Visualisation of liver tumours using hand-held real-time strain imaging: results of animal experiments

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Objective: Surgical resection is the only curative option for colorectal hepatic metastases. Intra-operative localisation of these metastases during hepatic resection is performed by intra-operative B-mode imaging and palpation. Because liver metastases are stiffer than normal tissues, elastography may be a useful complement to B-mode imaging. This paper reports quantitative measures of the image quality attained during intra-operative real-time elastographic visualisation of liver metastasis.

Methods: VX2 tumours were implanted in the liver of eight rabbits and were scanned *in vivo*. Measurements of the tumour dimensions obtained via elastography were compared with those obtained using B-mode imaging and with gross pathology.

Results: Measurements of tumour diameters were similar when obtained by intra-operative elastography and pathological measurement methods (mean difference $\pm$ standard deviation, 0.1 ± 0.9 mm). The contrast between tumours and normal tissues was significantly higher ($p < 0.05$) in elastograms (26 ± 10 dB contrast) than in sonograms (1 ± 1 dB contrast). Sensitivity and specificity for detecting tumours using intra-operative elastography were 100% and 88%, respectively, and positive and negative predictive values were 89% and 100%, respectively. In two cases elastograms were able to detect a tumour that was ambiguous in B-mode images.

Conclusion: Combined hand-held B-mode/strain imaging may provide additional information that is relevant for detection of liver metastases that may be missed by standard B-mode imaging alone, such as small and/or isoechoic tumours.

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Colorectal cancer is the fourth most common cancer in males and the third most common cancer in females worldwide [1, 2]. Approximately half of these patients either present with hepatic metastases or develop them during the course of their disease. Although ablative therapies are frequently used, resection of liver metastases, when possible, remains the preferred therapy for potential cure [3, 4]. The overall 5 year survival rates are in the range of 35–58% in several studies reporting on the results of hepatectomy conducted with curative intent [4, 5]. The pre-operative and intra-operative staging of metastases is essential to remove all metastases and increase the rate of cure. At the pre-operative stage, contrast-enhanced CT is the most commonly used modality to screen for metastases. It is highly sensitive, particularly since the introduction of helical CT and multidetector systems capable of scanning the entire liver in a few seconds, allowing for several scans during the liver's different circulatory phases [6]. MRI is very sensitive as well, and has the advantage of liver-specific contrast if required. MRI is also used for screening purposes, despite the fact that it is more time-consuming

than other methodologies and may be subject to motion artefacts [7]. According to different reports, these modalities detect >90% of liver metastases if their diameter is >5 mm [7, 8]. There is still a group of patients who undergo hepatic surgery without correct pre-operative diagnosis [8, 9]. The use of intra-operative ultrasound (IOUS) with or without contrast agents has proved to be efficient in finding, during hepatectomy, metastases that were not detected by pre-operative examinations [9, 10]. IOUS has been shown to yield significant new information, not identified on pre-operative imaging, which determines the resectability of the metastasis or changes the operative plan. IOUS is considered the gold standard, thereby achieving universal usage [9, 11]. However, the rate of hepatic recurrence following apparently curative liver resection is about 40% at 3 years [12]. This underlines the limitation of IOUS itself, and the need for a more accurate imaging technique cannot be overemphasised. The missed tumours may be small, isoechoic, deeply located or positioned in regions that are difficult to image [13, 14]. Therefore, surgeons also use visual and tactile sensory information intra-operatively to evaluate differences in mechanical properties between normal livers and tumours. Palpation provides tactile sensory information regarding the mechanical properties of materials intra-operatively. Palpation involves the application of a stress, with evaluation of the resultant

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displacement, strain and other mechanical responses that are thus subjectively evaluated. The primary mechanical property that is frequently evaluated when surgeons palpate hepatic tumours intra-operatively to assist resection is the relative stiffness of the liver when compared with a tumour. Stiffer tissues strain less than softer tissues under similar conditions, and tumours generally tend to be stiffer than normal livers. Therefore, ultrasonic elastography is an ideal imaging modality for probing the bioelasticity distribution in biological tissues [15]. The technique is based on the strain-gauge principle, according to which the stiff tissue strains less than soft tissue and when deformed externally by a mechanical compression. Because the stiffness rather than the backscatter is sensed remotely, tumours that are not detectable on sonograms might often be revealed with good resolution and good contrast in elastograms. Real-time ultrasound elastography is now used in a widespread manner in the clinic, and these systems have become commercially available [16–19].

Our long-term objective is to incorporate elasticity imaging within a medical device for the treatment of liver metastases using high-intensity focused ultrasound (HIFU) for eventual clinical use. In previous studies [20, 21], we have described the use of a toroidal transducer for HIFU ablation, which could represent a promising alternative for treating colorectal liver metastases. This device is designed to be used during surgery. We have also shown that elastography is useful in the evaluation of the region that has been ablated using this device [22]. In this article, we explore the feasibility of utilising hand-held real-time elastography for the visualisation of metastases. The hand-held approach was chosen to provide a straightforward complement to conventional B-mode images, which are currently used to define the extent of the metastatic disease. *In vivo* studies using a rabbit model of a liver tumour were conducted in order to provide quantitative measures of the image quality attained during intra-operative real-time elastographic visualisation of liver metastasis. During these experiments, the ability of extracorporeal strain images to detect these tumours was also evaluated as a secondary objective.

Methods and materials

Animals

Experiments were conducted *in vivo* in rabbit liver. Eight New Zealand white rabbits weighing between 3 and 4 kg were used in these experiments. One additional animal was used as a donor rabbit for tumour harvesting. Transplantable carcinomas of rabbit (VX2 tumours) were utilised. Details of their origin and histological characteristics have been described previously [23]. The experiments were conducted at the Institute of Experimental Surgery of the Léon Bérard Centre after local institutional review board approval. These experiments conformed to the requirements of the local Office of Animal Experimentation and were in accordance with the legal conditions set forth by the National Commission on Animal Experimentation.

Tumour implantation

The animals were kept on site for 7 days before the start of the experiments. A venous catheter was placed in an auricular vein for the pre-medication, which was performed 15 min prior to anaesthesia using a combination of ketamine (1.6 ml) and xylazine (0.1 ml). Anaesthesia was performed by intravenous injection of 25% of the pre-medication dose and was maintained by intravenous injection of the same dose every 15 min. VX2 cells were initially implanted in both hind limbs of a donor rabbit. This rabbit received 0.75–1.0 ml of freshly prepared VX2 cell solution in the gluteal muscles of the hind limbs. After 4 weeks of tumour growth, the hind limb tumours were harvested, and small tumour fragments (approximately 25 mg) were dissected from the viable tumour tissue. The abdomen was shaved and cleaned with povidone iodine solution using the anaesthesia protocol described above. These tumour portions were then implanted in the lateral right liver lobe of eight rabbits in a minilaparotomy procedure. The liver lobe and the abdomen were then sutured.

Experimental set-up

Elastograms were obtained using a linear array 12 MHz ultrasound imaging probe with 63% fractional bandwidth (model 8805; B-K Medical, Herlev, Denmark) connected to a B-K ultrasound scanner (Hawk™ 2102 EXL; B-K Medical). The area size of the imaging transducer was $9 \times 41 \text{ mm}^2$. The scanner was modified in order to allow acquisition of radiofrequency (RF) lines by a computer via an analogue/digital converter (CompuScope™ CS14100; GaGe, Lockport, IL) at a sampling frequency of 40 MHz.

Imaging procedure

16 days after tumour implantation, the rabbits were anaesthetised using the same protocol as described previously. First, images were acquired extracorporeally. The 12 MHz ultrasound imaging probe was held by hand and sonograms of the liver were acquired. After the sonogram imaging procedure, elastograms were acquired. A pre-compression of about 1–3 mm was produced manually to ensure good contact between the imaging probe and the region of interest (ROI). During the strain imaging procedure, the amplitude and speed of the axial displacement were optimised by the operator as a function of the strain images visualised at 8 frames per second (fps). Axial displacements of approximately 0.5 mm were applied around this initial position of the imaging probe to produce strain images that were judged satisfactory. This value appeared to yield a good compromise between the strain that can be applied without damaging any organ and the quality of the resulting strain images. Ultrasound data were captured continuously, and strain images were processed and displayed at 8 fps. Displacement estimation was performed using a time-domain cross-correlation algorithm [24] based on pre-calculated sum tables [25]. Strain was estimated using the staggered strain estimator [26]. The

displacement estimation (tracking) window length was set to 0.6 mm (approximately five pulse lengths) and the size of the strain estimation kernel ("staggering kernel") was increased until the subjective visibility of strain at the tumour location was maximised. A staggering kernel length of 0.9 mm was deemed satisfactory. The window shift was chosen to be as small as possible (0.3 mm) while still allowing the images to be produced at a speed of 8 fps. The same values were used for all acquisitions.

During all acquisitions, care was taken to minimise the lateral and elevational displacements (caused by transducer motion), thus optimising correlation between pre- and post-compression RF images. When strain images were deemed satisfactory, the acquisition system was paused and a cine-loop containing the previous 200 consecutive RF images was saved (corresponding to a recording time of 25 s). The dimensions of all tumours were measured in strain images and B-mode images.

After this first series of images, a laparotomy was performed and the ultrasound probe was housed in a sterile polyurethane envelope (Civco, Kaloma, IA). B-mode images of the liver were acquired. The ultrasound imaging probe was then used to manually exert a periodic pressure on the liver using the same methodology used previously for extracorporeal acquisition. The liver was pre-compressed manually by about 1–2 mm to ensure good contact between the imaging probe and the liver. During the strain imaging procedure, the amplitude and speed of the axial displacement were optimised by the operator as a function of the strain images visualised in real time. Axial displacements of approximately 0.5 mm were applied around this initial position of the imaging probe to produce strain images that were judged satisfactory. Again, the amplitude and speed of the displacement were optimised by the operator as a function of the strain images visualised at 8 fps. The diameters of all tumours were measured along two perpendicular axes in strain images and B-mode images. In both experiments (extracorporeal and intra-operative), normal zones of the liver were also scanned according to the methodology described above.

After the acquisition of the strain images, the animals were euthanised by a single intravenous injection of 5 ml of Doletal® (Vetoquinol, Paris, France). A total hepatectomy was then done to visually inspect the tumours' dimensions. Diameters were measured along two perpendicular axes using a calliper. All images of each technique were interpreted and evaluated independently by three examiners. Each image was examined independently three times by the examiners. All examiners were blinded to the results of each other.

Data analysis

Data are given as mean values $\pm$ standard deviation (minimum value minus maximum value). Measurements of the tumour dimensions obtained via elastography were compared with those obtained using sonograms. To determine the agreement between measurement methods, the intraclass correlation coefficient (ICC) was calculated [27]. The ICC compares the variability of measurements between different measurement methods on the same subject with the total

variability across all methods and all subjects. The ICC ranges between 0 and 1. Values closer to 1 signify within-subject variability smaller than between-subject variability. The agreement between measurements is also presented using Bland–Altman graphs [28].

The quality of elastograms was assessed by computing the contrast-to-noise ratio (CNR_e), which was defined as follows [29]:

$$CNR_e = \sqrt{\frac{2(\varepsilon_T - \varepsilon_B)^2}{\sigma_T^2 + \sigma_B^2}} \quad (1)$$

Here, ε_T and ε_B represent the mean strain in the tumours and in the normal background tissue, respectively, and σ_T^2 and σ_B^2 represent the variances in strain in the corresponding tissue. The ROIs within the tumours were chosen to be as large as possible while confidently remaining within the tumour boundaries. The ROI within the normal liver tissue was chosen close to the tumours. For each data set, the sizes of ROIs (tumours and normal background tissues) were identical.

The quality of elastograms was also assessed by computing the elastographic signal-to-noise ratio (SNR_e), defined as follows:

$$SNR_e = \frac{\varepsilon_T}{\sigma_T} \quad (2)$$

Contrast calculations were also performed using the ROIs that were selected previously for CNR_e calculations. Contrast was calculated using the following equation:

$$C = \left| 20 \times \log \left(\frac{\varepsilon_T}{\varepsilon_B} \right) \right| \quad (3)$$

Contrasts were compared using Wilcoxon tests. The significance level for all tests was fixed at $p < 0.05$. In addition, receiver operating characteristic (ROC) curves were used based on contrast measurements for elastograms and sonograms produced during intra-operative and extracorporeal procedures. ROC curves were used to illustrate the trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity).

Results

Images obtained from the extracorporeal experiments

A typical set of elastograms and the corresponding B-mode images obtained from an extracorporeal approach are shown in Figure 1. In these studies, the ultrasonic speckle patterns in the tumour regions and in the background tissues appeared to be isoechoic and were generally very similar to each other. A slight hypoechoic contour and a central hyperechoic spot were also characteristic of the VX2 tumours. Therefore, visualisation of the tumours in sonograms was very difficult, and only possible by comparing visual differences from a series of several images during the imaging procedure.

Figure 1. Extracorporeal experiments. Sonograms (top row) and the corresponding elastograms (bottom row) of a VX2 tumour in the liver of a rabbit oncology model. White arrows indicate the position of the tumour. Dark regions in the strain images indicate stiff tumour tissue as compared with the soft background. The imaged area was 38×34 mm and a linear greyscale map ranging from 0% to 2% was used for the display of elastograms.

The elastograms delineated the tumours with dark regions with improved contrast and boundaries that were more conspicuous. The mean strains within the tumours ranged from 0.12% to 0.75%. This variability may be explained by the variations in the amplitude of the stress applied during compression, as well as by out-of-plane motions. The computed contrast, CNR_e and SNR_e within tumours for all rabbits are summarised in Table 1 along with the comparisons of tumour dimensions. The contrast of the tumours observed in elastograms (19 ± 6 dB, range 8–24 dB) was significantly higher than the contrast of the tumours observed in sonograms (1 ± 1 dB, range 0–2 dB, $p < 0.05$).

Images obtained from the intra-operative experiments

In general, the quality of elastograms was higher when obtained during the open procedure and showed improved contour detection, improved contrast and

higher correlation with gross pathology. A typical set of elastograms and the corresponding B-mode images obtained from the intra-operative *in vivo* experiments is illustrated in Figure 2. As previously, tumours were isoechoic but delineated by hypoechoic boundaries and hyperechoic central spots. Tumours were delineated by dark regions in the elastograms because the stiffness was associated with low greyscale intensity. It was possible to clearly identify the tumour in elastograms. The mean strains within the tumours ranged from 0.24% to 0.35%. Figure 3 shows a photograph of the tumour visualised in Figures 1 and 2. In two cases, elastograms obtained from both the extracorporeal and the open procedure were able to detect a tumour that was ambiguous in B-mode images (Figure 4). The contrast between tumours and the normal liver in B-mode images was not improved by the intra-operative use of the imaging probe. The contrast of the tumours observed in elastograms (26 ± 10 dB, range 13–40 dB) was significantly higher than the contrast of the tumours observed in sonograms (1 ± 1 dB, range 0–2 dB, $p < 0.05$).

Table 1. Computed contrast, contrast-to-noise ratio (CNR_e) and signal-to-noise ratio (SNR_e) along with the comparisons of tumour dimensions. The average diameter of the tumours measured via gross pathology was 5.9 ± 2.0 mm

Criteria	Elastograms obtained extracorporeally	Elastograms obtained during the open procedure	Sonograms
CNR_e	4 ± 2	9 ± 2	
SNR_e inside tumour	3 ± 1	4 ± 2	
Contrast between tumour and background (dB)	19 ± 6^a	26 ± 10^a	1 ± 1
Average diameter of tumours (mm)	6.3 ± 1.2	6.2 ± 1.9	6.5 ± 1.3 (extracorporeal) 5.4 ± 1.6 (open procedure)
ICC with dimensions measured via gross pathology	0.74^a	0.83^a	0.56 (extracorporeal) 0.68 (open procedure)

ICC, intraclass correlation coefficient.

^aValues were significantly different from the ones obtained using sonograms. The significance level for all tests was fixed at $p < 0.05$.

Figure 2. Intra-operative experiments. Sonograms (top row) and the corresponding elastograms (bottom row) of a VX2 tumour in the liver of a rabbit oncology model. White arrows indicate the position of the tumour. Dark regions in the elastogram indicate stiff tumour tissue as compared with the soft background. The imaged area was 48×34 mm and a linear greyscale map ranging from 0% to 2% was used for the display of elastograms.

Measurement of tumour dimensions

Figure 5 shows Bland–Altman graphs used to evaluate the agreement between methods. Intra-operative elastography offers the more accurate estimation of actual dimensions of the tumours. Average biases were 0.064 [95% confidence interval (CI) = -0.461 to 0.590], -0.029 (95% CI = -0.967 to 0.910), 1.164 (95% CI = -3.208 to 0.879) and 0.486 (95% CI = -3.091 to 4.072) for intra-operative elastography, intra-operative sonograms, extracorporeal elastography and extracorporeal sonograms, respectively. The mean diameter difference between measurements taken by intra-operative elastography and gross pathology was 0.1 ± 0.9 mm. The interobserver variability was 0.2 ± 0.7 mm and the intra-observer variability was 0.2 ± 0.4 mm. In blinded analysis, the image reader correctly identified the presence of tumours in all intra-operative elastograms. One of the eight normal zones was incorrectly classified as a tumour. Sensitivity and specificity for detecting tumours were 100% and 88%, respectively, and positive and negative predictive values were 89% and 100%, respectively. Table 2 summarises sensitivity and specificity, as well as positive and negative predictive values, for all imaging techniques tested in this

study. Figure 6 shows ROC curves used to evaluate the trade-off between sensitivity and specificity for all imaging techniques. Areas under the ROC curves were 0.93 ± 0.03 , 0.77 ± 0.12 , 0.89 ± 0.05 and 0.75 ± 0.07 for intra-operative elastography, intra-operative sonograms, extracorporeal elastography and extracorporeal sonograms, respectively. Intra-operative elastography appears to differentiate well between tumoral and normal liver using contrast information.

Discussion

This study demonstrates the feasibility of performing real-time hand-held elastographic imaging of liver tumours under conditions similar to those found in a clinical setting. Overall, elastography resulted in increased lesion conspicuity and ease of detection. Elastograms were reconstructed at 8 fps with sufficient contrast to delineate the tumours and to gather quantitative information about the strain within the tumour. In our approach, the use of hand-held elastography is intended to provide a complement to standard B-mode images for tumours that are difficult to detect in sonograms. For example, in two cases out of eight, it was possible during the open procedure to identify tumours that were not seen in the sonograms. These tumours were missed because they were isoechoic, with smaller visual differences in the series of images acquired in the cine-loop. Hand-held ultrasound elastography may have a role to play in the detection of isoechoic tumours, which represent about 40% of the tumours encountered in a clinical setting [14].

It has been shown that conventional ultrasonography is particularly useful when applied intra-operatively for imaging liver metastases and has been utilised with great success for many years [30–33]. Propagation of ultrasonic waves is not hindered to any significant degree during liver metastasis surgery because laparotomy is performed prior to data capture. Sterility is preserved by the use of disposable sterile ultrasound covers, which allow for excellent ultrasonic wave transmission. Modern

Figure 3. Photograph of the tumour visualised in Figures 1 and 2. White arrows indicate the position of the tumour.

Figure 4. Sonograms (top) and elastograms (bottom) of a tumour not detected on sonograms. Images obtained using the extracorporeal approach (left) and during the open procedure (right). White arrows indicate the position of the tumour. A linear greyscale map ranging from 0% to 4% was used for the display strain images.

approaches to the treatment of liver tumours require individualised strategies and are largely dependent on diagnostic tools. It is the correct diagnosis and staging that determine further treatment strategy. Therefore, experimental conditions described in the present paper are well suited in the case of liver metastases. The high contrast achievable with elastograms complements the high resolution of tumour boundaries (when visible) in standard B-mode images. Although the contrast between tumour and the surrounding normal tissue was very low in sonograms, tumour dimensions were identified in B-mode images as demonstrated by the correlation with actual dimensions. This may be explained by the fact that many factors other than echo brightness (such as structure texture and visual differences from a series of images) contribute to lesion visibility in B-mode images. The assessment of boundary was primarily based on visual differences between several successive B-mode images. Combining hand-held B-mode/strain imaging is straightforward and allows for the advantages of both modalities to be used in a highly complementary manner. Real-time hand-held strain imaging allowed acceptable measurement of the lesion dimensions, and was a useful complement to conventional sonograms. In addition, advantages of ultrasound include widespread availability, real-time operation, relatively low cost and a lack of ionising radiation.

In clinical settings, liver metastases appear as stiff structures surrounded by more compliant regional liver parenchyma, while primary liver tumours (hepatocellular carcinomas) appear as compliant structures surrounded by relatively stiffer regional liver parenchyma [34, 35]. In our experimental conditions, liver tumours

implanted in rabbits appeared as stiff tissue regions surrounded by more compliant regional liver. This study has demonstrated that VX2 tumours in rabbit liver appear with equal B-mode image contrast to normal liver tissues. This is also the case in a clinical setting for liver metastases that sometimes appear isoechoic. Therefore, experimental conditions are closer to the case of metastatic disease in the liver. In this study, the scanning depth was limited to 4 cm owing to the liver anatomy. In the context of liver surgery for the treatment of liver metastases, it is relevant to work at high frequencies [9] and small scan depth, as the ultrasound probe is placed directly in contact with the liver. Rabbits represent an adequate model for evaluating the use of strain imaging for the visualisation of malignancies in the liver compared with the use of conventional sonography alone.

The results described in this paper highlight that strain images obtained using an extracorporeal approach also allow the detection of tumours, but the quality of elastograms was lower than those acquired during the open procedure. The main difference between strain images obtained extracorporeally or intra-operatively was observed in the detection of contours, which were harder to identify in extracorporeal images. This led to tumour dimensions estimated using the extracorporeal approach that were less correlated with the dimensions measured by gross pathology. A lower contrast was also observed in elastograms produced using the extracorporeal approach. This can be explained by liver movements due to breathing (40–60 breaths per minute). Breathing of the animal in such an extracorporeal approach poses a problem in the form of signal decorrelation due to motion. If not taken into account, this results in degradation of the

Figure 5. Bland–Altman graphs showing agreement between elastograms, sonograms and gross pathology. The differences between measurements are plotted against their means. Horizontal lines represent limits of agreement (± 1.96 standard deviations).

elastograms. Nevertheless, these effects can be reduced by gating the data acquisition within the breathing cycle and/or by speeding up the data acquisition rate. These movements were reduced during the open procedure by manipulating the liver during the acquisition of elastograms.

Intra-operative application of real-time tissue elastography for the diagnosis of liver tumours has been recently reported [36]. In this work, it was shown that the application of real-time elastography in surgical exploration provided significant information about the elasticity of liver tumours. Elasticity images were classified into four types according to the distribution and the degree of the strain contrasted with that of the surrounding liver.

This enables hepatocarcinoma to be distinguished from metastatic adenocarcinoma. In our study we used real-time elastography on an oncological animal model to provide image quality assessment using analyses based on CNR_e , SNR_e and boundary correlations, as well as comparisons with extracorporeal elastography, B-mode images and, importantly, with gross pathology.

There are some limitations to this study. Some elastograms demonstrate variations of strain contrast in tumours (mainly in extracorporeal experiments), which may reflect out-of-plane motions due to breathing or swiping of the transducer at the tissue interface, as well as the internal mechanical structures of tumour with

Table 2. Extracted criteria (sensitivity, specificity, positive and negative predictive values) for all imaging methods

Criteria	Elastograms obtained during the open procedure	Elastograms obtained extracorporeally	Sonograms obtained during the open procedure	Sonograms obtained extracorporeally
Sensitivity (%)	100	75.0	75.0	62.5
Specificity (%)	87.5	62.5	87.5	75.0
Positive predictive value (%)	88.9	66.7	85.7	71.4
Negative predictive value (%)	100	71.4	78	67.0

different stiffness values. Delineating the extent of these variations requires the production of strain images at frame rates higher than the 8 fps used in these studies. At the time of the experiments this was the maximum rate allowed by the system developed in the laboratory. This limitation arises from the RF data transfer rate between the ultrasound scanner and the computer calculating and displaying strain images. Our elastography imaging system is now capable of processing and displaying strain images at the frame rate of the ultrasound scanner (60 fps) [22]. With the improved frame rate, detecting the subtle changes in strain internal to the tumour should be possible, and remains a goal for future studies. In addition, a positive deviation of Bland–Altman graphs may indicate a systematic difference in extracorporeal experiments. The overestimation of tumour size by extracorporeal imaging may be due to intervening tissues with acoustic properties different from those of the liver, changing elevational resolution.

Another problem that could be encountered in the clinic is the generation of strain at depth. The amount of strain required to produce good-quality elastograms was about 1%, corresponding to 0.5 mm displacement using the maximal scan depth of 40 mm used in this study. However, for human liver, which is typically 70 mm thick, application of stress in the deepest region of the organ may be difficult. It is likely to result in a

combination of displacement and compression of the whole liver, as the nearest fixed boundary is the contralateral ribs. Extrapolating our data, displacements of about 0.7 mm in the superficial zones of the liver may be required in order to optimise elastogram generation. The ultrasound imaging probe can be placed at the top of the liver or under the organ when scanning is performed intra-operatively to produce such displacement. However, this may be an important limitation for an extracorporeal use of the technique. Therefore, there remain significant technical challenges to be overcome in the near future prior to using a curvilinear array at 12–14 cm penetration to perform ultrasound elastography in the liver. However, the aim of this study was to quantify the usefulness of real-time elastography for the diagnosis of liver metastases during surgical exploration. The intra-operative approach is routinely used clinically for the staging of liver metastases and overcomes this limitation using the ultrasound imaging probe from the surface or from the bottom of the liver to apply compression.

Data collected in this study show that hand-held elastography improves visualisation of malignancies in the liver compared with the use of conventional sonography alone. Combining hand-held sonography/strain imaging may offer key advantages for visualisation, and possibly interventional guidance for difficult tumours. Elastic contrast in such a combined system would provide

Figure 6. Receiver operating characteristic curves showing the trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity) for (a) elastograms and (b) sonograms produced during intra-operative and extracorporeal procedures.

a clinician with information about tissue mechanical properties while retaining all of the benefits of ultrasound guidance when tumours are difficult to visualise (mainly isoechoic masses, but also tumours located in difficult regions).

In conclusion, we have presented our initial results from *in vivo* studies investigating the utility of combined hand-held sonography/strain imaging for visualising liver metastases. The results of this study demonstrate the feasibility of the method for this application. It is feasible to perform ultrasound elastography intraoperatively (with possible application in resecting liver metastases) or extracorporeally (with possible application for the treatment of primary liver tumours). Features of elastographic images correspond to anatomical images. Elastograms must be visualised with displacement images, correlation images and sonograms to provide useful information. Ultrasound elastography can provide information on tumour extent that was not previously available. Given its low operating costs, real-time capabilities, widespread availability and lack of ionising radiation, combined hand-held sonography with strain imaging may be a useful method for guiding clinical interventions.

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References

- Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9:730–56.
- Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2009;18:1688–94.
- Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *Oncologist* 2008;13:51–64.
- Antoniou A, Lovegrove RE, Tilney HS, Heriot AG, John TG, Rees M, et al. Meta-analysis of clinical outcome after first and second liver resection for colorectal metastases. *Surgery* 2007;141:9–18.
- Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;239:818–25 (discussion: 825–7).
- Ong KO, Leen E. Radiological staging of colorectal liver metastases. *Surg Oncol* 2007;16:7–14.
- Blyth S, Blakeborough A, Peterson M, Cameron IC, Majeed AW. Sensitivity of magnetic resonance imaging in the detection of colorectal liver metastases. *Ann R Coll Surg Engl* 2008;90:25–8.
- Selzner M, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? *Ann Surg* 2004;240:1027–34 (discussion: 1035–6).
- Sietses C, Meijerink MR, Meijer S, van den Tol MP. The impact of intraoperative ultrasonography on the surgical treatment of patients with colorectal liver metastases. *Surg Endosc* 2010;24:1917–22.
- Torzilli G, Del Fabbro D, Palmisano A, Donadon M, Bianchi P, Roncalli M, et al. Contrast-enhanced intraoperative ultrasonography during hepatectomies for colorectal cancer liver metastases. *J Gastrointest Surg* 2005;9:1148–53.
- Conlon R, Jacobs M, Dasgupta D, Lodge JP. The value of intraoperative ultrasound during hepatic resection compared with improved preoperative magnetic resonance imaging. *Eur J Ultrasound* 2003;16:211–16.
- Gleisner AL, Choti MA, Assumpcao L, Nathan H, Schulick RD, Pawlik TM. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. *Arch Surg* 2008;143:1204–12.
- Charboneau JW, Reading CC, Welch TJ. CT and sonographically guided needle biopsy: current techniques and new innovations. *AJR Am J Roentgenol* 1990;154:1–10.
- Choti MA, Kaloma F, de Oliveira ML, Nour S, Garrett-Mayer ES, Sheth S, et al. Patient variability in intraoperative ultrasonographic characteristics of colorectal liver metastases. *Arch Surg* 2008;143:29–34.
- Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging* 1991;13:111–34.
- De Zordo T, Lill SR, Fink C, Feuchtnner GM, Jaschke W, Bellmann-Weiler R, et al. Real-time sonoelastography of lateral epicondylitis: comparison of findings between patients and healthy volunteers. *AJR Am J Roentgenol* 2009;193:180–5.
- Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, et al. Breast disease: clinical application of US elastography for diagnosis. *Radiology* 2006;239:341–50.
- Kanamoto M, Shimada M, Ikegami T, Uchiyama H, Imura S, Morine Y, et al. Real time elastography for noninvasive diagnosis of liver fibrosis. *J Hepatobiliary Pancreat Surg* 2009;16:463–7.
- Zhu QL, Jiang YX, Liu JB, Liu H, Sun Q, Dai Q, et al. Real-time ultrasound elastography: its potential role in assessment of breast lesions. *Ultrasound Med Biol* 2008;34:1232–8.
- Melodelima D, N'Djin A, Parmentier H, Chesnais S, Rivoire M, Chapelon JY. Ultrasound surgery with a toric transducer allows the treatment of large volumes over short periods of time. *Appl Phys Lett* 2007;91:193901.
- Melodelima D, N'Djin WA, Parmentier H, Chesnais S, Rivoire M, Chapelon JY. Thermal ablation by high-intensity-focused ultrasound using a toroid transducer increases the coagulated volume: results of animal experiments. *Ultrasound Med Biol* 2009;35:425–35.
- Chenot J, Melodelima D, N'Djin WA, Souchon R, Rivoire M, Chapelon JY. Intra-operative ultrasound hand-held strain imaging for the visualization of ablations produced in the liver with a toroidal HIFU transducer: first in vivo results. *Phys Med Biol* 2010;55:3131–44.
- Kidd JG, Rous P. A transplantable rabbit carcinoma originating in a virus-induced papilloma and containing the virus in masked or altered form. *J Exp Med* 1940;71:813–38.
- Zahiri-Azar R, Salcudean SE. Motion estimation in ultrasound images using time domain cross correlation with prior estimates. *IEEE Trans Biomed Eng* 2006;53:1990–2000.
- Luo J, Konofagou E. A fast normalized cross-correlation calculation method for motion estimation. *IEEE Trans Ultrason Ferroelectr Freq Control* 2010;57:1347–57.
- Srinivasan S, Ophir J, Alam SK. Elastographic imaging using staggered strain estimates. *Ultrason Imaging* 2002;24:229–45.
- Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420–8.
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–10.

29. Chaturvedi P, Insana MF, Hall TJ. Testing the limitations of 2-D companding for strain imaging using phantoms. *IEEE Trans Ultrason Ferroelectr Freq Control* 1998;45:1022–31.
30. Torzilli G, Procopio F, Botea F, Marconi M, Del Fabbro D, Donadon M, et al. One-stage ultrasonographically guided hepatectomy for multiple bilobar colorectal metastases: a feasible and effective alternative to the 2-stage approach. *Surgery* 2009;146:60–71.
31. Mazzoni G, Napoli A, Mandetta S, Miccini M, Cassini D, Gregori M, et al. Intra-operative ultrasound for detection of liver metastases from colorectal cancer. *Liver Int* 2008; 28:88–94.
32. Wildi SM, Gubler C, Hany T, Petrowsky H, Clavien PA, Jochum W, et al. Intraoperative sonography in patients with colorectal cancer and resectable liver metastases on pre-operative FDG-PET-CT. *J Clin Ultrasound* 2008;36:20–6.
33. Hagspiel KD, Neidl KF, Eichenberger AC, Weder W, Marincek B. Detection of liver metastases: comparison of superparamagnetic iron oxide-enhanced and unenhanced MR imaging at 1.5 T with dynamic CT, intraoperative US, and percutaneous US. *Radiology* 1995;196:471–8.
34. Yeh WC, Li PC, Jeng YM, Hsu HC, Kuo PL, Li ML, et al. Elastic modulus measurements of human liver and correlation with pathology. *Ultrasound Med Biol* 2002;28:467–74.
35. Fahey BJ, Nelson RC, Bradway DP, Hsu SJ, Dumont DM, Trahey GE. In vivo visualization of abdominal malignancies with acoustic radiation force elastography. *Phys Med Biol* 2008;53:279–93.
36. Kato K, Sugimoto H, Kanazumi N, Nomoto S, Takeda S, Nakao A. Intra-operative application of real-time tissue elastography for the diagnosis of liver tumours. *Liver Int* 2008;28:1264–71.