases (6.3%) occurred in hyperplastic nodules. The contrast agent used in the study was SonoVue® (Bracco Diagnostics), consists of sulphorhexaflorid (SF₆) microbubbles surrounded by phospholipids. SonoVue was injected as a bolus of 2.4 ml by a peripheral vein of the forearm. CEUS were performed using the Technos DU8 (Italy), Toshiba Aplio, Aloka SSD 5500, α-10 (Japan) and Philip IU22, GEL-9 (American) ultrasound system with specific imaging techniques. Transducers were used at a frequency of 2-5 MHz.

**Results**: 1. **Fundamental ultrasonography**

The diagnostic accuracy was 53% (17/32). Among the 9 tumors smaller than 2cm, there were 78% (7 tumors) did not be diagnosed correctly (table 1).

<table>
<thead>
<tr>
<th>Range of size (cm)</th>
<th>Lesion No.</th>
<th>Echogenicity</th>
<th>Halo</th>
<th>Correctly diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0~2.0</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2.1~3.0</td>
<td>12</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>3.1~4.0</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4.1~5.0</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>32</td>
<td>9</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

The well-differentiated tumors account for 75% (24/32). Eighty-one percent (17 tumors) of tumors smaller than 3cm
and 100% (9 tumors) of tumors smaller than 2 cm were well-differentiated. There is significant correlation between tumor size and differentiated degree. Figure 1 shows the tumors’ differentiated degrees with different sizes.

![Figure 1](image)

**Figure 1** The size distribution of different differentiation lesions

### 2. Contrast enhanced ultrasound

There were three enhanced patterns on CEUS which are shown in table 2.

<table>
<thead>
<tr>
<th>Proportion (%)</th>
<th>Enhancement patterns</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>fast enhancement and fast wash-out</td>
<td>malignant</td>
</tr>
<tr>
<td>3</td>
<td>fast enhancement and slow wash-out</td>
<td>possible malignant</td>
</tr>
<tr>
<td>22</td>
<td>slow enhancement and fast wash-out</td>
<td>uncertain</td>
</tr>
</tbody>
</table>

The diagnostic rate was 93.8% (30/32) by the first biopsy. The other 2 negative cases were confirmed as PHCCC by biopsy under the instruction of CEUS.

Small well-differentiated PHCCC has few blood supplies and is often accompanied fatty change. Study confirmed that the frequency of hyalinization was about 40% in HCCs in size 1-2 cm. Because of the specific pathological characteristics and lack of ‘halo’ on fundamental ultrasound, the diagnostic accuracy was only 53% before CEUS. This was lower than that of the previous report. It showed that diagnosis is difficult when the clear cell carcinoma is small and in early stage. In our study, some of the cases had cirrhosis or had HCC before, 47% of them were diagnosed as hyperplastic nodule or haemangioma. They should be paid more attention.

On CEUS, 75% (24 tumors) showed typical ‘fast enhancement and fast wash-out’ which was identical with the enhancement pattern of HCC. One tumor showed ‘fast enhancement and slow wash-out’. The 25 tumors are all correctly diagnosed. The other 7 small tumors showed slow or slight and slow enhancement in portal venous phase and fast wash-out and did not be diagnosed correctly.

In conclusion, investigation of contrast enhanced ultrasound patterns and CEUS instructed biopsy may be helpful.
for improving early diagnostic accuracy.

References
9th US Contrast

**S2-4**  **Comparison between contrast-enhanced ultrasonography and CT for detection of hepatic metastases.**

Takashi Kumada, Seiki Kiriyama, Yasuhiro Sone, Makoto Tanikawa, Hidenori Toyoda, Yasuhiro Hisanaga, Akira Kanamori, Kenji Takashima, Katsuhiko Otobe, Kenichi Takahashi.

Department of Gastroenterology, Ogaki Municipal Hospital.

**[Purpose]** To compare conventional B-mode ultrasonography (US), contrast material-enhanced (Sonazoid®) post-vascular (reticuloendothelial system-specific) phase US, and dual-phase spiral computed tomography (CT) for the detection of hepatic metastases.

**[Materials and Methods]** Consecutive one hundred ten patients with pathologically proved primary malignancy were entered in this study from January 2007 to September 2007. All patients were underwent conventional US, US in the post-vascular phase of Sonazoid®, and single-section or multi-section spiral CT. There are 33 women and 77 men, their age ranged from 34 to 89 years (median 71 years). Sites of primary tumors were as follows; stomach (n=39), colon (n=31), rectum (n=15), pancreas (n=8), lung (n=6), esophagus (n=4), others (n=7).

The ultrasound equipments used in this study were Aplio XG (Toshiba Medical Systems Corp. Japan) and ProSound α 10 (ALOKA CO., LTD., Japan). A bolus of 0.015mL/kg of Sonazoid® was injected via a 22-guage intravenous cannula, and contrast-enhanced scanning was started 30-60 minutes after injection by using phase-inversion harmonic US with mechanical index 0.21- 0.34, 10-15 frame per second, and a single focus zone 10 mm depth from the surface.

All images were reviewed four observers (US and contrast-enhanced US; 2 readers, CT; 2 readers). The number-that is zero, one, two, three, or four or more-were determined on the basis of conventional US, US in the post-vascular phase of Sonazoid®, and single-section or multi-section spiral CT up to ten. When the number of detected tumors was not corresponding in each imaging modality, the number was confirmed by using other imaging method, for example, SPIO MRI or angiography assisted CT.

**[Results]** Forty-four patients (40.0%) had hepatic metastases as judged at contrast-enhanced US and CT. Sixty-six patients had no metastases. Forty of the 44 patients (90.1%) with hepatic metastases detected by contrast-enhanced US and CT also showed conventional US. The number of lesions increased in 36.4% (16 cases) contrast-enhanced US compared with that of conventional US. The number of lesions increased in 20.5% (9 cases) contrast enhanced US compared with that of CT.

**[Conclusions]** The performance of contrast-enhanced US during post-vascular phase of Sonazoid® markedly improved the detection of hepatic metastases compared with conventional US and CT because of improved contrast between the enhanced parenchyma and the nonenhanced metastatic lesions.
Computer-aided Diagnosis for the Classification of Focal Liver Lesions by Use of Contrast-enhanced Ultrasonography

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Kurt Rossmann Laboratories for Radiologic Image Research

The concept and methodology of computer-aided diagnosis (CAD) to assist radiologists in detecting abnormal lesions and improving the sensitivity of the differential diagnosis have been developed and studied in various radiologic imaging methods. CAD may be defined generally as a diagnosis made by physicians who take into account the results of automated computer analysis of medical images. The computer output may be used as a “second opinion” for improving physicians’ decision-making and avoiding oversight. Although there were several studies on CAD schemes for the classification of liver lesions by use of CT and MR images to the best of our knowledge, there has been no application of a CAD scheme for the classification of FLLs in ultrasonography.

In this symposium, we will present the concept and methodology of CAD for the classification of focal liver lesions (FLLs) by use of contrast-enhanced ultrasonography.

Method: the CAD scheme was developed for classifying FLLs into liver metastasis, hemangioma, and three histological types of hepatocellular carcinoma (HCC), by use of micro flow imaging (MFI) of contrast-enhanced sonography. One hundred thirty-seven cases with 146 FLLs used in this study consisted of 40 metastases, 30 hemangiomas, and 73 HCCs: 24 well differentiated (w-HCC), 37 moderately differentiated (m-HCC), and 15 poorly differentiated (p-HCC). Pathologies of all cases were determined based on biopsy or surgical specimens. Tumor regions on MFI were determined manually by an experienced physician. The ultrasound equipment used was Toshiba Aplio. MFI was obtained at the fixed plane where the physician identified the location of focal liver lesion with the contrast-enhanced low mechanical index (MI) phase inversion harmonic imaging. In the MFI, the inflow high signals in the plane, which were due to the vascular patterns and the contrast agent (Sonazoid™), were accumulated following a flash scanning with a high MI ultrasound exposure. In our computerized scheme, the original, vessel-enhanced and temporally subtracted frame images of MFI were used for extracting image features which were related to the vascularity of focal lesions, replenishment patterns and the flow of the contrast agent. And then, extracted image features were used for seven independent artificial neural networks (ANNs) as seven decision nodes in the decision tree model for classifying focal liver lesions.

Results: Our preliminary results evaluated with a leave-one-lesion-out method for training and testing ANNs indicated that the diagnostic accuracies for classification of 146 liver lesions were 81.0% for metastasis, 86.7% for hemangioma, and 91.2% for HCC. In addition, the classification accuracies for histologic differentiation types of HCCs were 88.9% for w-HCC, 77.8% for m-HCC, and 57.1% for p-HCC.

Conclusions: The CAD scheme for classifying focal liver lesions by use of contrast-enhanced ultrasonography has a potential to improve diagnostic accuracy in histological diagnosis of HCCs and the other liver diseases.