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# Contrast-enhanced intra-operative ultrasound as a clinical decision making tool during surgery for colorectal liver metastases: The ULIIS study

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ABSTRACT

*Background:* Detecting more colorectal liver metastases (CRLMs) during surgery may help optimise strategy and improve outcomes. Our objective was to determine clinical utility (CU) of contrast-enhanced intra-operative ultrasound (CE-IOUS) using sulphur hexafluoride microbubbles during CRLM surgery.
*Method:* A prospective phase II trial performed at two comprehensive cancer research centres. Patients operated for CRLMs were eligible and assessable if intra-operative ultrasound (IOUS) and CE-IOUS had been performed and pathological results were available and/or 3-month imaging. CU was defined as the justified change in planned surgical strategy or procedure using CE-IOUS.
*Results:* Out of the 68 patients enrolled, 54 were eligible and assessable. 43 patients underwent pre-operative chemotherapy. The median number of CRLMs was 2 (range, 1–11). Pre-operative staging was performed using MRI. IOUS allowed identification of 45 new CRLMs in 13 (24.7%) patients. Compared to IOUS, CE-IOUS allowed identification of 10 additional CRLMs in 9 (16.7%) patients. Surgery was altered and justified in 4 patients only, leading to a CU rate of 7.70% (95 CI, [3.2, 18.6]). No missing CRLMs were identified by CE-IOUS.
*Conclusions:* Although the primary endpoint was not met for one protocol violation, secondary endpoints indicate that CE-IOUS has an intermediate added-value for surgeons treating CRLMs.
*Trial registration:* NCT01880554 (https://clinicaltrials.gov/).


## Introduction

Surgical treatment for colorectal liver metastases (CRLMs) is progressively changing. From extensive hepatectomies, mainly guided by pre-operative imaging, the practice has changed to parenchymal-sparing surgery (PSS) [1–3] requiring intra-operative ultrasound (IOUS)-guided navigation.

CRLMs are characterised by a high recurrence rate (64%) within 3 years [1] and as such, identifying more lesions during the surgery is essential. In the literature, IOUS has been shown to help discover additional CRLMs, up to 10% [4]-18% [5] more compared to computed tomography and 1%–20% [6–8] more compared to magnetic resonance imaging (MRI) scans. Some studies advocate new MRI sequences that could challenge the sensitivity of IOUS [6,9]. However, all published data thus far has only been analysed retrospectively. Further, no real experimental phase II or III studies on IOUS have been published comparing the use or non-use of an additional contrast agent.

Microbubble-based ultrasound contrast agents enable

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angiographies of small vessels and capillary beds. In the PSS context, it is possible to benefit from a dynamic real-time imaging modality for CRLMs with abnormal vascularisation. Isoechoic lesions, which account for approximately 35% of the CRLMs [10], are underappreciated on IOUS. Theoretically, they might be detected by using a contrast agent. Additionally, neoadjuvant chemotherapy could induce steatosis (which impairs ultrasound imaging) and cause a certain number of metastases to vanish posing diagnostic and therapeutic challenges that require the surgeon to adapt the surgical procedure accordingly. In this context, whether contrast-enhanced IOUS (CE-IOUS) performs better than IOUS alone must be investigated.

To evaluate the clinical utility (CU) of CE-IOUS, we conducted, to our knowledge, the first prospective and experimental phase II trial, the Ultrasound Liver Intra-operative Imaging with sulphur hexafluoride microbubbles study (ULIIS, NCT01880554).

## Patients and methods

Following approval by the Ethics Committee, this phase II study was performed in two regional comprehensive cancer centres. Our primary objective was to assess the CU of CE-IOUS in patients undergoing curative surgery for CRLMs. CU was defined as the justified change in planned surgical strategy or procedure using CE-IOUS. Our secondary objectives were to: 1. assess the performance of CE-IOUS (lesion-by-lesion analysis): detection rate of liver metastases in chemotherapy-free patients within 3 post-operative months and characterisation rate for focal liver lesions; 2. outline technical modalities of CE-IOUS; 3. describe the specific toxicity of intra-operative use of sulphur hexafluoride microbubbles (SHM) and finally, 4. assess the CU of CE-IOUS in the sub-group of patients with missing metastases.

### *Patients*

Patients aged $\geq$18 years with histologically proven colorectal cancer and CRLMs operable by resection and/or radiofrequency ablation were included between October 2011 and July 2015. Patients with or without metastases outside the liver, who had a hepatic MRI within 8 weeks prior to surgery were included. All patients had signed an informed consent. Patients allergic to any components of SonoVue® (Bracco Imaging, Milan, Italy), patients with recent acute coronary syndrome or those with unstable ischemic heart disease, or severe arrhythmias and patients with a shunt, severe pulmonary hypertension, an uncontrolled systemic hypertension, or with respiratory distress syndrome were excluded. Furthermore, pregnant or breastfeeding women, patients with contraindication to contrast agent, MRI and PET scans, patients with an indication of a liver surgery in two stages, and patients who, for psychological, social, or geographical reasons could not be monitored regularly were excluded.

### *Pre-operative staging*

For patients requiring upfront surgery for their CRLMs, the evaluation was made from liver MRI within 8 weeks (Reference standard). This evaluation was performed by the radiologist and validated by the multidisciplinary committee. The MRI protocol consisted of: AERA 1.5T (Siemens Erlangen) in transverse plane with T1w, diffusion and T2w sequences with or without breath-hold with the following parameters (ax T1 vibe Dixon, T Acq 16 s, slice thickness 3.5 mm, TR 7.14 ms, TE 2.39 ms and 4.77 ms, Flip angle 10 deg, Nex 1, Grappa 2, FOV 430 mm/ax T2 TRUPISP: TAcq 19 s, slice thickness 5 mm, TR 3.84 ms TE 1.92 ms, Flip angle 67 deg, Nex 1, Grappa 2, FOV 380 mm, ax T2 Blade fat saturation: Tacq 2.58 min, voxel size $1.2 \times 1.2 \times 4.5$ mm TR 3500 ms, TE 99 ms, Nex 1, Grappa 3, FOV 380 max diffusion: T Acq 4.12 min, voxel size $1.7 \times 1.7 \times 6$ mm TR 4200 ms, TE 60 ms, Grappa 2, FOV 430 mm, with 3b value of 50 s—400 s- 800 s/mm$^2$) and dynamic arterial with care bolus, arterial, portal and delayed acquisitions after Gd Chelates IV bolus injection. At least 2 baseline phases were acquired prior to contrast agent injection. Gadobenate dimeglunine (0.2 mM/kg) (Bracco, Italy) was injected intravenously at a rate of 2 mL/s followed by a 20 mL flush of 0.9% of NaCl solution helped by a MR compatible automatic injector (Sonic Shot 7, Nemoto Kyorindo). Dynamic sequences were acquired with the following parameters: ax vibe-twist-dixon sequence TAcq 19 s, voxel size $1.3 \times 1.3 \times 3.5$ mm TR 6.77 ms, TE 2.39 and 4.77 ms, flip angle 10 deg, acceleration factor 2 (CAIPIRINHA, FOV 450 mm).

The missing liver metastases were defined as any lesion present on the radiological assessment before chemotherapy that disappeared in pre-operative radiological assessment at the end of chemotherapy.

### *Intra-operative ultrasound: conventional and contrast-enhanced*

Patients were operated on by laparotomy. For the study, both teams used a convex T probe powered by a Profocus 2202 (B & K Medical, Denmark). We used SHM as the contrast agent which remains in the vascular compartment. A 2.5 mL (1/2 bottle) of SHM injection was administered intravenously in the axis of the duct and not in a secondary valve. Immediately after the injection, 20 mL saline was injected in the same way. Successive injections had a 10-min interval in between. Following the first SHM injection, a full examination of the liver was carried out, segment by segment, to search for new lesions. To minimise microbubble break-up, lower ultrasound output power was used, offering a lower quality of imaging than classical IOUS. The dual-screen mode allows checking whether the lesion is visible, suspected with difficulty or completely undetectable by conventional ultrasound output power (Fig. 1). The surgeon administered additional contrast agent injections if required. The maximum total dose allowed was 3 bottles of 4.8 mL.

CRLM were treated both by resections or IOA. IOA was performed by the surgeon himself and not by an invited radiologist. Both teams had previous experience in IOUS and needle positioning.

### *Visualisation of lesions*

Following SHM injection, healthy liver takes up the contrast uniformly while the metastases initially appear as a bright signal in an arterial phase (“wash in”). The metastases are then washed (“wash out”), which appear as gaps without contrast in venous phase. If the low signal disappears within 45 s, then the lesions are considered benign. Conversely, the low signal of malignant lesions lasts beyond 45 s and over several minutes. Indeterminate lesions are those that do not precisely correspond to either of the two previous definitions.

### *Study design and statistical analyses*

A patient was considered eligible and assessable for the primary endpoint if s/he was eligible, conventional IOUS and CE-IOUS had been performed, and pathological results were available (in case of liver resection or biopsy), and/or 3-month imaging (CT-Scan or MRI) was available (in the absence of pathological results).

Primary outcome variable was CU of CE-IOUS. The planned surgery decision was recorded following conventional IOUS, as well as with CE-IOUS during surgery. For a given patient, we concluded that the CE-IOUS had CU if the two planned decisions were different and if the modification was justified. A justification could

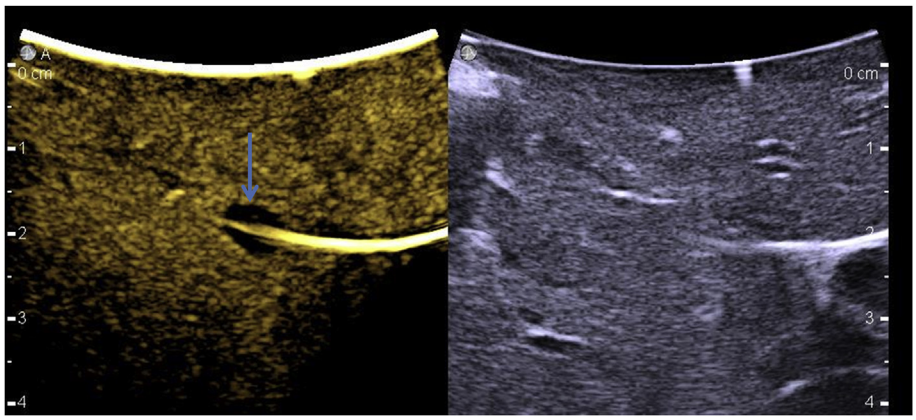

**Fig. 1.** Double mode of visualisation. Left: Ultrasound with Sonoview®; Right: Conventional ultrasound. An isoechoic colorectal metastasis invisible in the conventional mode can be clearly seen, close to a hepatic vein (arrow), in the contrast mode.

be: 1. pathological findings following CE-IOUS confirmed malignancy in case of larger resection, 2. pathological findings following CE-IOUS confirmed absence of malignancy in case of smaller resection in a given site that would have been treated without CE-IOUS, 3. for absence of liver resection, pathological exam of biopsy confirmed the absence or presence of malignancy of the lesions that were not removed, or 4. if biopsy was not feasible or interpretable, the justification of the surgical procedure has to be confirmed with the 3-month radiological follow-up (in the absence of post-surgery chemotherapy; otherwise in case of chemotherapy within 3 months, we considered that lesions were malignant).

In the literature, the reported CU of CE-IOUS was 2–33% [11,12]. We relied on a two-stage Simon's optimal design in order to minimise the expected sample size in case of low CU rate. Using unacceptable and acceptable CU rates of 5% and 15% respectively, a 10% type I error rate and a 15% type II error rate (85% power), a total of 52 eligible and assessable subjects was considered to be necessary, with 25 eligible and assessable subjects recruited at the first stage. At the end of the first stage, the trial was to be terminated if CU of CE-IOUS was observed in less than one patient. Otherwise, the second group of 27 subjects would be recruited. At the end of the trial, if CU of CE-IOUS was observed in 5 patients or more, CU of CE-IOUS would be claimed. Qualitative variables were described in terms of numbers and proportions (with 95% confidence interval). Quantitative variables were described in terms of mean and standard deviation if the normality assumption was satisfied; otherwise, we reported extreme values, quartiles and the median.

## Results

### *Patient characteristics*

A total of 68 patients were included across both participating centres. Patient characteristics are given in Table 1. Of note, due to a significant number of patients included that were either not eligible and/or not assessable, the steering committee decided to include up to 68 patients to guarantee 52 eligible and assessable patients as per the Simon's design (Fig. 2). Consequently, at the end of the trial, 54 patients were eligible and assessable. Among them, 43 patients underwent pre-operative chemotherapy. The median number of CRLMs was 2 (range, 1–11). Among the eligible and assessable patients, 49 had previous chemotherapy (all types of chemotherapy including adjuvant to the colon resection) and/or targeted therapy: 29 received one line of chemotherapy, 16 received two lines, 1 patient received three lines, 2 patients received four lines and finally, 1 patient received 5 lines of chemotherapy. Thirty patients got chemotherapy within 3 months postoperatively.

**Table 1**
Patient characteristics.

| | Eligible and assessable patients (N = 54) | |
|---|---|---|
| | N | % |
| **Sex** | | |
| Male | 36 | 66.7 |
| Female | 18 | 33.3 |
| **Age (years)** | | |
| Median | 63.68 | |
| **Localization** | | |
| Right Colon | 11 | 20.4 |
| Left Colon | 22 | 40.7 |
| Rectum | 19 | 35.2 |
| Transverse Colon | 2 | 3.7 |
| **Hepatic metastases** | | |
| Synchronous | 31 | 57.4 |
| Metachronous | 23 | 42.6 |

Pre-operative staging was performed using MRI in 54 patients (100%), CT scan in 37 (68.5%) and PET-scan in 20 (37%). The number and nature of the lesions identified by the three different stagings are reported in Table 2.

Finally, 22 patients underwent tumorectomies, 3 patients had intra-operative ablations only, 13 patients had anatomical resections, 15 patients had combined ablations and resections and one patient had to undergo a 2-stage procedure. Thirty-eight patients had CASH lesions (≥grade 1) in their liver.

### *Clinical utility of CE-IOUS*

Compared to MRI, IOUS allowed identification of 45 new malignant lesions in 13 (24.1%) patients. Compared to IOUS, CE-IOUS allowed further identification of 10 additional malignant lesions in 9 (16.7%) patients (Table 2). Surgery was altered in 5 (9.26%) patients but could only be justified in 4 (one lesion was justified by biopsy, three by resection and pathological examination and one lesion was ablated without previous biopsy). With a minimum requirement of 5 justified surgery alterations set by Simon's design methodology, from the first 52 eligible and assessable patients, surgery was altered and justified for only 4. As such, CU of CE-IOUS was not demonstrated (CU rate: 7.70% with 95% CI: [3.2, 18.6]).

### *Detection of malignant lesions by CE-IOUS in chemotherapy-free patients within 3 post-operative months*

The detection rate was evaluated in chemotherapy-free patients

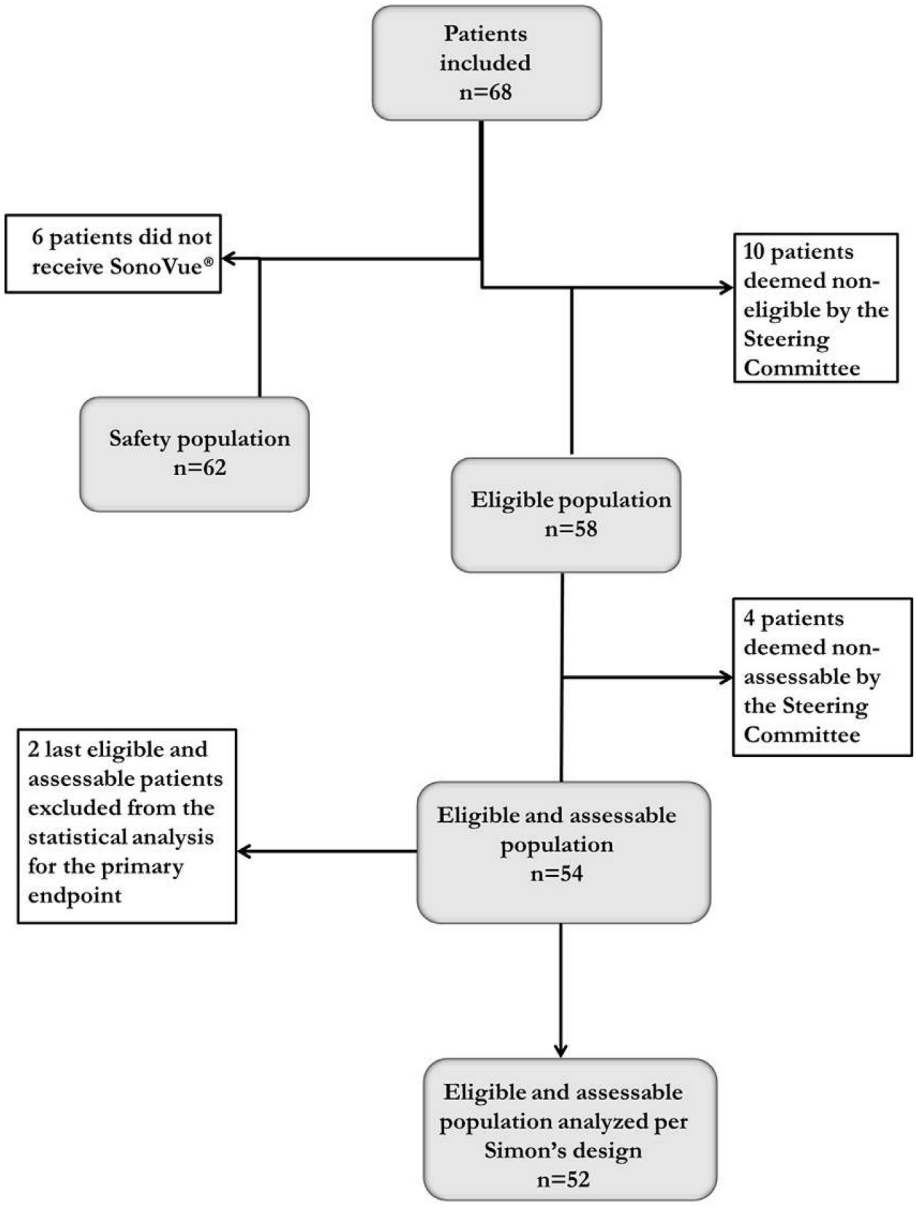


**Fig. 2.** Flowchart showing the patient inclusion process.

**Table 2**
Number and nature of lesions yielded by the three different stagings.

| | Pre-operative staging (MRI) | IOUS staging | | | CE-IOUS staging | | |
|---|---|---|---|---|---|---|---|
| | | Unchanged from MRI (nature has changed to) | New lesions from MRI | Total | Unchanged from IOUS (nature has changed to) | New lesions from IOUS | Total |
| Malignant lesions | 156 | 136 (5) | 40 | 181 | 181 (3) | 7 | 191 |
| Benign lesions | 2 | 1 (4) | 1 | 6 | 4 (0) | 0 | 4 |
| Undetermined nature | 6 | 2 (14) | 4 | 20 | 18 (0) | 2 | 20 |
| Nature missing/not available | 18 | 4 (9) | 0 | 13 | 6 (8) | 0 | 14 |
| Disappearance or not followed for any reason from previous staging | Not applicable | 7 | | | 0 | | |
| Total | **182** | 143 (32) **220** | 45 | 220 | 209 (11) **229** | 9 | 229 |

Description of the nature of the lesions identified at the different stages. The first line indicates that 156 malignant lesions were identified on MRI. Of the 156, 136 were identified as malignant on IOUS, 5 of the 26 other (182−156) lesions seen on MRI were identified as malignant on IOUS. Compared to MRI, 40 new malignant lesions were identified on IOUS. So, a total of 181 (=136 + 5+40) malignant lesions were identified on IOUS. Similarly, all malignant lesions identified on IOUS were identified as malignant on CE-IOUS. 3 of the 39 other (220−181) lesions seen on IOUS were identified as malignant on CE-IOUS. Compared to IOUS, 7 new malignant lesions were identified on CE-IOUS. So, a total of 191 (=181 + 3+7) malignant lesions were identified on IOUS.

within 3 post-operative months (CFP–3PO). There were 22 (40.7%) CFP-3PO. Among the 59 lesions considered malignant in them, 44 were diagnosed as malignant by CE-IOUS, i.e. a sensitivity of 0.75.

*Characterisation rate for focal liver lesions*

Similar to the detection rate, characterisation rate was based on CE-IOUS results and post-operative examination. Of the 114 lesions (malignant, benign or undetermined) subjected to post-operative examinations, CE-IOUS correctly identified the nature of 107 of them, giving a characterisation rate of 0.94.

*Technical modalities of CE-IOUS*

The median length of time during which contrast injection was useable for was 3 min 45 s [1:45:00–5:07:00]. One injection was administered in 3.7% of the patients, 83.3% received two, 9.3% received three and 3.7% received four injections, respectively. It should be noted, CE-IOUS was technically possible in 62 of the 68 patients.

*Specific toxicity of intraoperative use of SHM and surgical complications*

Out of the 62 patients included in the safety population (patients with at least one dose of SonoVue®), 15 (24.2%) patients had at least one severe adverse event. In total, 21 severe adverse events were reported and none were related to SHM injection.

*Clinical utility of CE-IOUS for missing metastases*

Among the 54 eligible and assessable patients overall, 12 patients (22.2%) had missing metastasis after neoadjuvant chemotherapy, and none of them benefited from a modified surgery due to CE-IOUS. In the 5 patients who had a therapeutic change, the decision was not influenced by the missing metastases.

## Discussion

IOUS was introduced few decades ago without a prospective evaluation of its real benefit in terms of information or CU. Similarly, CE-IOUS was also introduced based on retrospective experiences [13,14] or prospective cohorts without any power estimation based on *a priori* statistical hypothesis [15–17]. ULIIS on the other hand, to the best of our knowledge, is the first phase II study that addresses the added-value of CE-IOUS - and of IOUS - within an experimental design rather than an observational setting.

As per the protocol, the primary endpoint based on a maximal uselessness rate of 5%, a minimal CU rate of 15%, a type I error of 10% and a power of 85% was not reached. The rate could have been higher in the eligible and assessable population, but one surgery alteration was not justified as the surgeon failed to adhere to the protocol. This 'real-life' finding of an operator breach demonstrates that CE-IOUS driven biopsy is difficult to perform. In this case, the number of new lesions detected by CE-IOUS was above the set threshold.

Practically, CE-IOUS integrates IOUS diagnostic performance. IOUS identified just over 20% more lesions (all natures combined, Table 2) than in the pre-operative evaluation, a performance close to other reports [14,15]. The specific added-value in ULIIS was 4.1% of lesions in 8 patients (14.8%) (+9 new lesions; all types combined, not including lesions whose nature has changed Table 2). Some series do not report CE-IOUS specific yield [14]. Diagnostic performances can be influenced by some tissular alterations such as fatty liver [18] which drastically attenuate ultrasound imaging. Either obesity or chemotherapy, or both, could induce steatosis, in which case, CE-IOUS would be the only way to regain contrast in a "foggy white liver". The proportion of obese patients is on the rise and so is the use of neoadjuvant chemotherapy which is increasingly accepted in multidisciplinary team decisions. Hence, comparing the performance of CE-IOUS requires that the different populations are comparable in terms of neoadjuvant chemotherapy. CE-IOUS could serve different purposes depending on the type of patient population. Whilst IOUS alone may be enough for an upfront surgery (without pre-operative chemotherapy) with a low number of CRLMs, adding a contrast agent may be helpful to optimise IOUS in difficult cases with more lesions pre-treated with neoadjuvant chemotherapy. Among our patients who had their surgery modified, 4 out of 5 had pre-operative chemotherapy.

Additional caution needs to be exercised when comparing studies as the performance of both the IOUS devices and the quality of the pre-operative imaging may vary amongst teams and periods of study. Moreover, the timing of the surgical decision may also vary and perturb the comparison. Some teams decide the type of hepatectomy to perform on the basis of the pre-operative imaging and accept to change it intra-operatively only if new CRLMs are discovered in the intended residual liver [6]. Other teams [14,17], like us, make their decision only intra-operatively following the completion of IOUS and the rate of surgical alteration by CE-IOUS is the comparator. Consequently, the risk of comparative bias is high. As an example, Leen et al. [15] reported 29.8% of altered surgical plans for CE-IOUS (IOUS and CE-IOUS combined). In fact, only 13 patients among 57 (22.8%) had modified care due to CE-IOUS alone which may appear high compared to our 7.7% rate. One explanation could be that diffusion weighted-MRI was not used, leading to a weaker performance of pre-operative MRI. Moreover, only 107 metastases were resected in 60 patients suggesting that their series was less advanced compared to our series (229 lesions identified in 54 patients). Nevertheless, there is no mention of pre-operative chemotherapy, which might have diminished the added-value of CE-IOUS.

The main competitor of SHM is perflubutane suspension, mainly used by Japanese teams. The perflubutane microbubbles, after circulation into the vessels, are taken up by the Kupffer cells increasing the contrast between a normal hyperechoic liver parenchyma and hypoechoic tumoral lesion. However, the main advantage of this molecule is the duration of effect which is maximal around 10 min and lasts up to 30 min. Compared to gadoxetic acid (Gd-EOB-DTPA) enhanced-MRI, CE-IOUS showed a modification of surgical procedures in 14.7% of the patients with new lesions identified in 16% of the patients [16]. The discovery of new lesions is more likely to modify the PSS procedures than extended hepatectomies. Consequently, as PSS gains acceptance, CE-IOUS could potentially be practiced more. Finally, the use of perflubutane with a longer duration of imaging compared to sulphur hexafluoride may also explain a better yield in lesion detection.

Our study did not show any added-value for CE-IOUS in detecting missing metastases following pre-operative chemotherapy like some reports [19,20]. Missing metastases, also called vanishing metastases, pose a different problem to isoechoic lesions. The complete vanishing of small CRLMs is observed in 5–38% of the cases [21], even though the definition of a sterilised lesion is not homogenous in the pathological setting. More than necrosis, fibrosis could be the right surrogate marker of CRLMs response to chemotherapy; [22] calcifications may also be present in 20% of lesions [10] and may be helpful for diagnosis of missing metastases [23]. Finally, we cannot exclude complete true disappearance of lesions. Real missing metastases are, consequently, either small isoechoic viable CRLMs or very small lesions corresponding to a

scar. Indeed, below 5 mm, it is very difficult to distinguish small lesion either from normal vascular or biliary structures. Our study was not statistically designed to demonstrate the benefit of using CE-IOUS in detecting missing CRLMs as opposed to the DREAM EORTC 1527 ESSO 002 (NCT02781935). In the literature, only Arita et al. [24] reported an additional identification of 12 missing CRLMs in 131 patients using the perflubutane. Once again, it seems to be a difference in performance between the two contrast agents.

In practice, there is no limitation to using SHM for toxicity. No SHM-related adverse effects were observed in this study, even after injection of several bottle doses. The main limitation of CE-IOUS using SHM is that its clinical implementation depends heavily on the trained staff. First, preparation of the product is critical as it is injected in the axis of the vein followed by a flush of saline. Uninformed staff could unwittingly perform two manoeuvres that can disrupt the microbubbles: 1. injection in a 90° angulated catheter; 2. reinject the reconstituted solution back into the initial bottle before using it again. Furthermore, the reading-time window is short and the intensity of contrast varies from one case to another. A small dysregulation of the ultrasound generator immediately impairs the definition and clarity of the images. As SHM is non-toxic, several doses can be used iteratively. Nevertheless, performing an ultrasound-guided biopsy using SHM is difficult. Consequently, a pathological verification of lesions which can only be seen by CE-IOUS is equally hard. This could further explain why the CU endpoint was not reached in this study.

Finally, the cost of one injection of 5 ml SHM (SonoVue® Bracco Imaging, Milan, Italy) was at the time of the study 68.10 € excluding tax, which can be considered an intermediate cost. The valorization of the procedure to treat complex CRLM was estimated between 8703 € and 21 803 € per patient. Nevertheless, each team has to reconsider this regarding its own model of valorization.

As a routine care study, ULIIS has limitations like its dependence on the surgeon's expertise in IOUS navigation. The brevity of the window of lecture offered by the SHM is also a concern. As an added-value imaging study, ULIIS also has an intrinsic limit as the reference standard at each step cannot be the histopathological nature of the lesion. Each imaging technique has to be compared to a previous one: CE-IOUS was compared to IOUS which was compared to DW-MRI.

## Conclusions

Despite not statistically achieving the primary objectives of CU, the ULIIS study demonstrated a relevant added diagnostic value for CE-IOUS as a complement to IOUS for surgeons treating CRLMs, especially in advanced cases pre-treated by chemotherapy. More than ever, ultrasound guidance serves as an indispensable eye to the surgeons for treating CRLMs.

## Conflicts of interest

The authors declare no conflicts of interest.

## Disclosure

The authors do not have any financial interest in the Bracco Company. No support of any kind was provided by Bracco for the ULIIS study.

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