Detection of Liver Metastases

Comparison of Contrast-Enhanced Wide-Band Harmonic Imaging With Conventional Ultrasonography

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Objective. To compare the detection rate of conventional ultrasonography and contrast-enhanced wide-band harmonic ultrasonographic imaging in the detection of small liver metastases. Methods. Consecutive patients with histologically proved gastrointestinal carcinoma liver metastases were studied. Biphasic helical computed tomography, conventional ultrasonography, and contrast-enhanced wide-band harmonic imaging were performed on all patients within a 5-day period. The biphasic helical computed tomographic scans were reviewed and interpreted by a skilled radiologist. The number of lesions and their descriptive characteristics were recorded for analysis. In addition, videotape recordings of the conventional ultrasonography and contrast-enhanced wide-band harmonic imaging were blindly reviewed, after which the number of detected lesions and their characteristics were then compared with those detected on biphasic helical computed tomography, considered the standard of reference. Results. Twenty-eight patients (10 female and 18 male; age range, 45–72 years) were studied. Conventional ultrasonography detected 37 (59%) of all lesions visualized by biphasic helical computed tomography. The detection rate for contrast-enhanced wide-band harmonic imaging was significantly higher (61 [97%] of 63). In our series, two 10-mm lesions near the diaphragm were not visualized by wide-band harmonic imaging. Conclusions. The use of contrast-enhanced imaging techniques significantly improves the ultrasonographic detection of liver metastases. Our results achieved the sensitivity of biphasic helical computed tomography. Key words: liver metastases; ultrasonography; wide-band harmonic imaging.

Received September 11, 2000, from the Department of Internal Medicine I, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany. Revision requested October 28, 2000. Revised manuscript accepted for publication February 8, 2001.

D etection of liver metastases on ultrasonography is a widely accepted technique, but it has documented limitations. It is our experience that patient habitus and isoechoic lesions are the most common ultrasonographic imaging difficulties. Of note, previous studies suggested that neither ultrasonography nor computed tomography (CT) could detect all lesions in the liver when these imaging modalities were compared with intraoperative findings. The sensitivity of ultrasonography increases when liver lesions are larger than 15 mm in diameter.

Although we know that ultrasonography has a high spatial resolution, a tumor can be missed when it has the same or similar acoustic behavior as that of the surrounding liver tissue. Computed tomography is also known to have similar problems when a tumor has the
same absorption rate of X rays as the surrounding liver tissue. Biphasic helical CT has been able to overcome this imaging limitation.⁴

Because metastases of gastrointestinal tract carcinomas have a nearly exclusive blood supply from branches of the hepatic artery, they typically do not fill with contrast medium from the portal venous system and can be visualized as perfusion defects.⁵ Patients with hyperthyroid metabolic deficiencies or kidney disease and malfunction who have received ionizing radiation may also have a contraindication when contrast medium is administered. Although magnetic resonance imaging can play a significant role in the care of these patients,⁶ it remains considerably more expensive than ultrasonography.

Regionally it has been our experience that ultrasonography is the diagnostic imaging tool and modality of choice. This is primarily because highly trained and disciplined examiners both perform the procedure and interpret the findings.

Harmonic imaging has been used in ultrasonographic diagnosis for many years. In its early existence, it was used and referred to as second-harmonic imaging. With the use of filter techniques, the fundamental frequency is canceled out, allowing the second-harmonic portion to generate an image.⁷⁻¹¹ The use of these filtering techniques requires narrow harmonic bands, resulting in long ultrasonic pulses and leading to decreased spatial resolution.¹² A new technology, called phase inversion harmonic imaging, generates images by using 2 phase-inverted pulses sent one after the other.¹² When harmonic imaging techniques are combined with high-contrast bubble agents, signals emitted from the contrast bubbles are much stronger than those coming from tissue alone. Perfused areas of the liver (depending on the phase; see above) appear brighter (highlighted) with increased resolution when compared with nonperfused areas of the liver.

We report our first results in the detection of liver metastases by ultrasonography combined with a new imaging modality, contrast-enhanced wide-band harmonic imaging (WBHI).

**Materials and Methods**

To compare conventional ultrasonography and contrast-enhanced WBHI with helical CT, we examined only patients with known and biopsy-proven liver metastases. All patients underwent biphasic helical CT, conventional ultrasonography, and contrast-enhanced WBHI ultrasonography. All procedures were performed within 5 days on each patient. The order of examinations was not predetermined. The CT scans were performed with a Somatom Plus system (Siemens Medical Systems, Inc, Forchheim, Germany). After a scan without contrast media (slice, 8 mm; table feed, 10 mm; increment, 5 mm; and rotation time, 0.75 seconds) a biphasic helical scan (slice, 5 mm; table feed, 7.5 mm; increment, 5 mm; and rotation time, 0.75 seconds) was performed with iopromide (Ultravist; Berlex Laboratories, Inc, Montville, NJ) as the contrast medium (contrast volume, 150 mL; contrast flow, 3.0 mL; and delay, 25 seconds [arterial phase] and 70 seconds [portal venous phase]).

Lesions detected by helical CT were quantified by an experienced radiologist blinded to the ultrasonographic results. Ultrasonographic examinations were performed on all patients with a Sonoline Elegra Advanced system (Siemens Medical Systems, Inc, Issaquah, WA) equipped with investigational software for phase inversion harmonic imaging (ECI software; Siemens Medical Systems, Inc). All ultrasonographic procedures were performed with a 3.5C40 transducer (center frequency, 3.4 MHz). System parameters, including transmit frequency, transmit power, and overall two-dimensional gain, were determined by the examiner for optimal image quality. Scans performed in the harmonic mode were done using high transmit power (mechanical index, 1.2–1.6). The increased mechanical index caused the contrast bubbles to emit strong harmonic signals.

The first scan was conventional. Each patient was scanned after a (minimum) 8-hour fast. Standard ultrasonographic imaging system presets were used. No harmonic imaging procedures were performed. The examiner was instructed to optimize each series of patient images. Each scan was stored in its entirety on S-VHS videotape for blinded interpretation later. Each patient was scanned in 2 imaging planes. Both planes were transverse, with the first in the medioclavicular view and the second from the median plane. The examiner’s technique had to ensure that these 2 planes covered the entire liver from right to left. When necessary, additional transverse planes were acquired. The imaging planes were expressed by using the body mark pictograms on the ultrasonography system.
Thereafter, the contrast-enhanced examination was performed in the following manner. An intravenous line was established, and the harmonic imaging mode was activated on the ultrasonography system. The system setting and image quality were optimized for each patient. A bolus injection of 1 mL of Optison (octafluoropropane–containing microspheres of human albumin; Mallinckrodt Inc, St Louis, MO) was administered with an immediate flush of 10 mL of saline solution. The examiner then waited approximately 40 seconds. This delay allowed scanning of the liver in the portal venous phase. A slow sweep (approximately 5 seconds) in one of the transverse planes was performed beginning at the diaphragm and ending at the lower end of the liver. This video segment was stored on S-VHS videotape and on the cine loop of the ultrasonography system. The cine loop could replay the acquired video data at reduced speeds to 25% of normal. The reduced speed cine clip was then stored on S-VHS videotape.

This technique had 2 benefits. First, scanning ultrasonographic contrast media in the harmonic mode could destroy the bubbles, leading to a loss of contrast. By performing this slow, gentle sweep, the bursting effect was reduced. Second, if the recorded image sweep was too fast for the blinded reader, the digitally stored image sequence could be played back from the cine loop at a reduced speed. The bubbles would dissipate over approximately 5 minutes, after which a second sweep using the same technique would be acquired.

The videotapes, the identities of which had been masked, were then evaluated by a single blinded reader, different from the CT reader, who was responsible for counting the lesions and estimating their size. Note that, to ensure blinded reading, the examiner did not directly measure the lesions.

The results of helical CT, conventional ultrasonography, and contrast-enhanced WBHI were compared by the McNemar test.

**Results**

Twenty-eight patients (10 female and 18 male) with known and confirmed liver metastases were included in this study. Their ages ranged from 45 to 72 years (mean age, 61.1 years).

The nature of all metastases was confirmed by biopsy. The underlying primary tumors were colorectal cancer (adenocarcinoma, n = 22), pancreatic cancer (adenocarcinoma, n = 4), stomach cancer (intestinal type, n = 1), and esophageal cancer (squamous cell carcinoma, n = 1).

Overall, the patients had 63 lesions, as shown by helical CT. Most of the detected lesions were smaller than 20 mm in diameter (Table 1). In 10 patients (36%), contrast-enhanced WBHI detected more lesions than conventional ultrasonography.

Conventional ultrasonography detected 37 (59%) of all lesions shown by helical CT. Lesions missed by conventional ultrasonography were all between 5 and 25 mm, as measured on CT. Contrast-enhanced WBHI depicted 61 (97%) of 63 lesions shown by CT. This is a statistically significant increase in the detection rate \( P < .001 \).

The metastases appeared on the contrast-enhanced WBHI as perfusion defects and were therefore more easily detected than on conventional ultrasonography (Figs. 1 and 2). The 2 lesions missed by WBHI were both 10 mm and were located very close to the diaphragm.

Subdividing the lesions by size and location showed an improvement in the detection rate, especially for small lesions (<2 cm) and for lesions near the diaphragm (Tables 2 and 3).

### Table 1. Patient Data According to the Number of Lesions per Patient

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Helical CT</th>
<th>Conventional Ultrasonography</th>
<th>Contrast-Enhanced WBHI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Lesions/ Patient</td>
<td>Total No. of Lesions</td>
<td>Total No. of Lesions</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>9</td>
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</tr>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

\( \sum = 63 \) \( \sum = 37^* \) \( \sum = 61^* \)

\(^* P < .001.\)
Discussion

Ultrasonography is an inexpensive imaging modality that does not require the use of ionizing radiation. Depending on local factors, it can be used as the primary tool for liver tumor diagnosis and for follow-up imaging in patients with known lesions. Although conventional ultrasonography is commonly regarded as being less sensitive for the detection of liver tumors than helical CT, data from one radiology department suggest otherwise. Seemann et al.13 published compelling results of a comparison of high-end ultrasonography performed by skilled examiners and biphasic helical CT. They found ultrasonography to be the more sensitive imaging tool. This might be due to the partial volume effect in helical CT when using a slice thickness of 8 mm in the standard scan for tumor follow-up or screening.13

Every sonographer and sonologist, however, should be reminded of the common problems of poor scan conditions and isoechoic tumors, which can be difficult to visualize in the liver because of their acoustic properties.

This article describes a combination of new possibilities in abdominal ultrasonography: the use of ultrasonographic contrast media in combination with WBHI. Animal studies so far have reported better detection of liver lesions by perfusing the liver with contrast media.9,14,15 This new ultrasonographic modality seems to be superior to the technique published by Albrecht et al16 and Blomley et al.17 They used so-called late-phase imaging to detect liver tumors.17 This can only be done with another contrast medium (Leovist; Schering, Berlin, Germany). This substance produces a late-phase effect in the liver approximately 4 minutes after injection.18 For reasons not yet totally clarified, this agent somehow remains longer in areas of the liver containing reticuloendothelial system cells.19,20 When the liver is insonated after several minutes in the same manner as described earlier, the contrast bubbles give a strong harmonic signal, and the tumors not containing reticuloendothelial system cells are spared as “perfusion defects.” 17,21 This effect was first described by Blomley et al22,23 as “stimulated acoustic emission.” On the basis of what we know from those authors and our own experience, this effect can occur only once in a single area of the liver. The bubbles will be destroyed when exposed to the ultrasound
beam. When reexamination or examination in another phase is necessary, a new injection of contrast medium and repeated imaging after 4 minutes can be accomplished. With the examination technique described in our study, both an immediate reexamination and an examination in different phases of liver perfusion are possible. The amount of contrast medium needed for the effect described in our study is lower, thus reducing the cost of each examination.

Using the new ultrasonographic modality described in our study, we were able to achieve a detection rate for liver metastases significantly higher than when using conventional ultrasonography. Although a comparison of echo-enhanced ultrasonography and helical CT was not the primary aim of this study, it should be pointed out that echo-enhanced ultrasonography did not surpass helical CT in detecting liver metastases. Knowing that helical CT does not detect all liver metastases means that a considerable number of liver metastases remain undetected.

Ultrasoundography is a very specific tool; therefore, if it detects a lesion, it is not necessary to reconfirm the results with CT. Whether this ultrasonographic technique can replace CT for detection of primary and secondary liver tumors has yet to be evaluated.

When a lesion is detected by ultrasonography, the next step should be to further characterize the lesion or to obtain direct histologic proof. Characterization of liver tumors can be accomplished by closely watching the perfusion kinetics in the early phase and the vascular pattern on contrast-enhanced ultrasonography. In this respect, ultrasonography could replace other more expensive and potentially harmful imaging techniques.

Overall, we think that contrast-enhanced WBHI is a new and promising imaging modality that can make ultrasonography more reliable for the detection of liver metastases. Further development and use of this new modality will

### Table 2. Detection Rates According to Size of the Lesion

<table>
<thead>
<tr>
<th>Lesion Size, cm</th>
<th>Helical CT</th>
<th>Conventional Ultrasonography</th>
<th>Contrast-Enhanced WBHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2</td>
<td>34</td>
<td>26*</td>
<td>34*</td>
</tr>
<tr>
<td>&lt;2</td>
<td>29</td>
<td>11†</td>
<td>27†</td>
</tr>
</tbody>
</table>

*P = .008.
†P < .001.

### Table 3. Detection Rates According to Location of the Lesion

<table>
<thead>
<tr>
<th>Lesion Size, cm</th>
<th>Helical CT</th>
<th>Conventional Ultrasonography</th>
<th>Contrast-Enhanced WBHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left liver lobe</td>
<td>24</td>
<td>16*</td>
<td>24*</td>
</tr>
<tr>
<td>Right liver lobe, segments 5 and 6</td>
<td>21</td>
<td>14*</td>
<td>21*</td>
</tr>
<tr>
<td>Right liver lobe, segments 7 and 8</td>
<td>18</td>
<td>7†</td>
<td>16†</td>
</tr>
</tbody>
</table>

*P = .008.
†P < .004.
depend on the results of other centers conducting ongoing studies and the availability of new technologies. WBHI itself is available today; the only barrier is the availability of contrast media. In our country, the 2 above-mentioned agents (Optison and Levovist) are available. Several other pharmaceutical companies are working on new agents or are currently conducting clinical trials. The differences will be in the duration of the contrast effect and specificity to particular organs. We think that in light of these developments, we are at the beginning of a new era in ultrasonographic imaging.

References


