

Quantitative Imaging Analysis to Guide Biopsy for Molecular Biomarkers

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Abstract

Although resection and transplantation are primary curative methods of treatment for hepatocellular carcinoma, many patients are not candidates. In these cases, other treatment methods such as selective internal radiation therapy, chemotherapy, or external beam radiation are used. While these treatments are effective, patient-specific customization of treatment could be beneficial. Recent advances in personalized medicine are making this possible, but often there are multiple phenotypes within a proliferating tumor. While not standard, one could envision a serial longitudinal biopsy approach with more phenotypically-targeted therapeutics if one could detect responding and non-responding regions of tumor over time. This work proposes a method to determine active regions of the tumor that differentially respond to treatment to better guide biopsy for longitudinal personalization of treatment. While PET may serve this purpose, it is not easily used for real-time image guidance, is not effective for many types of tumors, and can be confounded by inflammatory responses. In this work, ten total patients with imaging sequences from before and after treatment were retrospectively obtained. Five of these were selected for analysis based on the total liver volume change. A two-phase alignment process comprised of an intensity-based rigid registration followed by a nonrigid refining process driven by bulk deformation of the organ surface was performed. To assess the accuracy of the registration, two metrics were used for preliminary results. The mean closest point surface distance was used to quantify how well the surfaces of the registered livers match and was found to be 2.65 ± 3.54 mm. Anatomical features visible in pre- and post-treatment images were also identified. After registration, the mean Euclidean distance between features was found to be 5.22 ± 4.06 mm. To assess potential areas of tumor change, the registered tumor pre- and post-treatment were overlaid.

1. Introduction

The average yearly mortality rate for liver cancer has increased for both men and women from 2011-2015 [1]. The primary curative methods of treatment for liver cancer are surgical resection and transplantation [2]. However, in most cases cancer is not discovered until the later stages [3]. Infiltration into both lobes, proximity to vascularization, and metastasis can all prevent the surgical treatment of liver cancer. In these cases, other forms of treatment including chemoembolization, external beam radiation, or selective internal radiation therapy.

Recent studies have shown intra-tumor heterogeneity occurs in many types of cancer, resulting in several different phenotypes being expressed in different regions of the tumor [4-5]. It has also been shown that treatments can be targeted for the phenotypes expressed by the tumor [6]. Liver cancer is no different [3]. Targeting liver cancer with personalized medicine could be a viable treatment for those who are not candidates for resection or transplantation. Tumor reduction of 50% has been observed when personalizing treatment of liver tumors [7]. However, this approach necessitates reliable biomarkers.

The problem with the implementation of personalized medicine in liver cancer is therefore the identification of reliable biomarkers. The most common minimally invasive method of obtaining biomarkers is through biopsy. While a biopsy retrieves a portion of the cancerous tissue, often the tissue may be necrotic or turn up inconclusive results in biomarker analysis. In addition, if a phenotype is obtained from the tumor, the phenotype might not be the most active portion of the tumor, resulting in a less effective targeted therapy.

The current standard of practice includes an imaging sequence and biopsy at discovery of the cancer. A treatment is selected, and a second imaging sequence is obtained 3-6 months after the initial imaging session. The purpose of this work is to use the imaging sequences that are already part of the standard of practice and perform a registration or overlay of the two images to identify the regions that are metabolically active and propagating. The identified regions will then be biopsied and treatment customized based on the biomarkers. We propose an image-registration based method. Through the use of image-based registration methods, the pre- and post-treatment tumors can be overlaid so that the clinician can easily determine which regions of the tumor potentially responded or continued to persist throughout the course of therapy.

2. Methods

2.1 Registration Process

Imaging data from ten patients who underwent chemoembolization of the liver were retrospectively analyzed. The imaging data included both Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). For each patient, two imaging sequences were obtained. One sequence was obtained before initiating treatment and the second was obtained between three and six months after treatment was started. It is known that liver volume can change, which could impact the spatial discrepancies in liver tumors [8]. To control for liver volume change, five of the

ten initial patients were selected for analysis on the criteria of a total liver volume change of less than five percent.

Liver and tumor were manually segmented from both the pre- and post-treatment imaging by an expert. The goal of the registration was to create an overlay of the pre- and post-treatment tumors. Volumetric registration was performed based on the liver surface features only. Internal alignment of features was left to smooth deformation interpolating polynomials, i.e. internal intensity features did not influence the nonrigid registration. Through this method, the expectation is that volume changes in the tumor would reflect true response or proliferation and would be free of intensity-based non-rigid registration changes.

For each patient, the liver was segmented from pre- and post-treatment images using ITK-SNAP and saved as a binary image mask. The first phase of the registration consisted of a rigid registration between the segmented liver surfaces using a method based on normalized mutual information [9]. The second phase consisted of non-rigid image registration of the binary liver mask images using the adaptive bases algorithm (ABA) [10]. A summary of the registration pipeline can be seen below (Fig. 1)

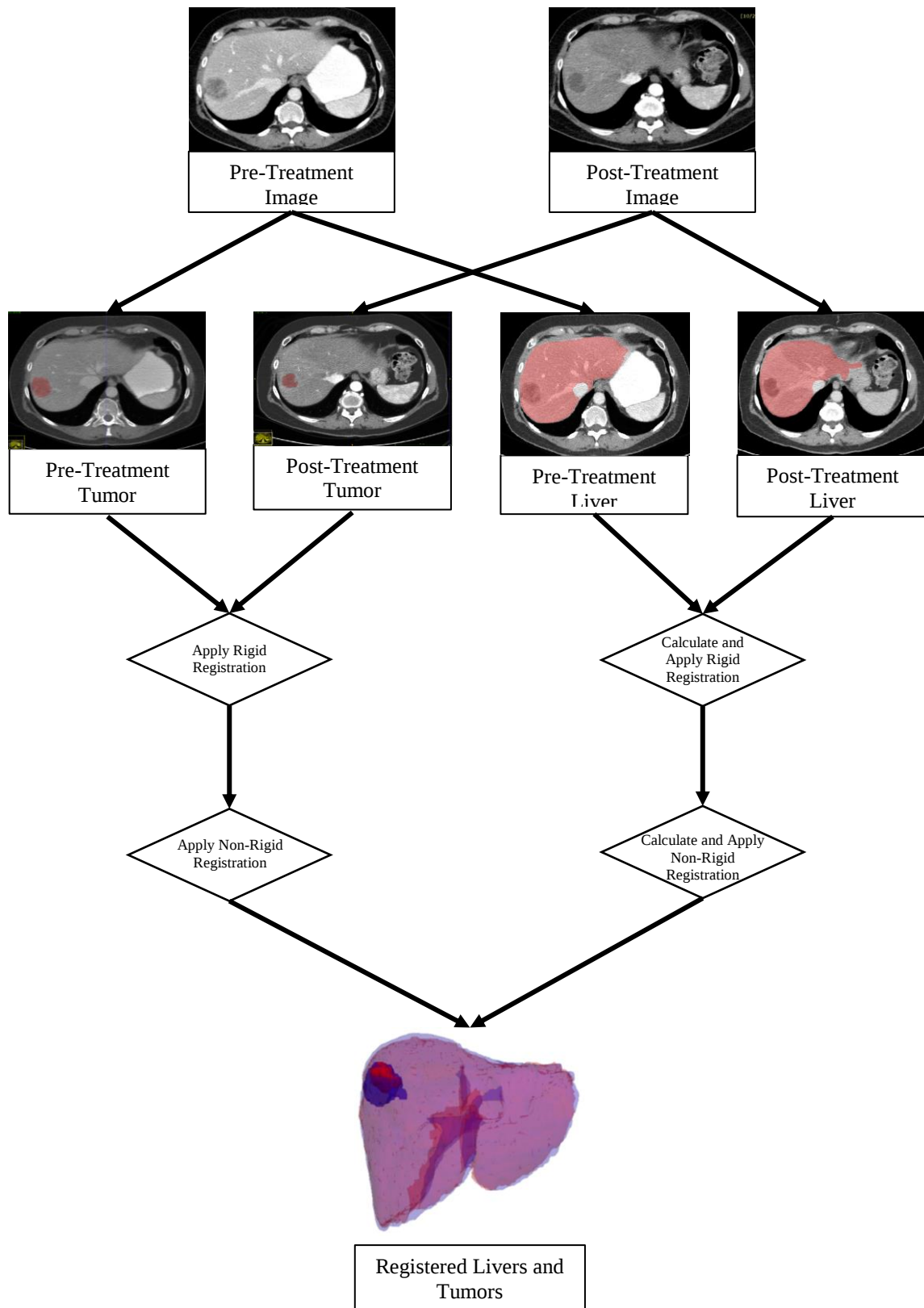


Figure 1: Overview of the registration pipeline for aligning the pre- (blue) and post-treatment (red) livers and tumors.

2.2 Registration Analysis

To analyze the accuracy of the registration, two methods were used. To assess the fit of the organ surfaces, a closest point metric was computed between the two registered full organ surfaces. This metric was computed by finding the closest point on the post-treatment surface for each point on the pre-treatment surface. The Euclidean distance was then calculated and averaged for all the points on the pre-treatment surface.

The accuracy of the registration for the internal nodes of the liver mesh was measured by manually marking making feature targets. Since the data used was from retrospective clinical cases, no true targets could be used. However, anatomical features that were easily identifiable and expected not to change between the pre- and post-treatment livers could be identified and used for targets, e.g. vessel bifurcations inside the liver. The targets were expertly segmented in the same way as the liver and tumor. The targets were registered using the previously computed registration based on the organ surface data. The distance between the centroids of the registered targets was computed. An example of the selected anatomical features can be seen below (Fig. 2).



Figure 2: A visualization of how the anatomical features are picked from the pre-treatment CT (left) the post-treatment CT (middle) and the error comparison that was used (right). The target can be seen in red on the CT images. In the comparison, the pre-treatment liver and feature target are depicted in blue. The post-treatment liver

3. Results

Table 1 shows the mean closest point distance between the pre-treatment and post-treatment liver surfaces. It also shows the target distance, which is the Euclidean distance between the centroid of the registered anatomical feature targets.

Figure 3 shows an overlay between the registered pre- and post-treatment liver surfaces as well as the overlay between the registered pre- and post-treatment tumors (left). It also shows a close up of the registered tumors (right). The pre-treatment liver and tumor are shown in blue and the post-treatment liver and tumor are shown in red.

Figure 4 shows a qualitative comparison of the segmented pre- (A) and post-treatment (B) tumors and a detailed overlay of their positions after registration (C). The segmented slice of the tumors can be seen in red. The overlay is posed in the same orientation as the CT slices. The pre-treatment tumor is shown in blue and the registered post-treatment tumor is shown in red.

Table 1: Mean closest point distance and target distance.

Case Number	Mean Closest Point (mm)	Target Distance (mm)
1	1.70±2.84	2.82
2	2.90±3.78	1.44
3	2.75±3.53	4.86
4	2.86±3.61	3.97
5	3.04±3.96	13.00

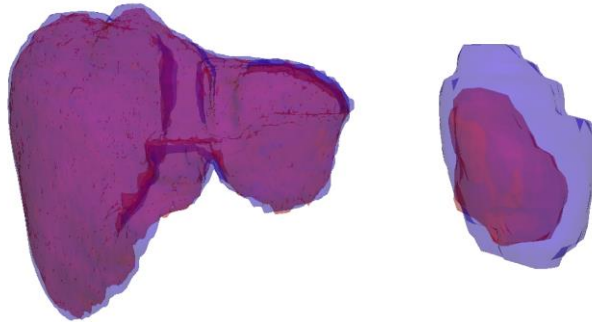


Figure 3: Overlay of the registered pre- (blue) and post-treatment (red) liver surfaces and tumors (a). Close up view of the overlaid registered pre- (blue) and post-treatment (red) tumors.

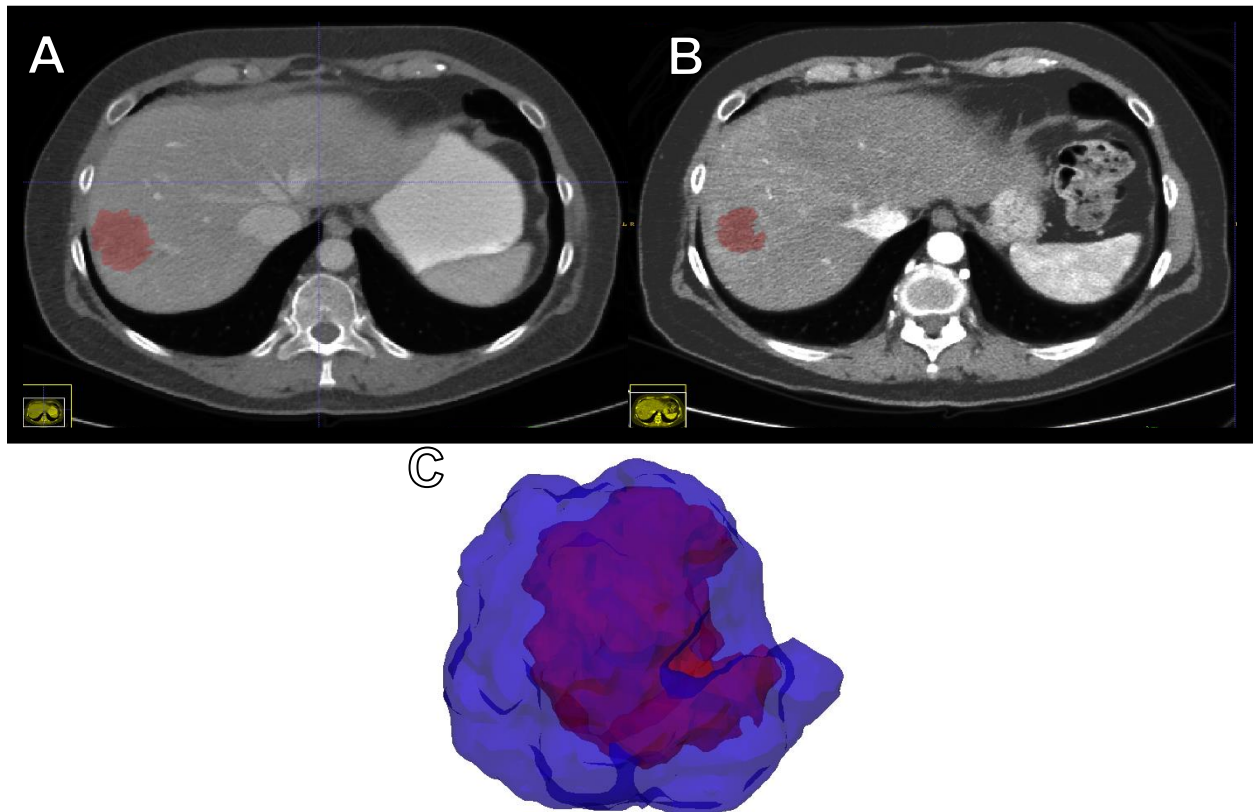


Figure 4: Qualitative comparison of corresponding slices of the pre- (A) and post-treatment (B) images with the tumor segmented. Overlay of pre- (blue) and post-treatment (red) tumor from the above segmentations (C).

4. Discussion

Qualitatively, the results look promising. As can be seen in both the CT images and the registered tumors, there is a large reduction on the left side and a stagnation on the top (Fig. 4). This qualitative comparison shows that the model can show the discrepancies in tumor growth.

While the results seem to be reasonably accurate overall, case 5 shows that the proposed method is not as robust as possible. The change in liver volume was accounted for, but the positioning of the feature target as well as the quality of the imaging played a role in the accuracy of the assessment. Some of the imaging sequences obtained had little contrast and identifying viable anatomical feature targets was challenging. In addition, some imaging sequences had axial spacing that was rather large (5mm). Furthermore, care was taken to match the resolution and phases (arterial vs venous) of the two imaging sequences to control for error introduced by differences in scanners. However, due to clinical restrictions, there were several instances where the imaging was taken on two different quality scanners.

The image registration approach is encouraging, but some surface misalignment did exist which could account for some misalignment in tumors. Due to the deformation in the liver surface between the initial scan and the follow-up scan, there were some instances of the anterior surface of the liver matching with the posterior surface of the other model. While this was limited to the anterior ridges of the liver surface, it may have been a contributing factor.

Although controlling the change in liver volume change to less than 5% between the two imaging sequences did seem to provide more consistent registration results, more investigation must be taken to analyze volume change. The liver volume change was disparate between the two lobes of the liver, even when examined as percentage change rather than an absolute change. In addition, the change in liver volume did not correlate with change in tumor volume.

5. Conclusions

The preliminary results indicate that the registration technique has considerable potential for identifying regions of tumor regression, progression, and lack of response during treatment. The average closest point distance for the full liver surface indicates a close alignment between pre and post-treatment livers. Since the internal displacements are calculated based on the surface information only, our close alignment of vessel target structures (low target error in Table 1) indicates that the internal displacements are likely representative of the nonrigid deformation inside the liver due to natural shape change. However, the predictive value of the accuracy of the alignment based on the target error depends on both the correct segmentation of corresponding anatomical features and the location of the targets in the liver. Target errors other than case 5 were quite satisfactory. This was most likely due to the location of the target with respect to the liver.

6. Acknowledgements

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7. References

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