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Use of contrast-enhanced intraoperative ultrasonography during liver surgery for colorectal cancer liver metastases – Its impact on operative outcome. Analysis of a prospective cohort study ☆

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ARTICLE INFO

Article history:
Received 9 May 2008
Received in revised form 20 June 2008
Accepted 20 June 2008

Keywords:
Intraoperative ultrasonography
Liver metastases
Liver tumours, diagnosis
Liver tumours, staging
Liver tumours, surgery
Contrast-enhanced ultrasound

ABSTRACT

Background: Preliminary reports led to discordant conclusions concerning the use of contrast-enhanced intraoperative ultrasonography (CE-IOUS) during surgery for colorectal liver metastases (CLM). The aim of this study was to evaluate the impact of CE-IOUS in patients undergoing surgery for CLM using an advanced preoperative imaging work-up, and well-established reference standards.

Materials and methods: Forty-seven consecutive patients underwent liver resection using IOUS and CE-IOUS for CLM. All patients underwent preoperative computed tomography (CT) and magnetic resonance imaging (MRI) within 2 weeks prior to surgery. CE-IOUS was performed by injecting intravenously 4.8 ml of sulphur-hexafluoride microbubbles (SonoVue, Bracco, Italy). Reference standards were histology, and 6-month imaging follow-up.

Results: IOUS discovered 43 additional lesions in 20 patients. CE-IOUS found 10 additional lesions not seen at IOUS in four patients, and confirmed all the IOUS findings. Fourteen CLM in 10 patients appeared within 6 months after surgery. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were, respectively: 66%, 0%, 98%, 0% and 65% for CT + MRI; 88%, 100%, 100%, 8%, 88% for IOUS and 93%, 100%, 100%, 13%, 93% for IOUS + CE-IOUS. In nine patients CE-IOUS afforded better definition of tumour margins thus helping in resection guidance.

Conclusions: CE-IOUS improves IOUS findings both for detection and for resection guidance. The combination of IOUS and CE-IOUS should be considered routinely in patients operated for CLM.

☆ Sponsored by an unrestricted educational grant from Bracco International BV.
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doi:10.1016/j.ejcsup.2008.06.004

1. Introduction

Intraoperative ultrasonography (IOUS) is still the most accurate diagnostic technique for detecting focal liver lesions (FLLs).[1,2] However, during surgery for colorectal liver metastases (CLM), IOUS shows a sensitivity of only 82%,[3] and therefore may miss nodules less than 1 cm in diameter. This is particularly evident in patients who undergo surgery after chemotherapy in whom CLM have a similar echo-pattern to the surrounding liver parenchyma. For this reason contrast-enhanced intraoperative ultrasonography (CE-IOUS) was proposed in 2004 both for CLM and for HCC detection,[4] but the preliminary results, although encouraging for HCC[5,6], remained inconclusive for CLM.[7–9] In particular, Fioole et al. recently concluded that CE-IOUS does not appear to be necessary in CLM surgery since it does not significantly improve the accuracy provided by preoperative computed tomography (CT) and IOUS.[9] However, in these studies, the criteria for estimating the diagnostic accuracy of CE-IOUS were lacking. Indeed, CE-IOUS findings were compared with a suboptimal preoperative diagnostic work-up based either on CT alone[9] or with CT and magnetic resonance imaging (MRI) used non-homogeneously.[7,8] In view of these drawbacks and of the very preliminary experiences with CE-IOUS, we were prompted to perform a more extensive analysis to assess the actual role of CE-IOUS in CLM surgery.

2. Method

2.1. Definitions

The reference standard for establishing sensitivity, specificity, accuracy, and positive and negative predictive values of preoperative imaging, IOUS and CE-IOUS were histology of the removed specimens and postoperative follow-up imaging. Any new metastasis detected within the first 6 months of follow-up was considered as a lesion not seen at preoperative (CT/MRI) nor at intraoperative imaging (IOUS and CE-IOUS).

A bright liver on IOUS was defined when liver–kidney contrast was evident, and the blurring of the intrahepatic vessels and the diaphragm both related to the diffusely increased liver echogenicity.[10]

2.2. Preoperative work-up

The preoperative imaging work-up consisted of an abdominal ultrasound (US), abdominal MRI and CT and chest spiral CT. CT and MRI were always performed within 2 weeks of surgery.

A tri-phase CT examination was performed using a Philips Mx 8000 IDT 16 multidetector CT scanner, and more recently a Philips Brillance 64 using the following settings: 16×1.5 collimation, 2 mm thickness, 1 mm increment and 1.2 pitch for the first scan, and 64×0.25 collimation, 2 mm thickness, 1 mm increment and 0.7 pitch for the second. CT enhancement was obtained using an iodinated contrast agent (Iomeron 300, Bracco SpA, Milan, Italy) injected in a peripheral vein at 3–5 ml/s. Contrast-enhanced arterial phase, portal-venous phase and late phase were evaluated following the bolus injection at 25–30 s, 45–65 s and 120 s, respectively.

MRI was routinely performed with two different 1.5 T magnets (Philips Achieva, Eindhoven, Netherlands or Siemens Simphony, Erlangen, Germany) with phase array coils. A liver-specific MR contrast agent (MultiHance, Bracco SpA, Milan, Italy) at a standard dose of 1 ml/kg was used; pre-contrast axial and coronal T2- and T1-weighted 2D sequences were first performed. A dynamic, axial, 3D enhanced study was then carried out at 17, 45 and 120 s, and at 60 min following a bolus injection of the contrast agent in a peripheral vein at 2 ml/s.

Patients were selected for surgery on a technical feasibility regardless of the size or number of metastases, at a multidisciplinary meeting.

2.3. IOUS and CE-IOUS

A J-shaped laparotomy was usually performed. After entering the abdominal cavity, liver mobilisation was achieved by dissecting the round and falciform ligaments. Division of adhesions was carried out as necessary to free the antero-superior and inferior surfaces of the liver before liver exploration with IOUS.

IOUS was performed using an Aloka SDD 5500 (Aloka Ltd., Tokyo, Japan) equipped with the standard 3–6 MHz convex probe, and the 7.5–10 MHz micro convex probe. Staging was completed by CE-IOUS using the standard convex probe working at 3–6 MHz frequency for B-mode and at 1.88–3.76 MHz harmonic frequency. In all patients, 2.4 ml of sulphur-hexafluoride microbubbles (SonoVue®, Bracco, Milan, Italy) was injected through a peripheral vein by the anaesthetist.

Ultrasound guidance was used to drive the dissection plane as previously described.[2]

All the IOUS and CE-IOUS assessments were carried out by the same surgeon (GT) who carried out also the hepatectomies. Informed consent was obtained from all patients but no approval was required by the Ethics Review Board of the hospitals involved in this clinical study because the contrast agent used is licensed for liver imaging in our country.

2.4. Inclusion criteria

The study included consecutively enrolled patients with CLM who underwent surgery and during this procedure received IOUS and CE-IOUS.

To be included in the study each patient had at least 6 months of postoperative follow-up.

Patients who after IOUS and CE-IOUS had explorative laparotomy only were excluded from the analysis since there was no histological confirmation of the tumour and most of them were lost to surgical follow-up.

2.5. Patient follow-up

The patients were followed up in our institution every 3 months by an expert hepatobiliary team who performed physical examination, liver function tests, serum carcinoembryonic antigen (CEA), US (twice a year) and CT/MRI (twice a year). At the 6-month follow-up each patient underwent CT/MRI unless the US examination at 3 months after surgery discovered a new lesion, in which case CT/MRI was performed earlier.

2.6. End-points

The study end-points were

- Overall sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and accuracy of IOUS alone and IOUS with CE-IOUS compared with findings of preoperative imaging.

2.7. Statistical analysis

Two-tailed Student *t* test was used to compare continuous variables.

Sensitivity, specificity, PPV, NPV and accuracy were calculated for preoperative diagnostic imaging, IOUS and CE-IOUS based on results at histology and evidence of new liver lesions within the first 6 months of follow-up.

Chi squared test was used for comparing sensitivity, specificity, PPV and NPV amongst preoperative imaging, IOUS and IOUS + CE-IOUS.

The *P* value was set at 0.05.

2.8. Patients

Between May 2005 and September 2007, 53 patients underwent a laparotomy following a diagnosis of CLM. Six patients (13%) were excluded from the analysis because they had an explorative laparotomy only due to peritoneal carcinomatosis (three patients), or lymph node metastasis (three patients). Forty-seven consecutive patients – 34 males and 13 females, mean age of patients was 64.4 years (median 66.5 years; range 36–85 years) – underwent liver resection using IOUS and CE-IOUS. The imaging diagnostic workup for all the enrolled patients included abdominal US followed by contrast-enhanced CT and MRI; five patients also received contrast-enhanced ultrasonography (CEUS), and three patients received fine-needle biopsy. The last 42 patients also had 18-FDG-PET. All CT and MRI scans were carried out within 2 weeks prior to the operation.

Median number of days from 18-FDG-PET to surgery was 20 (mean 26; range 3–90). Ten of the 47 patients had diffuse steatosis of the liver, four patients had cirrhosis, one patient had chronic hepatitis, and the remaining 32 patients had normal livers; all patients with liver steatosis had undergone previous systemic chemotherapy. The total number of tumours at preoperative imaging was 129 (median two per patient; mean 2.7 per patient; range 1–9 per patient), with a mean diameter of 3.2 cm (median 3; range 1–8) for the largest tumour. Thirty-one patients (66%) had multiple metastases at preoperative imaging. In the last 42 patients 18-FDG-PET disclosed globally 85 lesions (median two per patient; mean 2.8 per patient; range 1–9 per patient) compared to the 116 discovered by CT and MRI (median two per patient; mean 2.8 per patient; range 1–9 per patient).

3. Results

3.1. Detection

At IOUS, 170 lesions were detected (mean per patient 3.6; median 3; range 1–11) 43 of which were new lesions in 20 patients (43%) as compared to preoperative imaging. Moreover, IOUS ruled out a preoperative diagnosis of metastasis for two nodules in two patients. CE-IOUS discovered 10 additional CLM lesions not seen on IOUS in four patients (9%) (Fig. 1), amongst whom one patient had no additional sites on IOUS. Overall, IOUS and CE-IOUS disclosed 180 lesions (mean per patient 3.8, median 3, range 1–13), 53 of which were new lesions not detected at preoperative imaging in 21 patients (45%). The two lesions preoperatively diagnosed as metastases, but not confirmed by IOUS were also not visual-

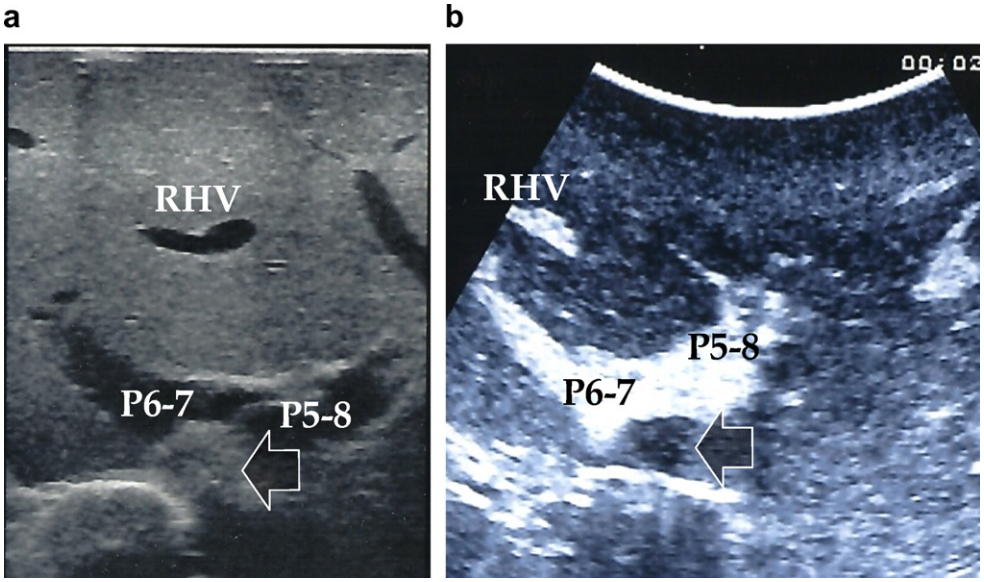

Fig. 1 – (a) This illustration shows a colorectal cancer liver metastasis (arrow) which was difficult to recognise after IOUS since it was located adjacent to the portal branches to segments 6 and 7 (P6-7) and to segments 5 and 8 (P5-8); (b) at CE-IOUS the lesion (arrow) appearing as a black hole is well evident. RHV = right hepatic vein.

ised at CE-IOUS. Fig. 2 summarises the findings provided by IOUS and CE-IOUS.

After IOUS and CE-IOUS, 35 patients (74%) were found to have multiple CLM. All the new lesions at IOUS and CE-IOUS were detected in the patients who underwent surgery for multiple CLM (mean per patient 3; median 3.8; range 1–9) at preoperative imaging, in all but three cases (90%). The mean number of preoperative lesions in this subgroup of patients was significantly higher than in the remaining patient population (3.8 versus 2; $P = 0.003$).

The diameter of the lesions detected only by CE-IOUS ranged from 0.3 to 1.1 cm.

Four new lesions on IOUS and none on CE-IOUS were detected in the five patients who were found to have a bright liver according to the aforementioned definition (Fig. 3).

Limiting the analysis to the last 42 patients who underwent also 18-FDG-PET in their preoperative work-up, IOUS and CE-IOUS disclosed globally 167 lesions (median 3 per patient; mean 4 per patient; range 1–13 per patient). In particular, 9 of the 10 new lesions detected only by CE-IOUS were found only in this subgroup of patients. Noticeably, there were three patients with no liver lesions at PET scan, but CT + MRI and IOUS + CE-IOUS found four, three and one lesion, respectively: all these patients received chemotherapy prior to preoperative staging and surgery. Additionally, 18-FDG-PET disclosed less lesions than CT + MRI in other 15 patients, and less than IOUS + CE-IOUS in other 22 patients. 18-FDG-PET disclosed more lesions than CT + MRI in three patients which were all confirmed at IOUS + CE-IOUS.

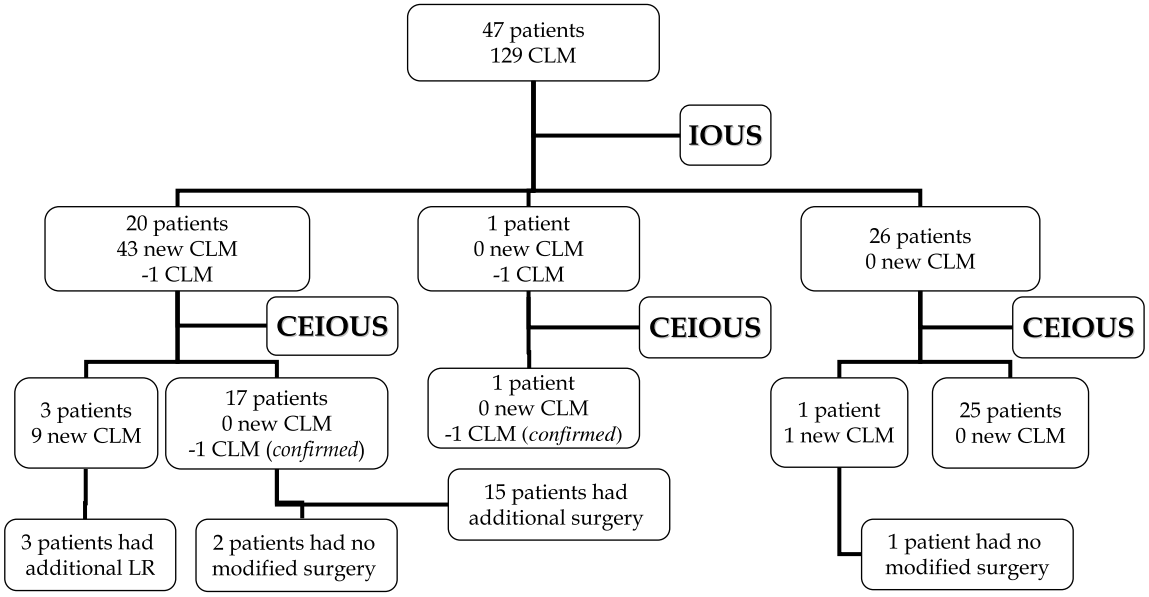

Fig. 2 – Flow-chart shows the additional findings of IOUS and contrast-enhanced intraoperative ultrasonography (CE-IOUS) and their output in terms of modified surgery.

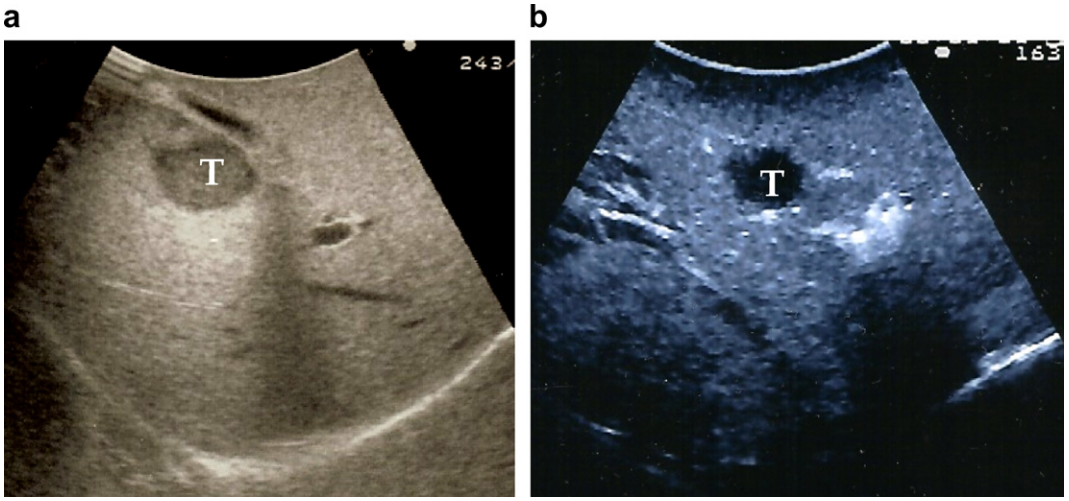

Fig. 3 – (a) The lesion (T) in a bright liver is visible since the contrast with the surrounding parenchyma is clear; (b) the contribution provided by CE-IOUS in this case is less dramatic than in that shown in Fig. 1.

3.2. *Resection guidance*

CE-IOUS allowed better visualisation of the tumour margins of the main lesions in nine of the 47 patients (19%) which in turn enabled a better definition of the resection area, and of the liver dissection plane, resulting in easier resection guidance (Fig. 4).

3.3. *Surgical outcome*

All 53 new liver lesions detected at IOUS and CE-IOUS in 21 patients were resected along with the 127 lesions diagnosed preoperatively as CLM and intraoperatively confirmed by IOUS and CE-IOUS. The distribution of the lesions was bilobar in 21 patients, limited to the right hemi-liver in 20 patients, and to the left hemi-liver in six patients. Major resection ($\geqslant$3 segments) was performed in two patients (4%). For 18 (86%) of the 21 patients with new lesions at IOUS and CE-IOUS the surgical approach was modified to include a limited resection. Amongst them were three of the four patients with new CLM at CE-IOUS. Fig. 2 summarises the findings provided by IOUS and CE-IOUS and their operative consequences.

At histology all the removed nodules were confirmed as metastases.

After a mean follow-up of 16 months (median 14 months; range 6–34 months), 27 (57%) patients had recurrent disease: in 19 (40%) the liver was involved. The mean disease-free survival time was 13 months (median 9; range 1–34) and the mean hepatic-free survival was 13 months (median 11; range 1–34); five (11%) patients died during the follow-up. Ten patients (21%) developed 14 new liver lesions in another segment within 6 months after operation (mean 2.8; median 2; range 1–4); all these nodules were less than 2 cm in diameter at the time of detection, and were considered as metastases not seen at preoperative (CT/MRI) and intraoperative (IOUS and CE-IOUS) imaging. Of these, five patients with six new CLM at follow-up had additional adverse factors at the time of surgery, such as lymph node metastases in four and major vascular invasion in one patient who had 10 lesions removed. Another four patients (9%) had new CLM within 12 months after surgery (8, 8, 9 and 12 months, respectively). All these CLM were less than 2 cm in diameter. Of the two patients with the FLLs diagnosed preoperatively as metastases but not confirmed by IOUS and CE-IOUS and therefore not removed, one is alive at 24 months after surgery, but with lung and hepatic recurrence 17 months after resection, and one had a new lesion 2 months after surgery and died 17 months after the operation. None of the new lesions detected postoperatively were at the site ruled out by IOUS and CE-IOUS.

Table 1 shows sensitivity, specificity, PPV, NPV, and accuracy of preoperative imaging, IOUS and IOUS + CE-IOUS in detecting CLM. Preoperative imaging had significantly lower sensitivity, specificity and NPV than IOUS and IOUS + CE-IOUS ($P < 0.05$). PPV did not reach significance for any of the comparisons. The sensitivity, specificity, PPV and NPV were not significantly different for IOUS and IOUS + CE-IOUS.

3.4. *Adverse reactions and costs*

No clinically evident adverse reactions were reported during and after the intravenous injection of the contrast agent.

Additional costs to the surgical procedure due to CE-IOUS, assuming the use of one sample of contrast agent per patient, were 61.36 euros/patient.

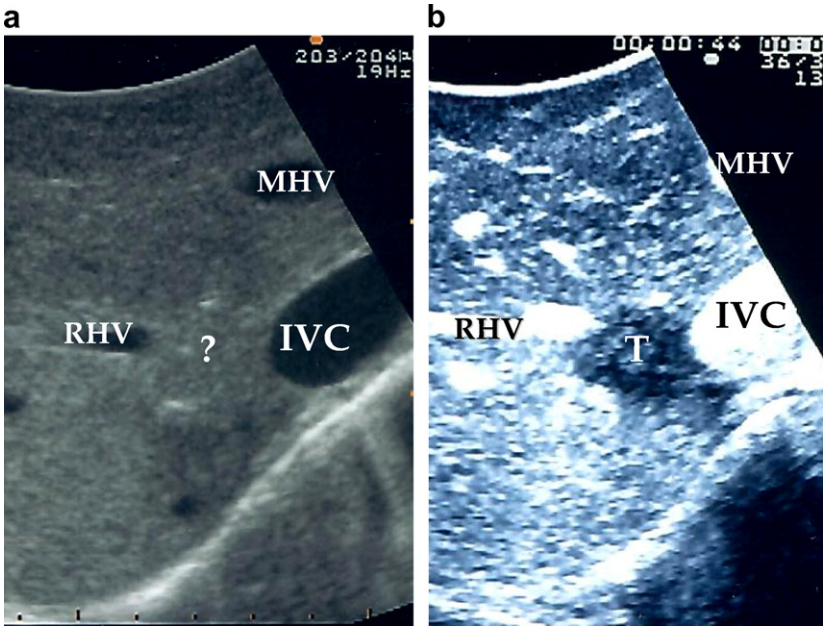

Fig. 4 – (a) The margins of the lesion invading the right hepatic vein (RHV) at its confluence into the inferior vena cava (IVC) are unclear at IOUS; (b) at CE-IOUS the lesion (T) becomes clearly visible by its margins and its relation with the RHV and the IVC. MHV = middle hepatic vein.

Table 1 – Sensitivity, specificity, positive and negative predictive values and accuracy of preoperative imaging, IOUS and contrast-enhanced intraoperative ultrasonography (CE-IOUS) in carriers of CRC liver metastases

	Preoperative imaging (CT + MRI)	IOUS	IOUS + CE-IOUS
Sensitivity	66	88	93
Specificity	0	100	100
Positive predictive value	98	100	100
Negative predictive value	0	8	13
Accuracy	65	88	93

4. Discussion

Complete surgical clearance of multiple CLM even in the presence of vascular infiltration is justified since, significant benefits in term of long-term survival are reported.[11] Tumour staging by IOUS does not appear totally adequate.[3] We have previously shown that CE-IOUS is able to improve IOUS sensitivity since it allows recognition of new CLM in 21% of patients, resulting in a reduced risk of down-staging, and an enhanced rate of treatment with curative intent.[7] These results were partially confirmed by multicentre, and, more recently monocentre experience.[8,9] However, the conclusions were not homogeneous. Leen et al. considered CE-IOUS a useful addition to IOUS, Fioole et al. concluded the opposite, although results apparently were not that different. All these studies were based on preliminary experiences in small numbers of patients with CE-IOUS, and moreover with different criteria for patients enrolment and data analysis. Reference standards were different amongst the series, and therefore the comparability of results was reduced, thus lowering the impact once a summary analysis was attempted.

It is important to establish how CE-IOUS should be considered, either as a new autonomous diagnostic tool, or as part of the IOUS procedure to be integrated with the findings of the unenhanced phase. In our opinion the latter should be considered more appropriate, since CE-IOUS is performed by the same operator immediately after IOUS, which undoubtedly guides CE-IOUS scanning. Indeed, CE-IOUS scans can be focused on other liver portions knowing what IOUS has demonstrated. On the other hand when establishing accuracy, CT and MRI are also considered independently, including both the unenhanced and enhanced phases.

The experience herein reported comes from work started in 2002. However, for this study only the most recent series was considered, thus excluding those patients who were part of the previously reported analysis.[7] Nevertheless, the 47 consecutive patients enrolled represent the largest reported series of CE-IOUS for CLM in a monocentric setting. An important point that differentiates this study from previous reports is the fact that all the patients underwent abdominal CT and MRI prior to surgery. All previous reports had heterogeneous preoperative diagnostic work-up with 66–100% of patients having only a CT exam.[7–9] In addition, in the previously reported studies preoperative examinations were carried out 2–6 weeks prior to surgery, i.e. a time interval which is too long to rule out the risk of possible development of new tiny lesions. In the present series all the patients were operated within 2 weeks of the preoperative imaging.

A further strength of this study is that, to establish the value of IOUS and CE-IOUS in improving intrahepatic staging and as consequence surgical radicality, not only histology was considered, but also the imaging follow-up. Indeed, accuracy, sensitivity, specificity, PPV and NPV were analysed based also on follow-up findings, which make this series different from those previously reported in which findings at follow-up were not considered[8] or were considered as a whole without time limit. Thus no attempt to differentiate between the new CLM which were missed at IOUS and CE-IOUS and those that developed postoperatively was made.[9] Six months of postoperative follow-up were considered adequate for discriminating the CLM missed during surgery from those that developed subsequently. Synchronous metastases are those lesions which appear within the 6 months after surgery[12]; conversely, in our series 9% of patients had new CLM from 6 to 12 months after surgery, and all of them after 8 months. Furthermore, all lesions detected intraoperatively in this series were removed and histological confirmation was obtained whilst in previous reports a significant proportion of patients received intraoperative thermal ablation of the new sites.[8,9] In the series of Leen et al. all patients who received ablation therapy underwent previous intraoperative fine needle biopsy (FNB), which was not the case in the series reported by Fioole et al. in which diagnostic confirmation was obtained only as follow-up findings for those who received ablation therapy: this method of evaluation may lead to inaccurate conclusions.[9]

Despite the more meticulous preoperative diagnostic imaging performed in our series using latest generation CT and MRI, IOUS and CE-IOUS impacted on the intrahepatic staging and the surgical approach by providing new findings in 55% of patients, with a significantly higher sensitivity, specificity and NPV than CT and MRI combined. Although, the two lesions detected at CT and MRI and properly unconfirmed at IOUS and CE-IOUS accounted for the shocking discrepancy amongst the respective specificities (Table 1), anyway, globally, these results support the message that IOUS and CE-IOUS should still be performed in spite of the advanced preoperative imaging. Certainly, the higher rate of patients with multiple CLM (74%) who underwent surgery in our series compared to the others, may explain the significance of the findings obtained with IOUS combined or not with CE-IOUS, and those at preoperative imaging: indeed, multiple CLM lesions are generally associated with a higher rate of missed lesions at preoperative imaging.[13] As further confirmation of that, 90% of patients with new CLM at IOUS and CE-IOUS received surgery for multiple metastases at

preoperative imaging, and had a significantly higher mean number of lesions detected preoperatively than the others. The high rate of patients with multiple lesions who underwent surgery together with the precise reference standard based on histology and follow-up could also explain the relatively high rate of patients with early recurrence (21%) despite the impact of IOUS and CE-IOUS findings.

Curiously, limiting the analysis to a subgroup of patients who had also PET scan prior to surgery, it appears that this diagnostic and staging modality is not that accurate when per liver lesion comparisons were made with CT and MRI, and consequently with IOUS and CE-IOUS. Furthermore, PET scan proved to be inadequate for those patients who had prior chemotherapy. Although, these data were retrospectively reviewed, they are in line with most of the prospective studies confirming that PET scan is particularly useful for extra-hepatic staging.[14–16]

Once it has been shown that IOUS and CE-IOUS provide significant additions to the findings of CT and MRI combined and also of PET scan by adopting precise reference standard methods, the non-significant difference between findings of IOUS and IOUS + CE-IOUS should be discussed. Indeed, this result could lead to CE-IOUS which is considered a useless additional modality, as concluded by Fioole et al.[9] However, based on these estimations the role of IOUS should be reconsidered too, since most of the findings in all series were obtained in patients with multiple CLM at preoperative imaging. Therefore, IOUS should be recommended only for selected patients; i.e. those who have multiple CLM. However, some concerns arise with this approach. Indeed, in this and all the previously published reports, CE-IOUS constantly provided new findings: in particular in this series CE-IOUS identified 10 lesions undiscovered by IOUS alone, and that in spite of the advanced preoperative imaging adopted. Although not significant, this is the confirmation that CE-IOUS adds something to IOUS in all the series examined and therefore, its routine use should be recommended. On the other hand, unenhanced CT, although providing less information than the enhanced modality, and additional irradiation, is still routinely performed since it adds some information.[17] A further series, based on a larger number of patients and on a strict protocol of reference standard, will probably consolidate the value of CE-IOUS, and help to better clarify its impact from a statistical point of view. Conversely, in our opinion there is already enough evidence for judging unethical a randomised trial comparing two groups undergoing surgery for CLM with IOUS alone and with IOUS and CE-IOUS together.

The only condition in which, in our opinion, the use of CE-IOUS could be reconsidered and eventually not performed is in the presence of bright liver at IOUS: indeed, in all these patients in whom the contrast between lesion and surrounding parenchyma was evident at IOUS, CE-IOUS did not add any new findings (Fig. 3). On the other hand, Leen et al. reported that CE-IOUS was not carried out in a patient with bright liver showing more than 10 CLM at IOUS.[8] However, the definition of bright liver could be biased by the operator's judgement, and there is not enough evidence to make a definitive conclusion, but there are reasons for supporting further evaluations of the real utility of CE-IOUS in these patients.

Enhancing the contrast between the tumour and the surrounding parenchyma has another advantage other than improved detectability, i.e. a better definition of the tumour margins and of the relationship with adjacent vascular structures[7] as in the example in Fig. 4. This situation provided by CE-IOUS was confirmed in 19% of our patients, and Leen et al. described a patient in whom CE-IOUS helped in defining tumour margins.[8] This additional information obtained with CE-IOUS was more evident in the present series, and in the one we previously reported,[7] than in those which have followed.[8,9] This is possibly due to the fact that this is a subjective finding and that in our series CE-IOUS was always carried out by the surgeon himself. Therefore the combination of ultrasound findings and surgical requirements could have enhanced the value of this additional information. Indeed, a better definition of tumour margins helps the surgeon to define the resection margin, which becomes crucial if the surgical team adopts a conservative approach to maximise the sparing of liver parenchyma by getting closer to the tumour margin under ultrasound guidance. Surgical policy, as we have repeatedly shown, provides benefit in terms of safety of the surgical treatment, technical feasibility of the resection itself and long-term survivals.[18–21] This surgical policy accounts for the high rate of modified operations based on IOUS and CE-IOUS findings.

All the patients we studied underwent CE-IOUS using a convex lower frequency echo-probe different from the other authors who used intraoperative high-frequency probes. Although, small and stable intraoperative probes are more suitable for surgical exploration especially when the liver is not yet well mobilised, lower frequency probes, as those used for CEUS, despite the lower resolution power than the higher frequency one, allow longer and stronger contrast enhancement. The longer time of exploration, the stronger enhancement which is obtained and the lower frequency itself all contribute to better exploration of the deeper portions of the liver, providing for, a better panoramic view than that obtained with higher frequency probes. Possibly in the future, the development of dedicated technology for CE-IOUS will allow a proper compromise between the different features needed for an optimal exploration. In our opinion, IOUS and, consequently CE-IOUS, are useful methods not only to establish the staging of the disease but also to guide the surgical manoeuvres. Accordingly it is crucial that they are performed by the surgeon himself to exploit all their potential and maximise their impact.

Some authors have raised concerns on the safety of CE-IOUS.[22] However, Piscaglia et al. have recently shown on a large multicentric series[23] how the rate of severe adverse events is really minimal (0.0086%). Furthermore, the intraoperative use of this technique is expected to be even at lower risk for any adverse event since it is restricted to patients undergoing advanced surgery performed under constant anaesthesiological control[24]. Indeed, in the present series no adverse events were clinically recorded during and after the administration of the contrast agent.

A further concern could be the additional costs provided by CE-IOUS. Considering that the end-point of CE-IOUS is the improvement in the detection power of occult CLM, and for this purpose it works, we believe that an additional cost

of 61.36 euro per patient is clinically more than justified by the results herein and elsewhere reported.

In conclusion, this study confirms in an homogeneously analysed prospective and monocentric series that IOUS sensitivity is enhanced by CE-IOUS in patients with CLM. The technique is safe and provides additional information despite advanced preoperative imaging and a meticulous IOUS. Furthermore, although subjective, CE-IOUS provides additional findings in a relevant portion of patients to assist in recognising the dissection plane since it defines the tumour margins more precisely. For all these reasons, CE-IOUS should be recommended routinely in patients with CLM; its use in the presence of a bright liver at IOUS remains to be better determined.

Conflict of interest statement

All authors have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

Role of funding source

Guido Torzilli was supported by Bracco Imaging Spa for the preparation of this article. The sponsor imposed no restrictions on the investigators in the writing of the manuscript. The corresponding author had the final responsibility to submit for publication.

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