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ORIGINAL ARTICLE

Contrast-enhanced intraoperative ultrasound improves detection of liver metastases during surgery for primary colorectal cancer

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Abstract

Background: Computed tomography (CT) is the most common staging investigation in colorectal cancer (CRC). Up to 25% of patients are found to have previously undetected hepatic lesions when intraoperative ultrasound (IOUS) of the liver is used during CRC resection. We aimed to assess the ability of IOUS to detect additional liver lesions/metastases at primary colorectal resection, and to evaluate whether contrast-enhanced IOUS (CE-IOUS) improves the detection and characterization of hepatic lesions.

Methods: We performed a single-centre, prospective pilot study. At CRC resection, patients underwent IOUS of the liver. Contrast-enhanced IOUS of the liver was undertaken using i.v. sulphur hexafluoride micro-bubbles (SonoVue®, 4.8 ml). Findings of CT, non-enhanced IOUS and CE-IOUS were compared. Changes in staging or management were noted. Additional lesions were corroborated with iron oxide magnetic resonance imaging (MRI).

Results: Among 21 patients, IOUS demonstrated additional lesions in seven (33%). Contrast altered the diagnosis of non-enhanced IOUS in four (20%) and changed the management strategy in three (14%) patients. Thus, IOUS in combination with the contrast agent altered the intraoperative or postoperative management plan in four patients.

Conclusions: In the first study of its kind, early results suggest that the ability of IOUS to detect additional metastases is improved by CE-IOUS, and that this may impact on surgical staging and management.

Keywords

colorectal liver metastases, intraoperative ultrasound, contrast

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Introduction

Colorectal cancer (CRC) represents one of the commonest solid tumours and accounted for almost a million cases worldwide in 2002, with mortality occurring in about half (529 000 deaths in 2002).[1] Approximately 50–60% of patients with CRC develop liver metastases during the course of their disease.[2,3] Of these, 15–25% present with synchronous liver metastases and an additional 20–25% develop metachronous metastases.[4–6] Assuming an annual incidence of a million cases, around 500 000 patients will develop colorectal liver metastases (CLM) and subsequently require some form of treatment.[1]

Hepatic resection offers by far the best opportunity for cure from CLM. However, the majority of CLM patients have unresectable disease at presentation.[7,8] Early detection improves the chances of life-prolonging treatment in terms of both local and systemic treatments. Therefore, it is desirable to detect CLM at an early stage.

Multi-slice contrast-enhanced computed tomography (CT) is the most commonly used preoperative staging investigation in primary CRC for detecting metastases. The sensitivity of CT for CLM is reported to be 73–85%.[9,10] Previously undetected liver metastases are still diagnosed at laparotomy in a significant proportion of patients. However, metastases are often missed

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at laparotomy, either because they are too small or too deep to palpate or because they are located in a liver segment inaccessible to view. The routine use of intraoperative ultrasound (IOUS) of the liver during primary CRC surgery is effective for detecting additional lesions.[11–13] However, around 15–20% of patients with a negative IOUS develop liver metastases within 2 years of follow-up.[11,13] Although some of this later disease may be microscopic at the time of IOUS, it is likely that some macroscopic lesions are missed as a result of their small size or atypical characteristics, because they mimic benign lesions or because they are iso-echoic with the hepatic parenchyma and thus invisible. An imaging modality with increased sensitivity and the capacity to distinguish benign from malignant with more clarity (and simplicity) is needed.

Contrast agents have long been used to improve CT and magnetic resonance imaging (MRI). Contrast-enhanced trans-abdominal ultrasound is now available for routine use. The i.v. micro-bubble (contrast) technology improves the accuracy of detection of metastases and characterization of focal liver lesions during trans-abdominal ultrasound, even to the extent of identifying lesions missed by high-quality CT.[14,15] This appears to extend to IOUS during liver resection for CLM, when the clinical impact can be immediate.[16,17]

The aim of our study was to assess the ability of IOUS to detect additional liver lesions/metastases at primary CRC surgery, and to evaluate whether contrast helps in the ultrasound detection and characterization of focal liver lesions in this setting. We report the first study using contrast-enhanced IOUS (CE-IOUS) of the liver to detect and characterize additional hepatic lesions during primary CRC resection.

Materials and methods

We report a prospective single-centre pilot study conducted between April and December 2007 at a tertiary referral centre. Regional ethics committee approval was obtained.

All patients underwent a multi-slice contrast-enhanced CT of the chest, abdomen and pelvis as a preoperative staging investigation, at the same tertiary hospital. The CT scan of the chest, abdomen and pelvis was performed with the Somatom® (Siemens Plc, Frimley, UK), with pre-contrast CT followed by post-contrast CT, using 1-mm cuts. The liver was analysed in all three phases (non-contrast, arterial and porto-venous washout).

All the included patients had a diagnosis of adenocarcinoma of the colon or rectum and were discussed by the CRC multidisciplinary team (MDT), which included two specialist gastrointestinal radiologists. The position, size and CT characteristics of liver lesions were then recorded in detail on a prospectively maintained database. Based on the MDT decision, patients whose cancers were amenable to curative open surgical resection were invited to participate in this study. Full informed consent was obtained. Patients who required emergency surgery (within 24 h of emergency hospital admission) were excluded as they would not have enough time to understand and consent to the contrast-enhanced scan.

At laparotomy, the liver was inspected and palpated for focal hepatic lesions and the findings were noted. The laparotomy incision was a standard incision made by the colorectal surgeon to remove the primary tumour; it was not extended to facilitate IOUS/CE-IOUS. A non-enhanced B mode ultrasound examination (mechanical index 1.1) was performed at a frequency of 10 Mz by a surgeon trained to perform both non-enhanced and contrast-enhanced ultrasound. We used the Bodedex-Korsolex (B-K) Pro Focus 2202® scanner and 8815® intraoperative probe (both B-K Medical ApS, Herlev, Denmark). A segment-by-segment examination was performed in a standard manner. Data recorded for each lesion included ultrasound characteristics, liver segment(s) involved, a detailed description of the relationships of the lesion to anatomical landmarks, an impression as to the benign or malignant nature of the lesion and comments regarding correlation with the CT data.

After the non-enhanced scan, the contrast, 25 mg of sulphur hexafluoride micro-bubbles (SonoVue®; Bracco Imaging SpA, Milan, Italy) diluted to 4.8 ml in saline, was prepared fresh by the anaesthetist and injected i.v. through a peripheral wide-bore cannula (16 G or 18 G). The cannula was then flushed with 10 ml of normal saline. An on-screen timer was started and scanning began immediately. Particular attention was paid to the classical three phases of ultrasound contrast: the arterial phase (the initial 30 s); the porto-venous phase (30 s to 2 min), and the delayed parenchymal phase (2–5 min). The CE-IOUS was performed using a standard mechanical index of <0.18. The frequency of the probe was set at 4.3 MHz in contrast-specific mode. The entire scanning period of 5 min was recorded in digital video format. The non-enhanced images were simultaneously visualized with low-frequency B mode on a dual-screen mode. This facilitated anatomical localisation of newly identified lesions.

Contrast-enhanced IOUS was always performed by starting with a known metastatic or other benign lesion (on non-enhanced IOUS) when present. The ipsi-lateral lobe was then scanned on a segment-by-segment basis, followed by the contralateral lobe. The characterization and location of lesions was documented in detail. Changes in the surgical management plan were noted. Where new lesions were identified, digital recordings of real-time scans were also examined by a radiologist experienced in contrast-enhanced trans-abdominal ultrasound.

We used MRI with liver-specific contrast (supermagnetic iron oxide [SPIO]) particles as an interim reference standard for the confirmation and characterization of additional lesions detected with IOUS or CE-IOUS. The use of MRI with liver-specific contrast also served two clinical purposes. Firstly, it provided a roadmap of the metastases to aid in treatment planning. Secondly, it provided a baseline from which to assess response to chemotherapy with subsequent MRI.

Patients without suspicious or new standard screening with trans-abdominal ultrasound at 3 and 6 months with serum carcino-embryonic antigen levels and a CT scan at 1 year.

Neither the surgeon performing the IOUS nor the radiologist were blinded to the findings of any of the investigation.

The findings of CT, non-enhanced IOUS and CE-IOUS were compared. Changes in the surgical staging or management of the disease were noted.

Statistical analysis

Statistical analysis was performed using SPSS Version 14.0. (SPSS, Inc., Chicago, IL, USA). Statistics were applied as a percentile difference between imaging modalities in the diagnosis of the lesions, and the difference in the proportion of patients in whom management strategies were altered. The difference is presented with 95% confidence intervals.

Results

Twenty-one patients with CRC were enrolled in this prospective pilot study over a 9-month period (April 2007 to December 2007). The male : female ratio was 12 : 9. The median age of the patients was 65 years (range 30–84 years).

Of the 21 patients, IOUS or CE-IOUS demonstrated additional or previously undetected liver lesions in seven patients. A summary of the seven patients is reported in Table 1. The ultrasound (non-enhanced and contrast-enhanced) characteristics of all identified lesions are detailed in Table 2. In these seven patients, multi-slice CT had demonstrated four lesions, laparotomy demonstrated six, non-enhanced IOUS demonstrated 17, and CE-IOUS demonstrated 18 lesions. Thus a total of 14 new lesions were diagnosed at IOUS + CE-IOUS. The entire liver scanning procedure took an additional 10 min, although the time was not recorded formally.

Non-enhanced IOUS demonstrated six new definitive metastases in three patients. In another three patients, IOUS detected lesions that were equivocal in their sonographic characteristics, but suspicious for metastases considering the primary diagnosis. Contrast confirmed the malignant nature of the lesions in the first three patients and identified a further metastasis in one of these patients. In the latter three, contrast defined equivocal lesions as clearly benign in two patients and clearly malignant in the third.

Contrast changed the diagnosis of non-enhanced IOUS in four patients, by identifying the benign nature of equivocal lesions in two patients and the malignant nature of an equivocal lesion in one, and by detecting an additional metastasis in one patient. SPIO-enhanced MRI corroborated these findings in these four patients. The other three patients with new findings on IOUS/CE-IOUS did not have MRI. One patient underwent an R2 resection and had a complicated postoperative recovery. One patient had a locally perforated tumour and four liver metastases on both IOUS and CE-IOUS and underwent a palliative bypass. The last patient had complete regression of the rectal cancer, on final histopathology, as a result of preoperative chemoradiotherapy. The latter patient had no evidence of metastases on a repeat CT scan. In each of the four patients in whom contrast altered the detection or characterization of lesions, the findings impacted on management. The findings changed planned chemotherapy and further consideration for liver resection in one patient, and changed the type of liver resection planned in another. Benign contrast characteristics prevented over-treatment in a third patient, and the presence of several metastases aided the decision for bypass-only for a difficult locally perforated primary lesion in the fourth patient.

Three patients with rectal cancer underwent downstaging chemoradiotherapy prior to resection. All of them had a repeat staging CT scan after the downstaging and the cancers were resected at 4–6 weeks after the repeat CT scan.

In the remaining 14 of the 21 patients no focal liver lesions were seen. These patients did not undergo an MRI of the liver. There was no evidence of hepatic metastases in these patients during an outpatient clinic follow-up period that ranged between 9 and 16 months.

In summary, IOUS demonstrated additional lesions in seven of 21 patients (33.3%, 95% confidence interval [CI] 14.6–57.0%). Contrast changed the diagnosis compared with non-enhanced IOUS in four patients (19.0%, 95% CI 5.4–41.9%). Intraoperative US (with and without contrast) demonstrated previously undetected metastases in three patients and changed management in three patients (14.3%, 95% CI 3.0–36.3%). In one of these patients, initially unilateral metastatic disease (on CT) was found to be bilateral.

Discussion

In the first published study on contrast ultrasound of the liver during primary CRC surgery, we have demonstrated that sulphur hexafluoride CE-IOUS of the liver improves the detection of hepatic metastases in patients with primary CRC. The demonstrated improvement in hepatic staging in patients could (if reproduced in other studies) have a significant impact on the management of these patients.

None of the preoperative staging modalities used in CRC are as accurate or sensitive as IOUS of the liver. This includes CT,[13,18] positron emission tomography (PET)[19] and probably MRI.[20,21] In our study, CE-IOUS altered the diagnosis of non-enhanced IOUS in 19% of patients. Although the frequency of detecting additional lesions by CE-IOUS was similar to that of IOUS, CE-IOUS seemed to more accurately characterize these lesions. The better characterization of the lesions by the contrast material is particularly advantageous in the setting of resection for primary CRC, where equivocal lesions, which are statistically more suspicious for metastases, present a dilemma with important clinical consequences.

The total scanning time of only 5 min is a potential limitation in characterizing all lesions identified. However this can be overcome by repeating the contrast injection for up to a total of 9.6 ml of SonoVue®. Furthermore, once the sonographer is experienced,

Table 1 Summary of results in seven patients with additional findings on intraoperative ultrasound (IOUS) and contrast-enhanced-IOUS

Patient details	CT findings	Laparotomy	IOUS	CE-IOUS	Contrast made a difference?	Change in management	Histology of CRC
Age, years/sex							
73/M	1 cyst	0	2 cysts	2 cysts	No	No	Sigmoid colectomy T3N0
77/F	1 cyst (segment II)	2 cysts (segments II, VI)	1 equivocal (segment II)	1 metastasis (segment II)	Yes	Yes Oxaliplatin-based chemotherapy	Anterior resection T4N0
			2 cysts (segments VI, VII)	2 cysts (segments VI, VII)			
82/F	0	0	2 lesions (segment V); 1 equivocal	Both benign	Yes	Probably	Right hemicolectomy T3N0
61/M	2 metastases (segments II, IV)	2 metastases	4 metastases (1 in segment II, 2 in segment IV, 1 in segment V)	All confirmed as metastases	No	No R2 resection	Abdomino-perineal resection T4N1
30/F	0	1 lesion (segments II) (felt benign)	2 (segment II, metastasis; segment VI, benign)	3 (segment II, metastasis; segment VI, benign; segment VII, metastasis)	Yes	Yes Had neoadjuvant chemotherapy and liver resection	Anterior resection T3N2
77/F	0	1 equivocal lesion (segment II) (soft on palpation)	3 metastases (1 in each of segments II, VI, VII)	Same as IOUS	No	Locally perforated, aided decision not to resect	Palliative bypass
65/M	0	0	1 equivocal	1 benign	Yes	No	Left hemiolectomy. T0N0

CT, computed tomography; IOUS, intraoperative ultrasound; CE-IOUS, contrast-enhanced intraoperative ultrasound; CRC, colorectal cancer; M, male; F, female

Table 2 Ultrasound characteristics of all identified lesions

Patient (age, years/sex)	IOUS characteristics and impression	CE-IOUS characteristics and impression
1 (73/M)	2 lesions – anechoic with no wall = cysts	2 lesions
		Arterial phase: no rim enhancement Portal and delayed phase: no contrast uptake
2 (77/F)	a) Hypoechoic with irregular border = equivocal	a) Arterial phase: hypo-intense with peripheral rim enhancement Portal phase: rim enhancement fades Delayed phase: dark defects ('black holes') on background of bright parenchyma = metastasis (classical contrast appearance)
	b) As patient 1 = cysts	b) Cyst (as patient 1)
3 (82/F)	a) Hyperechoic with irregular border = equivocal	a/b) Continuous uptake of contrast, no 'black holes' Parenchyma bright in all 3 phases
	b) Mildly hypoechoic, regular border = benign	= benign
4 (61/M)	4 similar lesions	Classical contrast appearance of metastases ('black hole') (1 lesion not visible in delayed phase)
	Hypoechoic rim, hyperechoic centre (classical appearance of metastases)	
5 (30/F)	2 lesions	3 lesions
	a) Classical appearance = metastasis	a) Classical metastasis ('black hole')
	b) Hyperechoic with posterior enhancement	b) Centripetal filling in delayed and portal phase, brighter than contrast bright parenchyma = haemangioma
		c) Classical metastasis
6 (77/F)	Classical appearance = metastases	Classical metastases
7 (65/M)	Hyperechoic with irregular border = equivocal	As patient 3 = benign

IOUS, intraoperative ultrasound; CE-IOUS, contrast-enhanced intraoperative ultrasound; M, male; F, female

the vial of the contrast can be divided into two doses of 2.4 ml, allowing up to four separate injections (using two vials). SonoVue® probably does not provide enough time to perform ultrasound-guided biopsy of lesions not visible with non-contrast imaging. However, nearly all newly identified liver lesions in this series were visible using non-enhanced IOUS and thus could be biopsied without contrast, if appropriate. In the setting of CRC, biopsy is not advisable for the majority of cases as it is known to be associated with a worse longterm survival following liver resection.[22,23] Indeed, definitive imaging with contrast may reduce the perceived need for biopsy.

The CE-IOUS findings were corroborated by CE-MRI in our study. In the absence of histopathological proof of new IOUS/CE-IOUS findings, it was felt appropriate to use the best non-invasive modality for characterizing and detecting liver metastases.[24–26] Contrast-enhanced MRI also provided a road map and baseline for comparison for future management and follow-up. It would be reasonable to argue that a routine preoperative CE-MRI could be performed prior to CRC resection to improve staging. However, in the setting of liver resection for CRC metastases, it has been shown that IOUS provides the most sensitive and predictive information.[20,21] In a recent international multicentre study, contrast-enhanced trans-abdominal ultrasound was reliable in detecting and characterizing focal liver lesions compared with CT and MRI.[27] This may be largely because cross-sectional imaging continues to be limited in detecting and characterizing sub-centimetre lesions.[20,27] Contrast-enhanced IOUS would be expected to produce better results than contrast-enhanced trans-abdominal ultrasound because of the additional benefits of access and of using higher-resolution non-enhanced IOUS. However, there have also been clear and dramatic improvements in non-enhanced IOUS alone over recent years and CE-IOUS cannot be assumed to surpass these improvements.[27] Therefore, as in liver resection, the benefit of CE-IOUS over IOUS in the setting of primary CRC requires testing.

This study was limited by the small and non-consecutive nature of the cohort. The reasons for this were logistical and do not indicate case selection. There was also a limited period of radiological follow-up. Patients with normal CE-IOUS did not undergo a follow-up MRI scan and the duration of further routine surveillance imaging was short. However, to date, no patient with normal CE-IOUS has developed recurrence in the liver. Existing data strongly suggest that MRI in these cases would be unlikely to reveal further disease.[28] Although the impact of CE-IOUS may be different in a larger consecutive series, it seems unlikely to be negated.

Obstacles to routine hepatic IOUS or CE-IOUS in CRC resection include the need for additional operating time and specialist equipment, both of which have financial and logistical implications. The logistics relate mainly to the availability of a trained ultrasonographer in theatre. Despite several studies supporting liver IOUS during CRC resection, its routine use is uncommon.[11–13] One reason for this is a lack of ultrasound training for colorectal surgeons. However, it is likely that CE-IOUS would facilitate the training process, because contrast produces more definitive images, which serve to confirm or negate the impression gained from non-contrast images, and thus provide a means of self training.[14] This may be especially true with newer agents, which give a slower washout of contrast, potentially leading to improved training opportunities and metastasis detection rates.[29] The financial implications of routine CE-IOUS would be relatively minimal compared with the benefits likely to result from the earlier detection of liver metastases and the consequent improvements in survival.

Liver resection at the time of primary CRC resection has been shown to be safe and overall is associated with fewer complications.[30] The confident use of IOUS and CE-IOUS by colorectal surgeons may provide opportunities for this treatment option in a greater number of cases. In our own experience, even when a combined resection is not to be considered, an accurate description of intraoperative findings by the colorectal surgeon is invaluable when considering cases for future liver resection.

Conclusions

The preliminary results of this study suggest that in the setting of current standard preoperative imaging, high-resolution intraoperative ultrasound of the liver during colorectal primary resection demonstrates additional hepatic lesions. In this setting, characterization of hepatic lesions is improved by the addition of sulphur hexafluoride micro-bubble contrast agent. This may lead to an impact on the surgical staging and treatment of lesions.

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Conflicts of interest

None declared.

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