Computer-Aided Solutions for the Assessment of Focal Liver Lesions in Contrast-Enhanced Ultrasound

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The fifth most common type of cancer worldwide is a focal liver lesion (FLL) [1], which constitutes 70-90% of primary liver cancer cases [2], with over 500,000 incidents per year [3]. FLLs refer to specific type of abnormalities of the liver, depicted as focal/ellipsoidal regions [4]. Thus, any 2D slice of an FLL, results in an approximately elliptical shape. FLLs are solid or liquid-containing nodules foreign to the normal liver anatomy, and can be classified as either relatively harmless lesions (benign), or progressively worsening lesions that can potentially result in death (malignant).

The potential for the early distinction between a malignant and a benign FLL is of significant importance as, if a malignancy (~25% of FLLs assessed in the UK [5]) is diagnosed sufficiently early, there is an enhanced possibility of non-surgical therapeutic intervention and healing. On the other hand, early diagnosis of a benignity (~75% of FLLs assessed in the UK [5]), leads to the earlier discharge of the patient [4] due to the FLL not requiring treatment, and hence leads to reduced distress to patients and their families [6], as well as reduced healthcare costs [5].

Currently, the accepted diagnostic pathway followed as the standard care protocol for liver imaging starts with an initial appointment, where a conventional (B-mode) US scan is made [4]. During such a scan, potential FLL candidates may be detected but cannot be classified as benign or malignant, due to low spatial resolution and low signal-to-noise ratio. As a consequence of such an inconclusive scan, the patient is referred for additional follow-up screening, using a contrast-enhanced (CE) technique, based on either computed tomography (i.e. CE-CT), or magnetic-resonance imaging (CE-MRI), or ultrasound (CEUS).

Contrast-enhanced ultrasound

Contrast-Enhanced Ultrasound (CEUS) is a technique based on medical ultrasound but which requires the intravenous injection of non-nephrotoxic contrast-enhancing material [7]. This material offers a brightness enhancement to the apparent blood flow, and thus increases the contrast between the FLL and its surrounding healthy tissue, i.e. the parenchyma.

CEUS has gained acceptance for use in the detection and characterisation of very small FLLs, leading to rapid and appropriate clinical care [1, 8, 9], as it can often be carried out during the same appointment as the initial US scan, which can be critical for effective treatment. According to radiological studies, CEUS shows a significant improvement in sensitivity and specificity over CT and MRI [10], and its diagnostic accuracy for the evaluation of malignant FLLs is higher than 95% [11]. Furthermore, it is recognised as the most cost-efficient imaging solution for classifying an FLL as benign or malignant [5,10], since it is easy to perform, and uses portable and relatively low cost equipment that

Figure 1. Example of the brightness intensity changes over the duration of the three phases of a CEUS examination. The blue and the red curves describe the average intensity of the regions of the FLL and the parenchyma, respectively. The current example illustrates the behaviour of a lesion with hyper-enhancing behaviour during the arterial phase (intensity increase within FLL prior to parenchyma) and hypo-enhancing behaviour during the late phase (intensity decrease in the FLL prior to the parenchyma). Such behaviour is typical for a malignant FLL.

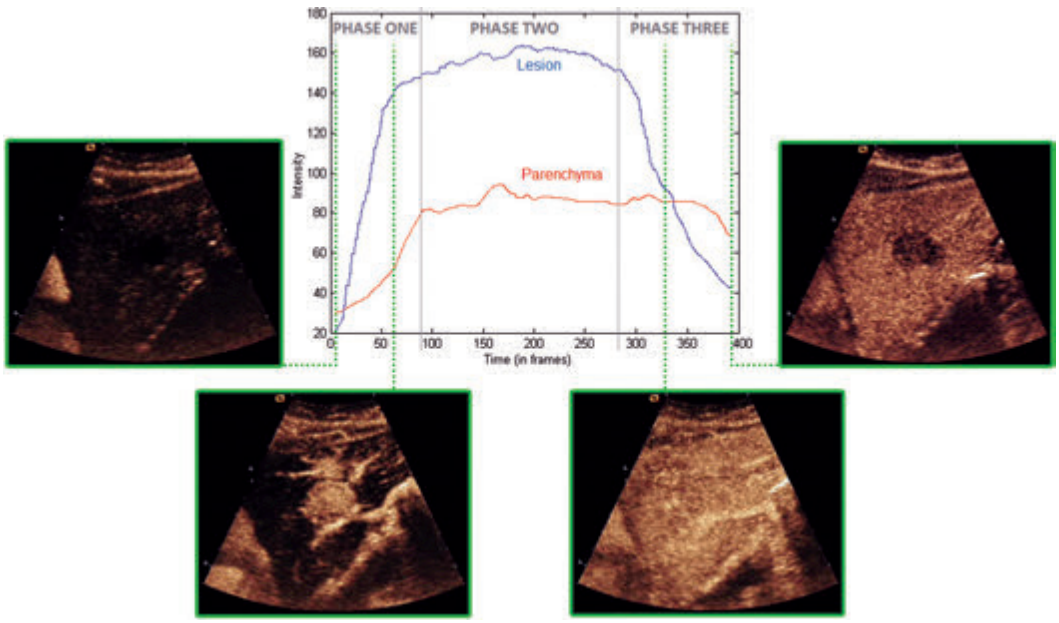
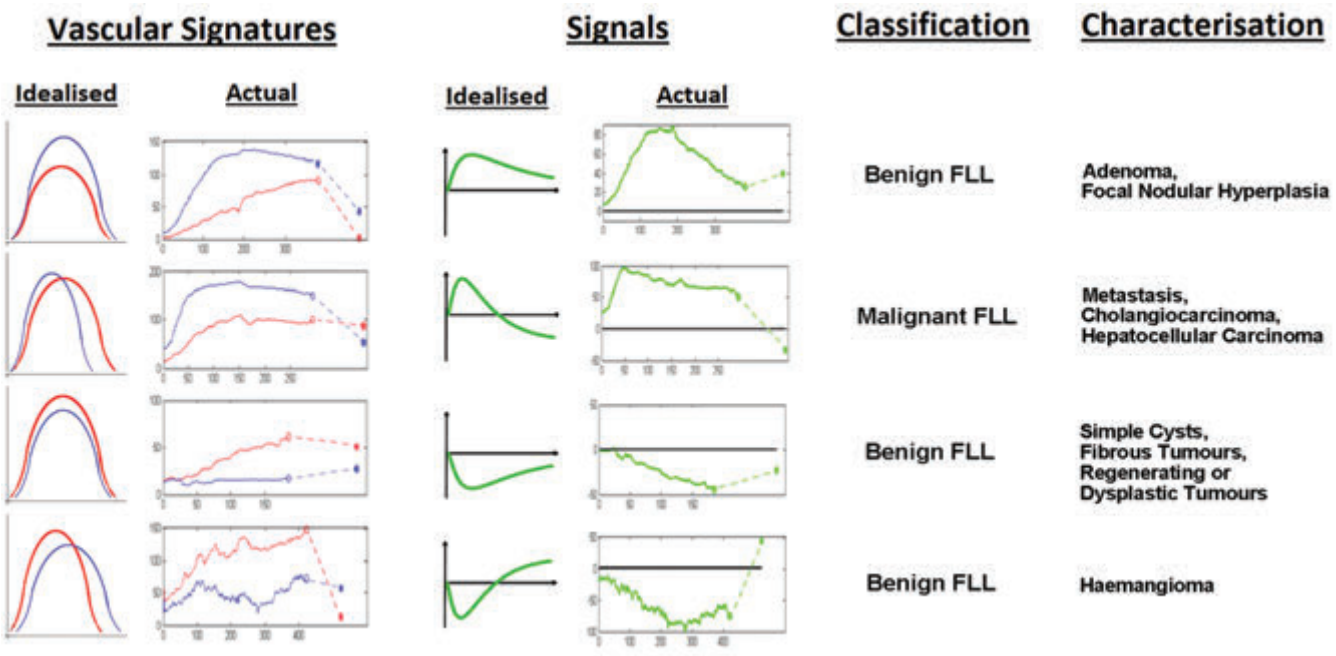


Figure 2. Schematic examples of the four major vascular signatures with their corresponding "signals", for FLL classification. In the first two columns of graphs, the blue curves depict the temporal profile of the brightness intensity of the FLL, while the red curves show the corresponding profile for the parenchyma. In the second pair of columns, the FLL "signals" are depicted, which are derived by subtracting the red curve from the blue curve. The dashed line is used for the period between the end of the acquired video (solid curve) and the acquisition of the static image in the late phase (the final single dot). Finally the last two columns on the right depict the corresponding classifications and potential characterisations into different medical conditions, respectively.



allows its presence in every clinic and even at the bedside. Additionally, the philosophy of the use of CEUS is bound with the European campaign "EuroSafe Imaging" [12] to reduce the radiation burden on the population from medical imaging – particularly for child and young adult patients – and is consistent with the 'ALARA' ("As Low As Reasonably Achievable") principle for radiation dosage [13].

A CEUS liver scan is divided into three different phases over time (Figure 1), whose durations vary mainly depending on the physiopathology of the patient's liver and heart. Typically, the data acquired during such a scan comprise a video sequence covering the whole first (arterial) phase and part of the second (portal venous) phase, as well as at least one static image of the third (late) phase. Recording the brightness intensity changes for different tissues during a CEUS scan allows estimation of the perfusion dynamics of these tissues. These perfusion curves lead to the differentiation of the nature of the tissues [10]. Specifically, the difference of perfusion between an FLL and its surrounding parenchyma over time allows for the distinction between a benign and a malignant FLL due to their different dynamic behaviour (Figure 2).

Current Clinical Practice

The current methodology for evaluating the behaviour of FLLs is the offline manual assessment and interpretation of CEUS examination data. Although CEUS is such an effective technique, interpretation of its data is a highly time-consuming process, requires extensive input and a high-level of expertise from specially trained radiologists and still leads to subjective (operator-dependent) results, which are prone to misinterpretation and human error [10]. Currently, such assessments are performed through a series of tasks, namely, i) identification of a reference frame in the video sequence where the FLL is sufficiently represented and well-distinguished from the parenchyma, ii) manual annotation of the FLL boundaries in this reference frame, iii) observation of the temporal dynamics of the perfusion (i.e. dynamic behaviour) of the tissues, iv) classification of the FLL as benign or malignant, and the characterisation of its exact nature, e.g. Adenoma, Cyst, Haemangioma.

Proposed solutions

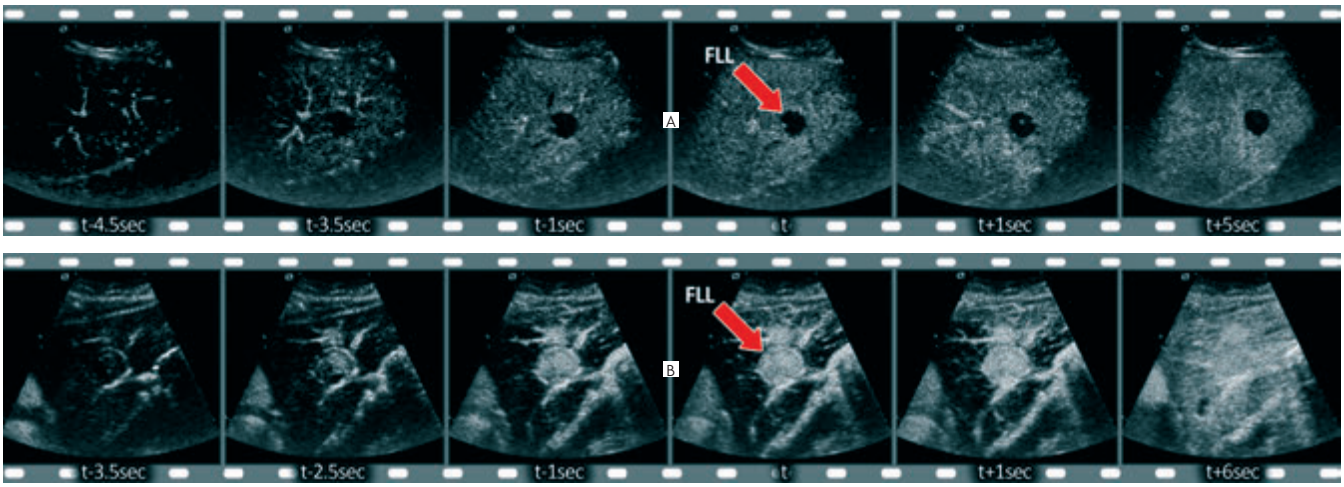
Several contributions have been made over recent years towards understanding, quantifying and automating the assessment of the dynamic behaviour of FLLs, especially when observed using CEUS. The fields of image feature extraction, image segmentation, motion estimation, statistical analysis and machine learning have been investigated to develop novel non-invasive automated computational algorithms, able to improve the current clinical practice, and support clinicians make their evaluations faster, more easily, more objectively and with greater confidence, whilst helping to improve the repeatability and reproducibility of the assessment of such CEUS examination data.

Firstly, we proposed a deterministic fully automatic method [14], for the first task of identifying the optimal reference frame, where an FLL is well-distinguished from the parenchyma and well-represented in the image plane (Figure 3). The method is based on the hypothesis that the optimal reference frame for initialising an FLL occurs when high contrast between the regions of the FLL and the parenchyma is obtained. The method assesses the root mean square contrast [15] of the brightness intensity values of local neighbourhoods within the ultrasonographic image (US mask), for each frame, and suggests as the reference frame, the one where this measure is maximised, hence have similar contrast to the frame suggested by radiologists.

Subsequently, we proposed a fast semi-automatic solution for identifying the FLL boundaries in a reference frame of a CEUS recording, initialised only by the sole input of a single seed point [16,17]. An initial approximation of the FLL is estimated by an improved active ellipse model that uses rectangular force functions to iteratively contract and expand. A novel boundary refinement method is then applied to iteratively classify boundary pixels rapidly, according to a probabilistic model, which outperforms existing iterative approaches, such as the fastest Level Set method [18], in terms of both accuracy and computational efficiency.

Furthermore, the assessment of the haemodynamic status of an FLL, during of a CEUS recording, requires the compensation of

Figure 3. Examples of FLLs. (A) and (B) illustrate the haemodynamic behaviour of a hypo- and a hyper-enhancing FLL, which are the behaviours of benign and potentially malignant FLLs, respectively. The example frames show the behaviour observed in the whole liver from the time that the injected contrast medium reaches the liver (first frame) until the stabilisation of the intensity increase (last frame), including the reference frame (at time t), as chosen by the method proposed in [24]. Note that the appearance of the FLL is essentially the same in frames immediately around the reference frame (±1sec), but the FLL may be indistinguishable from the parenchyma at the beginning, or at the end, of this sequence.



the relevant motion between the transducer and the patient to allow for the accurate quantification of the perfusion of the FLL and the parenchyma, leading to the classification of FLLs as benign or malignant. Reviewing the literature reveals approaches that use manual annotations of ROIs in all acquired frames [19-21], others that carefully selecting videos with minimal apparent motion [22,23], and others accounting for automated motion correction [24-26]. We proposed methods for accurate automated motion correction [27-30] and performed an extensive analysis of various direct [31] and feature-based [32] methods for motion compensation. Compact and Real-time Descriptors (CARD) [33] were found to be the optimal method for compensating for motion in CEUS recordings [34].

Finally, we proposed a deterministic fully automatic methodology for distinguishing between potentially malignant and benign cases, by holistically assessing the global spatial configuration of local variations of perfusion curves within the US mask [35]. The only input for this distinction is a video sequence entailing at least the entire duration of the arterial phase. Regions of potential malignancy within the US mask are also localised in [35], by exploiting the perfusion dynamics of different tissues. This is achieved by extracting a novel low-dimensional feature vector that encompasses information of a region's dynamic behaviour during the provided video sequence and combines it with the region's location information, to identify and group together neighbouring regions with almost identical dynamic behaviour through clustering. Providing a prompt response to the radiologist, by identifying areas of potential interest (e.g. malignancies) and characterising specific areas selected by the radiologist, is expected to further increase the confidence of the radiologists when making a diagnosis.

Potential clinical contributions

To summarise the effectiveness of the proposed algorithms in a meaningful way, the solutions proposed by our group [14,16,17, 27-30,34,35] have all been quantitatively evaluated on real clinical data from a retrospective multi-centre study, leading to the potential of them being applied in the current diagnostic pathway of standard care. Specifically, the obtained results show comparable performance to those achieved through the manual process, but with more objectivity and fewer interactions, i.e. the proposed methods can be carried out faster and more easily.

Specifically, through the proposed fully automatic pipelines for both the initialisation of the FLL assessment [14, 16, 17], the early diagnosis of patients with benign FLLs and the objective localisation of potential malignancies [35], an improved repeatability and reproducibility of the assessment of the examination is achieved, compared to the current manual pathway, implying greater confidence on the reliability of the diagnostic decision. Furthermore, lower healthcare costs [5] and reduced distress to the patients and their families [6], can be achieved through the deterministic fully automatic early diagnosis and discharge of patients with benign FLLs. Providing a prompt response to the radiologist, by automatically localising potential malignancies may increase the radiologist's awareness of such regions within the US mask, that they might otherwise have missed, or even assist in the training of inexperienced radiologists. Monitoring, and quantification of, the dynamic behaviour of FLLs during CEUS video sequences can enable radiologists to further investigate specific parameters of groups of lesions. Finally, all of these proposed solutions help towards reducing the time required by radiologists to assess FLLs offline in CEUS data from several minutes to a few seconds, and reduce their effort accordingly.

Future directions

The issue of the FLL's apparent motion across the 2D image plane, instead of within, is still an unsolved problem. The solution of this would allow for a more refined accurate quantification of the FLL's perfusion, and could form the basis for characterising FLLs to their exact nature, e.g. Adenoma. Machine learning algorithms can be employed to model the behaviour of individual FLLs, either in the spatial or in the temporal domain, by assessing either the enrichment patterns of the FLL's micro-vasculature [8,10], or by parameterising the FLLs' perfusion curves (Figure 4), respectively.

Clinical expertise provided from King's College Hospital in London, UK, and Evgenidion Hospital in Athens, Greece, will assess the effectiveness and acceptability of the proposed methods from the perspective of their clinical value.

Conclusions

Offline assessment of CEUS examination data is essential for diagnosis, staging, treatment planning, and follow-up of FLLs. This article has discussed research

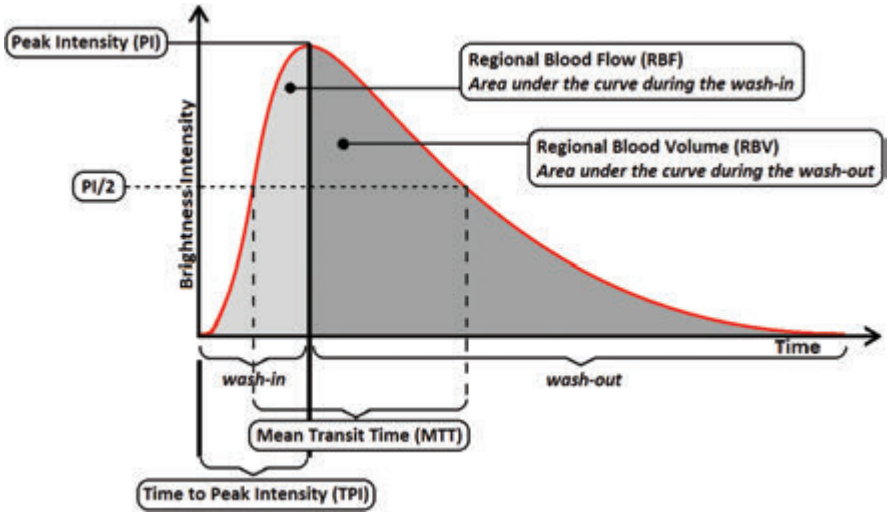


Figure 4. Visualisation of the perfusion parameters typically used by radiologists to describe different aspects of a ROI's perfusion and to determine its functional features. The 'Peak Intensity' (PI) is the highest intensity value of the perfusion curve. The 'Time to Peak Intensity' (TPI) denotes the duration from time zero (the start of the sequence) to the time when PI is reached. The 'Regional Blood Flow' (RBF) is estimated from the integral of the curve from time zero until TPI, whereas the 'Regional Blood Volume' (RBV) is estimated from the integral of the curve, from TPI until the complete wash-out. The 'Mean Transit Time' (MTT) is the interval from the time that the intensity first reaches 50% of the PI during its increase until it again reaches 50% of the PI during its decrease.

conducted on computer-aided solutions for the assessment, quantification and evaluation of FLLs in CEUS screening recordings, in an attempt to improve healthcare by bringing closer together the computational capability to medical experts and their anatomical knowledge.

Quantitative analysis of all results on real clinical data from a multi-centre study was used to evaluate the level of confidence of the decision of the proposed solutions and demonstrated the value of these methods in a diverse dataset acquired using the current standard care protocol.

The proposed methods have contributed to both expanding previous work and opening up new research directions towards the automation of image interpretation tasks routinely performed manually by radiologists in the clinical environment.

The aim is to assist clinicians assess and evaluate FLLs faster, more easily and more objectively, whilst producing results less dependent on human initialisation and therefore increasing confidence in their diagnostic decisions. Application of the proposed methods in clinical practice may assist in the creation of standardised criteria for quantification in clinical imaging, avoiding operator-dependent results, and therefore aid in the widespread utilisation of CEUS, even in non-specialist centres and clinics, leading to minimal turnaround times, lower costs to healthcare services and less patient distress.

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