Evaluation of 3D Deformable Registration to Improve Subtracted Dynamic Contrast Enhanced Liver Images for Characterization of Treated Hepatocellular Carcinoma

Dinesh K. Sundarakumar[1], Gregory J. Wilson[1], Sherif Osman[1], and Jeffrey H. Maki[1]
[1]*Radiology, University of Washington, Seattle, WA, United States*

Introduction: Subtraction images are an integral part of routine multiphasic dynamic contrast enhanced magnetic resonance imaging (CE-MRI) examinations of the liver. These are particularly useful for characterizing enhancement of intrinsically T1 hyperintense lesions such as some hepatocellular carcinomas (HCC) and regenerative/dysplastic nodules, as well as many ablated HCCs. The liver undergoes considerable displacement and, to a lesser extent, elastic deformation due to variations in breath-holding between phases. This results in misregistration artifacts on subtraction images, which are particularly problematic when evaluating subcapsular lesions and lesions smaller than 2 cm [1]. The purpose of this study was to quantify hepatic displacement occurring between different breath-holds in multiphasic contrast-enhanced MRI of the liver, and to evaluate the role of a fully automated 3D registration algorithm on the quality of subtracted images.

Methods: A retrospective analysis identified 25 consecutive cirrhotic patients (20 male/5 female, 35-72 years) with a treated hepatocellular carcinoma (HCC) and at least one coexisting small T1 hypointense hepatic cyst. Breath hold dynamic 3D mDIXON datasets (Achieva 1.5T, Philips Healthcare, Best, NL) were transferred to a FDA approved dedicated Liver Workstation (CADStream^{TM} Version: 5.3.1.218, Merge, Chicago, IL) and registered native and subtraction images were created using the CADStream's fully automated 3D deformable registration algorithm (Fig. 1). The algorithm evaluated incorporates a combination of rigid and isotropic elastic non-rigid transformation using feature-based detection and matching methods which are independent of the image intensity [2,3], and therefore not influenced by implicit signal intensity data (which is the actual variable of interest in dynamic hepatic MRI). By default, this software registers pre-contrast, arterial and equilibrium phase data to the portal venous phase (Fig. 1). The relative displacement of cysts occurring over the 4 dynamic phases was used as an estimate of hepatic displacement pre- and post registration. Pre/post registration displacements and subtraction "band" artifacts (SBA) were evaluated by paired T-test. Subtraction image quality (5 point scale, blinded observer) for treated HCC (IQ) and global subtraction artifact level (SQ) of the subtraction images pre- and post registration were compared using the Wilcoxon signed rank test.

Findings: Twenty-five treated HCCs (average size: 2.8 cm, range 1.5 - 8.9 cm) were analyzed (one per patient). 13 such lesions were intrinsically T1 hyperintense, and 12 T1 hypointense. Eighteen of the 25 (72%) were subcapsular, with 7 (28%) central. Fifteen HCCs (60%) were located in the same segment as the cyst that was used as the marker for motion evaluation.

The average total displacement (c/w portal venous phase) was significantly less for the post- vs. pre-registered images; (non-contrast, arterial, delayed) 2.4, 1.6, 1.3 mm *vs.* 4.0, 3.2 and 4.6 mm respectively ($p < 0.01$). Breaking down average displacements by axis, craniocaudal (CC) improvement was greatest: 2.6 *vs.* 0.8 mm, with medio-lateral (ML) and anterior-posterior (AP): 1.3 *vs.* 0.7 and 1.5 *vs.* 0.8 mm pre- vs. post-registration respectively. The reduction in CC displacement was statistically significant in all three dynamic phases.

The IQ and SQ scores for the post-registered subtracted images were significantly better compared with pre-registration: 4.4 *vs.* 3.4 and 4.6 *vs.* 3.3 respectively ($p < 0.01$). SBA for the pre- *vs.* post-registered subtraction images decreased from 5.3 to 2.4 mm, 6.1 to 2.6 mm, and 5.2 to 2.8 mm for arterial, PV, delay respectively ($p < 0.01$).

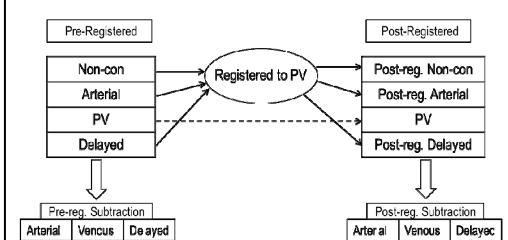

Figure 1. Schema of operations. Registration of other phases to portal venous phase (PV) results in post-registered (Post-reg) series. Note that the portal venous phase itself remains unchanged. The Post-reg subtracted series generated by the workstation uses Post-reg Non-con (post registered non-contrast) phase as mask image.

Discussion: This study demonstrated considerable hepatic displacement (averaging 4-5 mm, but ranging up to 15 mm) in all patients due to inconsistencies in diaphragmatic/liver positioning during repeated breath-holds. Displacements were, as expected, greatest in the cranio-caudal (CC) direction, but also more pronounced on the delayed phase - likely relating to the lengthy delay (approximately 5 minutes) following the earlier scans (relatively rapid back-to-back non-contrast, arterial, portal venous). After registration, mean displacement decreased by a factor of 3 for CC and near 2 for ML and AP.

Displacements confined to the cranio-caudal axis can, in principle, be registered by a purely rigid z-axis transformation. But both AP and ML displacements were found to be sizable, and would be expected to cause subtraction artifact without registration. The investigated algorithm achieved significance for reduction of AP and ML displacements in the arterial and delayed phases.

Registration prior to subtraction led to considerable improvement in subjective HCC assessment confidence (IQ). Additionally, there was a significant decrease in subtraction band artifacts (SBA) along the liver margin, allowing for improved assessment of the subcapsular regions, especially in the dome and inferior margins (Fig. 2). Similarly, the overall subtraction artifacts (SQ) within the liver significantly decreased, in part due to the associated decreased misregistration of intrahepatic structures such as vessels. In 23 out of 25 cases, registration successfully mitigated subtraction artifacts. In our study, 17 out of 25 (68%) HCC lesions were subcapsular, and in the majority of cases were well-characterized post-registration (in 12 of 17 cases, the diagnostic confidence grade improved from 3 to 4 or 5; in 4 of 17 cases the grade improved from 4 to 5; in one case it remained grade 5 after registration) due to significant reduction in subcapsular subtraction artifacts. This may in part explain the significant subjective improvement in registered subtraction diagnostic confidence in lesion depiction, with the above mentioned limitations at least partly overcome by registration. Finally, any false positive enhancement (often seen in cysts on subtraction images) resolved after registration, further suggesting the potential role for registration in the evaluation of small hepatic lesions.

Figure 2. Effects of "Band" artifact (SBA) on the characterization of subcapsular lesions. **A-D,** Subtracted pre-registered arterial (**A**) and venous (**B**) images show misregistration of perinephric fat in segment 6 causing false positive (in venous phase) enhancement in the treated HCC (arrow) as well as obscuring a small cyst (curved arrow) in the same segment. No band artifacts are noted in the post-registered arterial (**C**) and venous (**D**) subtracted images. Thin linear enhancement is noted around the treated HCC (white-arrow, C) and no enhancement is seen in the cyst (curved arrow).

Conclusion: Application of automated registration of liver in multiphasic MR examination reduces phase-to-phase hepatic displacement and resulting lesion misregistration artifacts in subtraction images. Readers expressed significantly improved diagnostic confidence in the post-registered subtractions. Further study is warranted to evaluate the full impact of non-rigid registration on lesion characterization.

References: 1) Yu et al. *J Comput Assist Tomogr* 2005; 29:51-58. 2) Rajaraman et al. *Magn Reson Imaging* 2011; 29:668-682. 3) Melbourne et al. *Phys Med Biol* 2007; 52:5147-5156.