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# Additional value of contrast enhanced intraoperative ultrasound for colorectal liver metastases

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**Abstract**

*Background:* Substantial recurrence rates following partial liver resection for colorectal liver metastases (CRM) imply that small metastases remain undetected using intraoperative ultrasound (IOUS). The aim of this study was to evaluate the additional value of contrast enhanced IOUS (CE-IOUS) when compared to preoperative contrast enhanced computed tomography (CE-CT) and IOUS in liver surgery for CRM.
*Methods:* After obtaining informed consent, 39 consecutive patients with CRM were included prospectively for evaluation. The study population consisted of 26 male and 13 female patients with a median (range) age of 62 (49–83) years. A lesion-per-lesion analysis was performed with histopathological examination as the reference standard after resection and follow-up for unresected lesions. The added value of CE-IOUS in correctly diagnosing malignant lesions was statistically evaluated, using receiver operating characteristic curves.
*Results:* A total of 234 lesions were identified, 137 of which were malignant, according to the reference standard. The addition of CE-IOUS did not improve the diagnostic accuracy when compared to the combination of CE-CT and IOUS ($P = 0.617$). In one of two patients with newly detected lesions on CE-IOUS the extent of resection changed.
*Conclusions:* The addition of CE-IOUS to preoperative CE-CT and IOUS does not improve the ability to characterize already detected lesions. In a small number of patients it appears to facilitate the detection of new metastatic lesions with implications on surgical strategy.


*Keywords:* Intraoperative ultrasound; Ultrasound contrast agent; Colorectal liver metastases; Diagnostic accuracy

## 1. Introduction

Partial liver resection is a potentially curative surgical technique for patients with colorectal liver metastases. Preoperatively, the resectability of these tumours is evaluated with contrast enhanced computed tomography (CE-CT). The reported sensitivity of this investigation for colorectal liver metastases varies between 64.7 and 94.0% and is highest in the portal-dominant phase [1–5]. If colorectal liver metastases are not resectable, local ablation or chemotherapy are alternative treatment options. During surgery, intraoperative ultrasound (IOUS) is associated with the highest sensitivity (95–99%) and specificity (95–100%) concerning the number and localization of the liver lesions and their relation with major vascular and biliar structures [1,2,4,6]. However, the substantial recurrence rates after partial liver resection imply that many small metastases remain undetected using IOUS [7]. Newly detected lesions on IOUS smaller than 5 mm are rarely observed [6]. In recent years addition of contrast has been used to improve the results of conventional ultrasound (US). Several studies report similar diagnostic preoperative performance and confidence as CE-CT in patients with proven or suspected liver metastases at baseline

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US [8–11]. Although many series report improvement of detection rate and accuracy using contrast agents in conventional US, less is known about the results of contrast enhanced IOUS (CE-IOUS). Only two series report about the additive value of CE-IOUS describing the identification of additional colorectal liver metastases in respectively 13% and 19% of patients [12,13].

The aim of this study was to evaluate the additional value of CE-IOUS when compared to preoperative CE-CT and IOUS for colorectal liver metastases with regard to characterization and detection of new lesions.

## 2. Patients and methods

### 2.1. Patients

From March 2003 until April 2005 a total of 39 consecutive patients eligible for surgery (resection or local ablation) for colorectal liver metastases were included prospectively for evaluation. The study population consisted of 26 male and 13 female patients with a median (range) age of 62 (49–83) years. After obtaining informed consent for all examinations the patients were enrolled in an institutional review committee approved protocol. The indication for partial liver resection or local ablation was based on lesions identified on CE-CT. During operation, the liver was imaged by IOUS and CE-IOUS, immediately following laparotomy and mobilization of the liver. All procedures were in accordance with the ethical standards of the World Medical Association (Declaration of Helsinki).

### 2.2. Computed tomography

Triphasic spiral CT was performed in all patients, using a 16 detector-row spiral CT scanner (MX 8000; Philips Medical Systems, Eindhoven, The Netherlands). Patients were prepared with 1000 ml oral contrast (40 ml Telebrix Gastro (300 mgI/ml) diluted in tap water). After injection of 150 or 200 ml (body weight <90 kg or >90 kg, respectively) of intravenous contrast (Iopromide 300 mgI/ml; Ultravist, Schering, Berlin, Germany) at 5 ml/s through an 18G canula in an anticubital vein, arterial, portal, and late phase images were obtained 15, 50, and 300 s, respectively, after the enhancement in the aorta at the level of the diaphragm reached 100 Houndsfield Units (HU). Subsequently, 2 mm slices of the various phases were reconstructed at 1 mm intervals.

### 2.3. Intraoperative ultrasound

The ATL HDI 5000 (Philips, Eindhoven, The Netherlands) with a linear 8–4 MHz transducer, especially designed for intraoperative use, was used to examine the liver in longitudinal and axial orientation. First, baseline IOUS (mechanical index 0.9) was performed. Lesions already detected on CE-CT were identified, localized and characterized. Then, a segment-by-segment examination was performed in a standardized way searching for new metastases.

Immediately after infusion of the intravenous contrast agent CE-IOUS was performed, using continuous insonation (mechanical 0.14, kept constant in all phases) from 15 to 45 s (arterial phase) and from 60 to 150 s (sinusoidal phase) after contrast injection. Again a segment-by-segment examination of the liver was performed in a standardized way.

### 2.4. IOUS contrast

The contrast agent used was a suspension of stabilized sulphur hexafluoride ($SF_6$) microbubbles in saline (SonoVue®, Bracco, Milan, Italy). It was prepared just before administering intravenously as a bolus of 2.4 ml through a central venous line. After injection of the sulphur hexafluoride microbubbles, an additional 20 ml of saline was injected to ensure that all the solution was administered. In case of prolonged CE-IOUS, a second bolus of 2.4 ml was administered.

### 2.5. Image registration

After analysing the liver using one of the three imaging modalities, the localization and characterization of all detected lesions were registered. In every patient, detected lesions were numbered in cranio-caudal order, their diameter recorded in mm and their anatomic position drawn in schematised transverse diagrams of the segmental anatomy of the liver [14]. When multiple metastases were observed in one liver segment, mutual relations were drawn in the diagram.

Lesion nature was defined using a five-point scale (5: definitely malignant, 4: probably malignant, 3: indeterminate, 2: probably benign and 1: definitely benign) [15]. The diagnostic criteria for colorectal liver metastases and benign tumours are mentioned in Table 1. On all imaging modalities, lesions with indeterminate imaging findings were scored accordingly as probably benign, indeterminate, or probably malignant. After every imaging study the resectability of the lesions was assessed and the surgical strategy was defined.

All CT images were reviewed by the same hepatobiliary radiologist together with two participating researchers, who were aware of the patients' clinical history. Intraoperative investigators were not blinded to the results of preoperative imaging, reflecting daily practice. All lesions identified during IOUS and CE-IOUS were recorded and images of the lesions were reviewed by an experienced HPB-radiologist.

### 2.6. Reference standard

The reference standard consisted of histopathological examination of the resection specimen and follow-up by CE-CT. The resected specimen was laminated transversally in slices of 5 mm thickness for microscopic examination. Segmental location [14], diameter, as well as histopathological diagnosis were noted for all resected lesions. Histopathological examination was considered the best reference standard. When histopathological data were lacking, follow-up CE-CT was used as reference standard.

Evaluating follow-up, growth was considered a hallmark for malignancy, since patients did not receive postoperative chemotherapy in a standard way. Growth was defined as an increase in lesion diameter of more than 50% for lesions >1 cm on preoperative CE-CT. Considering growth in subcentimeter