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● *Original Contribution*

AUTOMATIC IDENTIFICATION OF THE OPTIMAL REFERENCE FRAME FOR SEGMENTATION AND QUANTIFICATION OF FOCAL LIVER LESIONS IN CONTRAST-ENHANCED ULTRASOUND

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Abstract—Post-examination interpretation of contrast-enhanced ultrasound (CEUS) cineloops of focal liver lesions (FLLs) requires offline manual assessment by experienced radiologists, which is time-consuming and generates subjective results. Such assessment usually starts by manually identifying a reference frame, where FLL and healthy parenchyma are well-distinguished. This study proposes an automatic computational method to objectively identify the optimal reference frame for distinguishing and hence delineating an FLL, by statistically analyzing the temporal intensity variation across the spatially discretized ultrasonographic image. Level of confidence and clinical value of the proposed method were quantitatively evaluated on retrospective multi-institutional data (n = 64) and compared with expert interpretations. Results support the proposed method for facilitating easier, quicker and reproducible assessment of FLLs, further increasing the radiologists' confidence in diagnostic decisions. Finally, our method yields a useful training tool for radiologists, widening CEUS use in non-specialist centers, potentially leading to reduced turnaround times and lower patient anxiety and healthcare costs. (E-mail: s.bakas@kingston.ac.uk or s.bakas@uphs.upenn.edu or s.bakas@gmail.com) © 2017 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Contrast-enhanced ultrasound, Focal liver lesions, Computer-aided detection, Reference frame, Automation, Reproducibility, Liver cancer, Ultrasound, Contrast agents.**

INTRODUCTION

Contrast-enhanced ultrasound (CEUS) is an extension of the basic ultrasound (US) technique, which requires an intra-venous injection of a contrast-enhancing agent that provides enhancement of the blood pool and allows for the distinction of a focal liver lesion (FLL) from the surrounding liver parenchyma, by increasing their contrast (Chiorean et al. 2015; Harvey et al, 2001, Mischi et al. 2014; Quaia 2007). CEUS performed immediately following a B-mode US examination often allows immediate diagnosis and appropriate patient management. CEUS has gained acceptance for use in the detection and characterization of FLLs (Dietrich et al. 2006; Llovet et al. 2003, 2005; Quaia 2011b, 2012; Sidhu 2014; Sporea et al. 2010; Wilson and Burns 2010), with a comparable sensitivity and specificity to computed tomography (CT) and magnetic resonance (MR) imaging (Claudon et al. 2013). Recently, CEUS using Lumason/SonoVue (Bracco Diagnostics, Milan, Italy) has been approved for diagnostic liver imaging in the United States (Seitz and Strobel 2016). The diagnostic accuracy of CEUS for the evaluation of malignant FLLs is >95% (Strobel et al. 2009; Westwood et al. 2013). Furthermore, CEUS is recognized as the most cost-efficient imaging solution for distinguishing between benign and malignant FLLs (Claudon et al. 2013; Westwood et al. 2013), using portable and relatively

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low-cost equipment (Sirli et al. 2010) that allows it to be available widely and even at the patient's bedside.

Despite these advantages, post-examination interpretation of the CEUS cineloops is a time-consuming and labor-intensive process, based on manual assessment of the acquired data by highly experienced and specially trained radiologists. However, this assessment leads to subjective results (Claudon et al. 2013) and is dependent on the clinician's experience when acquiring the data, independent of the patient's physiologic status and breathing patterns. Initially, the radiologist reviews the entire recorded sequence to identify a reference frame manually, by visual observation, where the FLL is sufficiently well distinguished from the parenchyma and well defined within the US image, which we refer to as the *workspace* (Fig. 1). Ideally, this frame is expected to demonstrate maximum contrast between the two regions of interest (ROIs) (*i.e.,* the FLL and the parenchyma) and to facilitate their differentiation. This is usually done during the initial *arterial* phase of the examination. Because of the variety of vascular enhancement patterns of FLLs (Albrecht et al. 2004; Anaye et al. 2011; Brannigan et al. 2004; Claudon et al. 2013; Nicolau et al. 2006; Sugimoto et al. 2009; Wilson and Burns 2006), it is not straightforward to specify a fixed time window to predict robustly the point in time at which the maximum contrast will be achieved for any particular case, either as an actual time interval or as a constant fraction of the whole duration of the examination.

The aim of this study is to detect automatically and deterministically the optimal reference frame in a CEUS FLL screening recording where the two ROIs are best distinguishable, hence to assist the radiologists and allow for the segmentation and eventually the quantification of these ROIs. However, neither of these ROIs are localized before identifying the reference frame, therefore direct measurement of the contrast between them is impossible. The automatic computational approach proposed here investigates how the variation of intensity across the workspace changes through time, after spatially discretizing the workspace into local patches, in an attempt to imitate the manually performed procedure and bring the benefits of computational analytics closer to medical experts and their anatomic knowledge. A CEUS FLL screening recording is assumed to be captured in CEUS mode, after the injection of the contrast agent and with the transducer focused on the liver area.

MATERIALS AND METHODS

Materials

Data. The clinical data used for evaluating the proposed method describe retrospectively analyzed cohorts acquired with different protocols from 2 independent

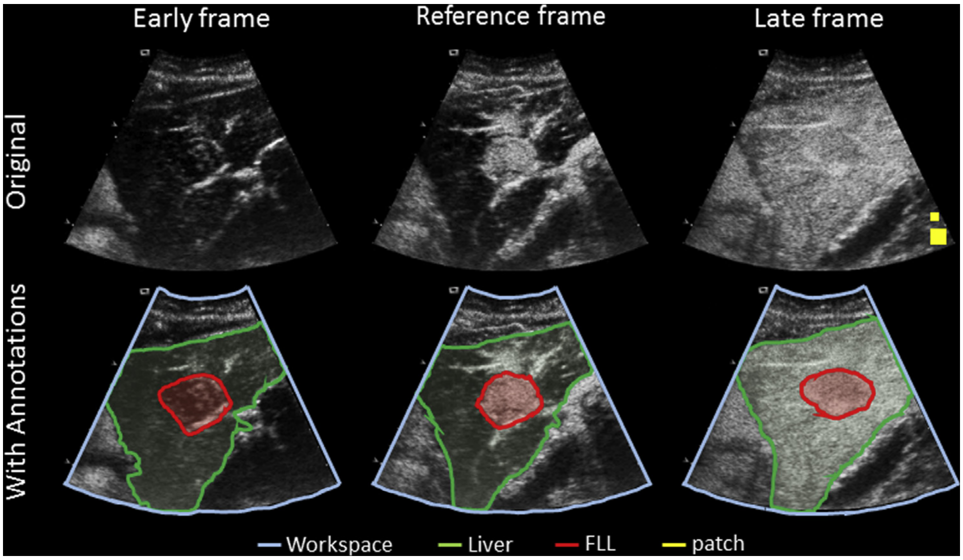

Fig. 1. Example frames for the same clinical CEUS cineloop. The top row of images illustrates the original frames; whereas the bottom row of images have included annotations attempting to approximate the boundaries of the lesion and the surrounding parenchyma, whilst accounting for visible deformations in the image plane. The *early frame* does not depict the lesion or its boundaries at all clearly. The *reference frame* is the radiologist's decision on the frame for the focal liver lesion initialization, where it is sufficiently well distinguished from the normal parenchyma and well defined in the image plane. In the *late frame*, the area surrounding the lesion has become isoechoic to the lesion and so is no longer well defined. The two *yellow* patches shown in the *Original Late frame* denote examples of 32 × 32 and 16 × 16 pixels in size. CEUS = contrast-enhanced ultrasound.