The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: A prospective double-blinded study

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Received 22 June 2006; received in revised form 23 November 2006; accepted 24 November 2006

Abstract

Objective: To compare sensitivity and specificity of contrast enhanced ultrasonography (CEUS) with conventional ultrasonography (US) in detection of liver metastases in patients with colorectal adenocarcinoma (CRC) in a patient-by-patient analysis.

Materials and methods: A prospective study of 461 consecutive patients referred to the Department of Colorectal Surgery, Aarhus University Hospital with primary or local recurrence of CRC. In order to detect possible liver metastases all patients underwent liver US, followed by CEUS by another investigator.

Multislice CT scanning (MDCT), and intraoperative ultrasonography (IOUS) were then performed. Fine-needle biopsy was performed on all suspicious lesions. Each examination was interpreted blindly and the combination of biphasic MDCT, IOUS, follow up and biopsy was the gold standard.

Results: Standard of reference found liver metastases in 54 patients (14.8%). Contrast enhanced ultrasonography improved the sensitivity significantly in detection of liver metastases from 0.69 by US to 0.80 (p = 0.031). In 24 patients, CEUS found a higher number of metastases than US (p < 0.001). The specificity (0.98) and the positive predictive value (0.86) was the same.

Conclusion: Contrast enhanced ultrasonography improves sensitivity in detection of liver metastases in patients with CRC and in nearly half of the cases CEUS found a higher number of metastases than US.

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Keywords: Ultrasound contrast agent; Liver neoplasms; Metastases; Colon cancer; Rectum cancer

1. Introduction

Colorectal cancer is one of the most common cancers in United States and other industrialized nations. Up to 15–25% of patients have synchronous liver metastases, and a similar proportion of patients develop metachronous liver metastases after colorectal resection with curative intent [1,2].

Preoperative detection of liver metastases in patients with CRC is important for the therapeutic strategy. In patients with colon cancer and liver metastases detected preoperatively, synchronous therapy of the colon cancer and liver metastases is a possibility. Also, the detection of liver metastases in patients with rectum cancer influences the use of adjuvant preoperative irradiation or chemoirradiation. Therefore, it is crucial to have a preoperative imaging modality with a high sensitivity in detection of liver metastases. Moreover, detection of all metastases and their localization is essential to optimize the therapeutic strategy, including liver surgery and Radio Frequency Ablation (RFA).

High specificity of the preoperative imaging is required. The prevalence of solid benign liver tumors has been reported to be more than 20% in autopsy series [3]. In patients with malignancy up to 50% of lesions under 20 mm in size are benign [4] and for lesions less than 10 mm in size about 80% are benign [5].

Conventional transabdominal ultrasonography (US) is still used in detection of liver metastases, even though sensitivity is known to be relative low (53–77%) [6,7] compared with CT (85%) and IOUS (95%) [8,9]. The US sensitivity depends on the size of a metastasis, and is only 20% for metastases less than 10 mm [6]. Moreover, the echogenicity of the metastases is
important: isoechic metastases are difficult to detect, because they have the same or similar acoustic behaviour as the surrounding normal liver tissue, while hyperechogenic metastases can mimic haemangiomas [10]. Finally, it is well known that sensitivity of US is reduced in patients with obesity, high lying diaphragm, interposition of intestine, tissue-composition or lack of co-operation.

Recent studies have shown that the US technique using intravenous contrast media (CEUS) (Fig. 1), seems to improve sensitivity in detecting liver metastases with about 50% (from 63 to 91%) and improve specificity from 60 to 88% [11,12]. These promising results are similar to the best-reported results of CT. However, most studies have included patients with established metastases [13,14] or selected patients with a high frequency of metastases [12], probably leading to a greater accuracy than in unselected patients. Finally, some of the previous studies are including a small number of patients and some without clear gold standards [11,15].

The purpose of this study was to assess sensitivity and specificity of CEUS compared with US in detection of liver metastases in a group of unselected patients with CRC. The gold standard was all together biphasic MDCT, IOUS, biopsy of suspicious lesions and in case of inconsistency control MDCT, US and CEUS 3 months later.

2. Materials and methods

2.1. Patient population

In the period from June 2003 to May 2005, 461 consecutive patients were referred to and evaluated at the Department of Colorectal Surgery, Aarhus University Hospital with known or strongly suspicious of primary or local recurrence of CRC. Forty-five patients were not included according to the exclusion criteria: pregnant and breast-feeding women, known allergy to X-ray contrast and allergic to sulphur hexafluoride, renal insufficiency (s-creatinin >200 μmol/l), severe heart failure, known right-left shunts, serious pulmonary hypertension (pulmonary pressure >90 mmHg), out of control systematic hypertension and ARDS, tumor origin from known malignancy different from colorectal neoplasia (for example sarcoma or lymphoma) (Fig. 2). Another 51 patients were not included for logistic reasons, mainly due to absence of members of the research team. Thus, 365 patients were included and comprised 161 women and 204 men, mean age 67 years (age range 23–93 years). Of these, 274 (75%) were primary CRC cases and 57 (16%) were local recurrence of CRC. In 5 (1%) patients the finally histology examination showed other cancers than adenocarcinoma, and in 29 patients (8%) benign tumor.

Within 2 days first US, CEUS and biphasic MDCT (n = 365) were performed. Ultrasonography and CEUS were always done before MDCT. Operation and IOUS (n = 239) was performed within 0–19 weeks (mean, 23 days). Fine-needle biopsy (n = 47) was performed on suspicious lesions after the MDCT had been performed.

For all imaging modalities the findings were immediately documented according to a standard protocol, including number, size and localization of the liver lesions. The liver was mapped according to the classification of Coinaud [15] identifying eight segments. Up to five metastases in each patient was counted. In patients with more than 5 metastases the division was semi-quantified in 6–10 and more than 10. Benign lesions were also registered.

If any inconsistency in results on standard of reference was found, a control CT, CEUS and, when indicated, a fine-needle biopsy were performed 3 months later. If fine-needle biopsy was not possible any progression of size and number of lesions was classified as metastases.

The study was approved by the local ethics committee of the County of Aarhus.

2.2. Sonographic examination technique

Conventional US and CEUS were performed by one of three radiologists with between 7 and 25 years of experience. We used a commercially available US system (EUB 8500, Hitachi...
(CFM)) with curved 3.5-MHz transducer and phase inversion technique. The acoustic power was preset at mechanical index (MI) of 0.08–0.18 (mean 0.10). The contrast used for the CEUS was Sonovue (Bracco, Italy) 8 µl/ml. We used 2.4 ml contrast in all cases, administered through the brachial vein as a bolus followed by a flush with 5-ml isotonic saline. If there were any unclear findings of the CEUS with 2.4 ml, a repeated CEUS was immediately performed after destruction of the bubbles from the “first scanning”. The scan delay was 30 s, and the duration of the scanning was, in all cases, 2 min. If any unclear lesion was founded in portal phase the scanning was continued up to 6 min, the time of the infusion was reported for each CEUS. No patients were excluded because of obesity or other difficult scanning conditions.

For every US examination, two of the investigators were randomly chosen to perform a conventional US or a CEUS, in a longitudinal and transversal plane of the liver, with the patients placed in, respectively, supine and oblique left position. The scanning conditions were assessed: “Good scanning conditions” was when posterior and lateral surface of the liver clearly could be visualized by a subcostal medioclavicular approach. “Poor scanning conditions” was when posterior and/or lateral surface of the liver could not be visualized satisfactorily and “Moderate scanning conditions” was when as posterior and lateral surface of liver could be visualized, but not clearly. Initially the investigator assesses the morphology of lesions (i.e. fatty sparing, haemangioma and cyst) and the liver in general, including assessment of diffuse parenchymal changes such as steatosis or cirrhosis. Metastases were defined as solid, obvious round, oval or lobulated focal liver lesions that were neither simple cysts, haemangioma, focal nodular hyperplasia nor fatty sparing.

The second investigator, who performed the CEUS, was blinded for the results of the first US to prevent observers bias. Initially this investigator also made a conventional B-mode scanning in the same way as mentioned above. At CEUS metastases were defined as round, oval and lobulated hypoechoic focal defects in a usually contrast-enhanced liver parenchyma in the portal venous or delayed vascular phase.

The investigators evaluated CEUS and US at the time of examination and the results were recorded on CD-ROM.

2.3. Multidetector CT scanning

All examinations by MDCT were performed after US and CEUS and were obtained with the same imaging system (Phillips Marconi M x 8000, 4-slice). A scan of the liver was performed with 2.5 mm collimation, increment 1.6, pitch factor 1.25, table speed 0.75/sek and 120 kV with a maximum to 150 mA/slice. A scan in the arterial contrast phase (scan delay about 30 s) and in the portal venous contrast phase (scan delay 70 s), respectively, were performed. The arterial scan delay was controlled and calculated by bolus-chase technique with bolus threshold at 150HU. A 100 ml contrast (Visipaque 270 mg/ml (Amersham Health) was injected with 4 ml/s. One of two investigators blinded to the results of the US and CEUS evaluated the images. The number, size and location of metastases were documented.

2.4. Intraoperative ultrasonography

Intraoperative ultrasonography (IOUS) was performed by a commercially available US system (EUB 6000, Hitachi) with 5.0–10.0 MHz transducer (T-shaped probe) as a part of the routine procedure in CRC surgery. A surgeon and one of the ultrasonography investigators, who did not perform the CEUS, completed the procedure. The IOUS was first performed without any knowledge of results of the preoperative ultrasonography examinations. After that the “code was cracked” and the results of the US and CEUS were evaluated. If preoperative examinations showed metastases, which were not detected by the initial IOUS, IOUS and palpation were repeated.

2.5. Standard of reference (gold standard)

The standard of reference was the number of metastases revealed by the combination of US, CEUS, MDCT, IOUS, fine-needle biopsy, palpation and repeated IOUS. If there were any inconsistencies in results an additional US, CEUS, MDCT and, if relevant, fine needle biopsy were performed 3 months postoperatively.

3. Statistics

In a patient-by-patient analysis the sensitivity and specificity of the diagnosis of malignant lesions were assessed by US and CEUS, and compared with McNemar’s test. It was assumed that 45 patients with metastases were found, dispersed of expected sensitivity of 0.7 and 0.9, respectively, US and CEUS. These probabilities and expected number of patients result in a power-calculation on 80% of the study. Ninety-five percent confidence intervals (CI) for overall sensitivity were calculated using the binomial distribution. The Wilcoxon matched-pairs signed-rank test was used to compare the numbers of detected metastases by US and CEUS and unpaired Student’s test was used to compare the average size of liver metastases.

A p value of <0.05 was considered statistically significant.

4. Results

A total of 54 patients (14.8%) had liver metastases and comprised 47 patients with primary CRC and 7 patients with local recurrence of CRC.

The 54 patients with liver metastases identified by standard of reference were based on following: 37 patients were identified with US, CEUS and MDCT confirmed by IOUS (n = 12) and fine-needle biopsy (n = 29). In additional six cases liver metastases were identified with CEUS, and all of these patients were also detected with MDCT and all confirmed by fine-needle biopsy. Further five cases were founded by MDCT and not by US or CEUS (all confirmed by fine-needle biopsy). Of the last six cases, four cases were founded by IOUS (three confirmed by fine-needle biopsy and one by follow-up) and two cases by intraoperative palpation and fine-needle biopsy (both very small and located on the surface of the liver).
Table 1
Comparison of US and CEUS in detection of liver metastases from CRC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional ultrasonography (US)</th>
<th>Contrast enhanced ultrasonography (CEUS)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity for metastases, patient-by-patient analysis</td>
<td>0.69 (37/54)</td>
<td>0.80 (43/54)</td>
<td>0.03</td>
</tr>
<tr>
<td>Specificity for metastases patient-by-patient analysis</td>
<td>0.98</td>
<td>0.98</td>
<td>1.0</td>
</tr>
<tr>
<td>The average size of missed liver lesions</td>
<td>1.23 cm (range 0.8–2.5)</td>
<td>1.15 cm (range 0.8–2.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Mean numbers of metastases per patient</td>
<td>5.32</td>
<td>6.11 (6.83&lt;sup&gt;a&lt;/sup&gt;)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean number of metastases per patient if both US and CEUS found metastases.

In 26 cases there was a suspicion of liver metastases by at least one of the examinations: US, CEUS, MDCT and/or IOUS, while 3-month follow-up including fine needle biopsy (n = 6) disproved it.

Based on the gold standard solitary metastasis was identified in 13 patients, 2 metastases in 5 patients, 3 in 2, 4 in 7, 5 in 1, 6–10 in 10 patients and finally more than 10 metastases in 16 patients.

Contrast enhanced ultrasonography identified significantly more patients with liver metastases than conventional US. Thus, CEUS found 43 of the 54 patients (79.6%, CI: [66.5–89.4%]), while US only identified 37 of 54 patients (68.5%, CI: [54.4–80.5%]). The difference (11.1%, CI: [0.9–21.3%]) in sensitivity was significant (p = 0.031).

Contrast enhanced ultrasonography, compared with US, found significantly more metastases confirmed on standard of reference in 24 (46%) out of all 54 patients (p < 0.001). When both US and CEUS found lesions, CEUS found more metastases in 18 (49%) out of 37 patients (p < 0.001). In only one patient US identified more metastases than CEUS (3 metastases versus 2 metastases).

Both US and CEUS had a specificity at 0.98 (Table 1). In the 17 false-negative patients on US, 6 patients were found by CEUS. Four of the six patients had 1 metastasis, one had 2 (both in same segment) and one had more than 6 metastases. The average size of liver lesions missed by US was 1.23 cm (range 0.5–2.5).

Of the 11 false-negative patients on CEUS, US detected none. Eight patients had one metastasis, one patient had two metastases, one had three metastases and one patient had more than five metastases (Table 2). The average size of the missed liver lesions was 1.15 cm (range 0.5–2.5), which was not significantly different from average size of lesions found by US (p = 0.23). They were located both in the right and left side of the liver (1 in segment 2, 3 in segment 3, 2 in segment 4, 1 in segment 5, 2 in segment 6, 4 in segment 7 and 1 in segment 8). Only five patients had lesions, which could be detected by preoperative MDCT, while six were identified by IOUS and palpation performed on average 26 days (15–35 days) after the US and CEUS.

With both “good” and “moderate/poor” scanning conditions CEUS found more metastases compared with US. With “good” scanning conditions (n = 167) sensitivity of US and CEUS was 76.0 and 84.0%, respectively; “moderate/poor” scanning conditions (n = 198) sensitivity of US and CEUS was 76.0 and 84.0%, respectively. The differences were not statistically significant.

Table 2
Liver metastases missed by US and CEUS

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Number(s)</th>
<th>CEUS</th>
<th>US</th>
<th>CT</th>
<th>IOUS</th>
<th>Size (cm)</th>
<th>Location (segment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>2</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>+&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5; 1.5</td>
<td>3+6</td>
</tr>
<tr>
<td>47</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>57</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0.8</td>
<td>4</td>
</tr>
<tr>
<td>88</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>231</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>–</td>
<td>0.9; 1.0; 1.0</td>
<td>6/7/7</td>
</tr>
<tr>
<td>282</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>1.0</td>
<td>7</td>
</tr>
<tr>
<td>294&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.8</td>
<td>2</td>
</tr>
<tr>
<td>313</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>1.2</td>
<td>5</td>
</tr>
<tr>
<td>352</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>1.0</td>
<td>8</td>
</tr>
<tr>
<td>379</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0.8</td>
<td>3</td>
</tr>
<tr>
<td>429&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (&gt;5)</td>
<td>0</td>
<td>0</td>
<td>(0)</td>
<td>–</td>
<td>0.5</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>2.0</td>
<td>7</td>
</tr>
<tr>
<td>70</td>
<td>1</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>–</td>
<td>1.5</td>
<td>8</td>
</tr>
<tr>
<td>101</td>
<td>1</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>–</td>
<td>1.0</td>
<td>7</td>
</tr>
<tr>
<td>186</td>
<td>2</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>1.2; 1.2</td>
<td>4</td>
</tr>
<tr>
<td>457</td>
<td>1</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>–</td>
<td>1.75</td>
<td>6</td>
</tr>
<tr>
<td>459</td>
<td>&gt;5</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> (0), Metastases not detected.
<sup>b</sup> (+), Metastases detected.
<sup>c</sup> (–), Not performed.
<sup>d</sup> Palpation + FNA.
<sup>e</sup> US 4 weeks later.
5. Discussion

The main finding of this study is that CEUS compared with US was the most sensitive clinical preoperative screening method for liver metastases from CRC. In a patient-by-patient analysis sensitivity was significantly improved from 68.5 to 79.6%. Contrast enhanced ultrasonography increased the number of metastases detected in 46% of our patients with liver metastases in comparison with US. In nearly all cases (five of six patients), when US did not find liver metastases and CEUS did, the number of metastases was one or two, and the patients were thus candidates for liver resection. The clinical benefit of using CEUS compared with US seems relevant.

The main strength of our study is the study design, which was consecutive, prospective, double-blinded and with a clearly and well-defined gold standard, compared to other studies [11,16]. To assess the role of CEUS in preoperative screening of liver metastases in clinical practice, we included patients with primary or local recurrence of CRC without known liver metastases. The prevalence of liver metastases was 14.8% in our study, which is slightly lower than expected [7]. Other studies have used a population with a very high prevalence (63–65%) of liver metastases or have included patients with established metastases [11,12,17]. This selection may lead to a greater accuracy [7].

We compared the sensitivity on a patient-by-patient analysis and not as a lesion-by-lesion analysis, like most earlier studies [13,18]. It is well known that in case of many liver lesions it can be difficult to compare the same lesions at US and CEUS, despite assignment of lesions to their Couinaud segment. Thus, with many liver lesions and a lesion-by-lesion analysis there is a potential source of error [18]. Only one previous study with patient-to-patient analyses has shown a significant increase in sensitivity, but the prevalence of liver metastases in this study was 64%. Other studies did find the same tendency of increasing sensitivity by CEUS compared to US [11,12].

There were also some limitations in our study. We may have overestimated the sensitivity of both US and CEUS, because firstly the standard of reference had included IOUS in only 66% of the patients. Secondly, the MDCT was performed according to the existing protocol from our department. The volume of 100 ml contrast with iodine concentration of 270 mg/ml is less compared to 150–170 ml used in other studies [19,20]. However, this bias would properly not influence the significant difference in sensitivity of liver metastases by US and CEUS. On the other hand, the time difference (mean 23 days) between US/CEUS and IOUS may result in an underestimation of the sensitivity of US/CEUS, because of the risk of developing metastases over time. When comparing the accuracy of two imaging modalities in detecting liver metastases, the problem will always be to define the gold standard. We used the combination of US, CEUS, MDCT, IOUS, fine-needle biopsy, palpation and repeated IOUS. And to further improving the standard of reference we made a follow-up 3-month later if any inconsistency of results in the primary examinations.

Another limitation is, that we performed the IOUS without total surgical mobilization of the liver, which may lead to a suboptimal visualization of all liver segments. Finally, in 10 out of 54 cases fine-needle biopsy of liver lesions was not performed mainly due to technical reasons. However, in four of these cases the lesions were confirmed by follow-up at the Department of Oncology, Aarhus University Hospital.

This study is the largest series of patients without known liver metastases where the sensitivity of CEUS in detecting liver metastases has been evaluated. The results are in accordance with earlier studies [11–13,17]—the sensitivity of detecting liver metastases is significantly improved by CEUS. Moreover, CEUS found significantly more numbers of cases with more metastases. Several studies have shown an improved specificity by CEUS compared with US and CT [12], but in our study the specificity was 0.98 for both US and CEUS.

The problems with large body habitus, intervening bowel gas, movements and patient tolerance are not eliminated by CEUS. Even though sensitivity was improved with contrast in the group of patients with “moderate/poor” scanning conditions, it was still lower than for the group with “good” scanning conditions. These observations were not significant most likely because the subgroups were too small and must be interpreted cautiously. Our observations are in accordance with the fact that the effect of CEUS and pulse inversion mode response is diminished at depths of more than 12 cm [18].

At present CEUS may not replace CT (and MRI) in the preoperative screening of liver metastases from CRC, due to its limitations such as scanning condition, observer dependence and problems comparing long video sequences in a follow-up.

In conclusion, our results show that conventional US should be replaced by CEUS in detecting liver metastases from CRC, as CEUS improves the detection of liver metastases and makes US more reliable.

Acknowledgements

Financial support for this study was provided by The Danish Cancer Society and Aarhus County.

We thank Jeanette Slot, nurse of the ultrasound unit, for her assistance and Niels Trolle Andersen for advice and assistance with statistical analysis.

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