Contrast enhanced ultrasound (CEUS) in the evaluation of liver metastases

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Abstract
Liver metastases are the most frequent malignancies of the liver. The grayscale sonographic appearance of metastases varies: they can be hypoechoic, hyperechoic, they can present a peripheral halo, they can have an infiltrative or cystic appearance. On contrast enhanced ultrasound (CEUS), in the arterial phase, liver metastases can be hyperenhancing (hypervascular ones) or hypoenhancing (hypovascular ones). All liver metastases present wash-out in the portal and late phases, a typical enhancement pattern. CEUS sensitivity is superior to standard ultrasound for the diagnosis of liver metastases being similar to the one of contrast CT.

Key words: liver metastases, contrast enhanced ultrasound (CEUS)

Introduction
Liver metastases are the most frequent malignancies of the liver. 25-50% of patients with a known non-hematological malignancy have liver metastases at the time of diagnosis [1].

The sensitivity of conventional ultrasonography (US) for liver metastases is relatively poor (53%–77%) [2], inferior to that of computer tomography (CT) and magnetic resonance (MR) imaging. The use of second generation US contrast media has improved significantly the sensitivity for the detection of liver metastasis. Contrast enhanced ultrasonography (CEUS) has improved both the detection and characterization of focal liver lesions.

The most common sites of primary malignancies that seed into the liver are:
- Gastrointestinal tract (via portal circulation):
  - Colorectal carcinoma,
  - Pancreatic ductal adenocarcinoma,
  - Esophageal cancer,
  - Gastric adenocarcinoma,
- Breast cancer,
- Lung cancer,
- Genitourinary system:
  - Ovarian cancer,
  - Endometrial cancer,
  - Renal cell cancer,
  - Melanoma,
  - Sarcomas.
The grayscale sonographic appearances of metastases vary, depending on several factors such as the histology of the primary tumor and the treatment received by the patient.

**Hypoechoic metastases** are most common ~ 65%. This type of liver metastases is frequent in lung cancer, breast cancer, pancreatic cancer, and lymphoma.

**Hyperchoic metastasis** can be found in colorectal cancer, renal cancer, neuroendocrine and carcinoid tumors.

**Metastases with peripheral halo** are common in many cancers.

**Calcified metastases** appear in mucinous adenocarcinomas (gastrointestinal, ovarian).

**Cystic metastases** are very rare, in: squamous cell carcinoma, ovarian cancer, pancreatic adenocarcinoma, colorectal carcinoma (CRC).

**Poorly defined (infiltrative) metastases** can be seen in melanoma, breast cancer and lung cancer.

**Isoechoic metastases** and nodules smaller than 1 cm in diameter may not be detectable in standard ultrasound. Occasionally, non-metastatic liver lesion can be identified in cancer patients and must be correctly characterized.

Early detection of liver metastases in patients with known malignancy is important for establishing therapeutic strategy, and crucial for the survival prognosis.

**Ceus aspect in liver metastases**

CEUS examination for the detection of liver metastases is always initiated by performing a standard ultrasound. After screening standard ultrasound examination for metastatic liver lesions followed by the contrast study to confirm or not confirm the diagnosis. Standard ultrasound allows first the characterization of liver lesions but also the characterization of the surrounding liver (presence of steatosis, heterogeneous appearance - suggestive of cirrhosis), elements that may be useful in establishing the final result.

**CEUS plays an important role in the characterization and also in the detection of liver metastases.**

**CEUS for the characterization of liver metastases**

After injection of ultrasound contrast media, liver metastases have characteristic features in all three phases (arterial, portal and late phase) (Table I) [3].

All metastases have a predominantly arterial blood supply, but the degree of this arterial perfusion is variable. Hypovascular metastases have low arterial perfusion, and this type of metastases are usually seen in patients with adenocarcinoma or squamous cell carcinoma, most likely related to colorectal cancer, gastric cancer, pancreatic cancer or ovarian cancer. In the arterial phase, hypovascular metastases enhance only in the periphery ("rim enhancement") (fig 1), but some authors describe also a more diffuse enhancement, especially when the tumor is small [4].

Hypervascular metastases are frequent in neuroendocrine tumors, malignant melanoma and sarcoma, and also in renal, breast or thyroid cancer. These metastases have a very high arterial perfusion and display a diffuse or inhomogeneous enhancement in the arterial phase (fig 2, fig 3).

In the portal and late phases, both hyper- and hypovascular metastases appear as dark defects, while the enhancement persists in normal liver parenchyma (fig 4-7).

The metastases do not retain the contrast agent like the normal liver parenchyma. This rapid and complete

<table>
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<td>Hypo-/non-enhancement</td>
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</tr>
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</table>
Fig 1. Liver metastases with rim enhancement pattern in the arterial phase

Fig 2. Liver metastases with rapid enhancement in the arterial phase

Fig 3. Hypervascular metastases with arterial enhancement pattern

Fig 4. Liver metastases with „wash out” in the portal phase

Fig 5. Liver metastases with „wash out” in the late phase

Fig 6. Liver metastases with „wash out” in the late phase
“wash-out” in the metastasis can be explained by a consistently lower fractional vascular volume when compared to normal liver parenchyma [5], and also by the absence of portal supply to the neoplastic lesions.

**Rim-like enhancement and early and complete washout of the lesion are typical of metastases, while complete enhancement with a later washout is most suggestive of a hepatocellular carcinoma (HCC). In these cases, differentiation from HCC can be difficult.**

Another major indication for CEUS is the follow-up of patients undergoing conventional chemotherapy associated with drugs that inhibit tumor angiogenesis, in which antiangiogenic drugs are expected to reduce the lesion’s vascularity that can be evaluated by means of CEUS [6, 7].

## 2. CEUS for the detection of liver metastases

The use of second generation ultrasound contrast agents (SonoVue) in combination with low MI contrast-specific US techniques has clearly improved US imaging of the liver.

When comparing the results of standard ultrasound with CEUS, most of the studies [2,8,9,10,11,12,13] showed that the detection of liver metastases was significantly improved by CEUS (between 5% and 62%), with one study showing a 107% improvement. However, this study also found that US had a remarkably low sensitivity (0.40) [8] (Table II).

Liver metastases are very frequent in colorectal cancer; 15-25% [14] of patients with colorectal cancer (CRC) will develop metachronous liver metastases during the follow up. The management and prognosis of these patients depend heavily on the early detection of metastases. The most effective surveillance strategy has not yet been established.

Many studies [2,8,9,11,15] that compared CEUS for the detection of liver metastases with contrast CT, showed similar sensitivities (Table III).

Intraoperative ultrasound (IOUS) is considered the gold standard to stage metastatic liver disease. However, small lesions are easily missed if they have acoustic characteristics similar to the surrounding parenchyma. A recently published study [16] involving 39 patients with 137 identified malignant lesions concluded that the use of CE-IOUS in addition to preoperative contrast enhanced CT and IOUS did not improve the ability to characterize previously detected lesions. This study also showed that only in a small number of patients did CE-IOUS (contrast enhanced intraoperative ultrasound) facilitate the detection of new liver metastases or had implications on a surgical strategy.

### Ceus limitations

CEUS has the same limitations as standard ultrasound: patients with a poor acoustic window, obese, uncooper-
tive patients. It is also an operator dependent method, the experience of the physician performing CEUS being an important element that influences the diagnosis accuracy.

In conclusion CEUS is more sensitive than conventional US for the detection of liver metastases and could be useful for the staging of patients with gastrointestinal cancer. The sensitivity of CEUS examination is similar to that of contrast CT but CEUS is a noniradiant method and also the ultrasound contrast agent is not nephrotoxic. CEUS has the same limitations as standard ultrasound and its sensitivity is dependent on the operator’s experience.

Conflict of interest
None of the authors had any conflict of interest.

Bibliography