Supplementary Material 1.

1. Tumor segmentation

In most cases, tumor burden analysis is limited to sophisticated processing and patent commercial software, leading to the utilization of linear tumor measurement, like diameter or cross-product on a single axial slice, as a proxy for actual volume. Here, we use a open-source software ITK-SNAP (www.itksnap.org/pmwiki/pmwiki.php) with a region-growth computed algorithm to calculate tumor volume and enhanced volume, with the aim of a cost-effective, standardized, and repeatable measurement in routine clinical settings.

The segmentation processes were based on a seed-growing algorithm, namely region-growth algorithm. This algorithm was based on voxel thresholding, thereby quantifying the signal in a voxel-by-voxel fashion.

1) Four quadrate regions of interest (ROIs), within the ipsilateral lobe of the lesion if possible, were prescribed on the magnetic resonance imaging (MRI) at the late arterial phase (20 sec) in areas adjacent to tumor boundaries, away from blood vessels, liver boundaries, and other structu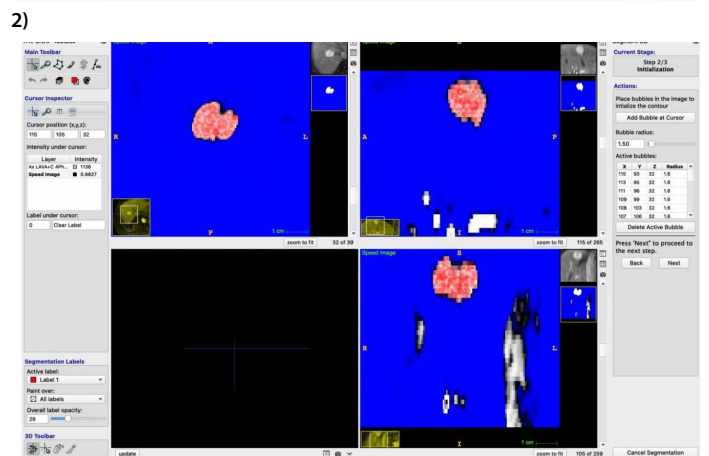res. And at least 2 ROIs were 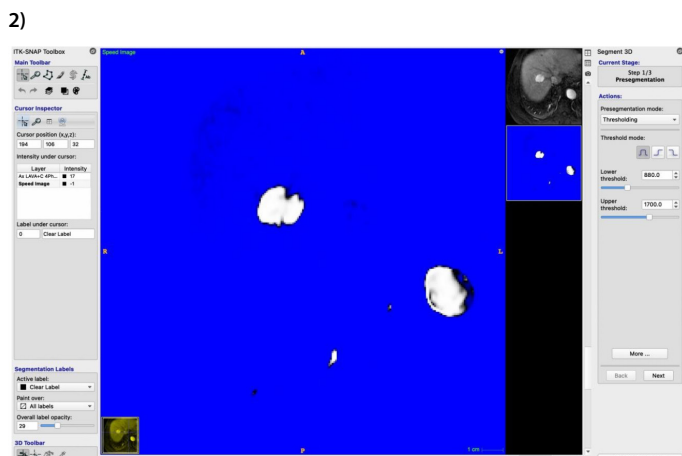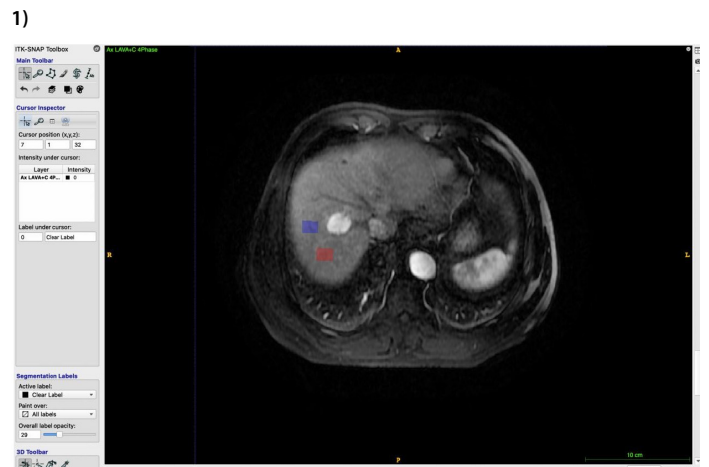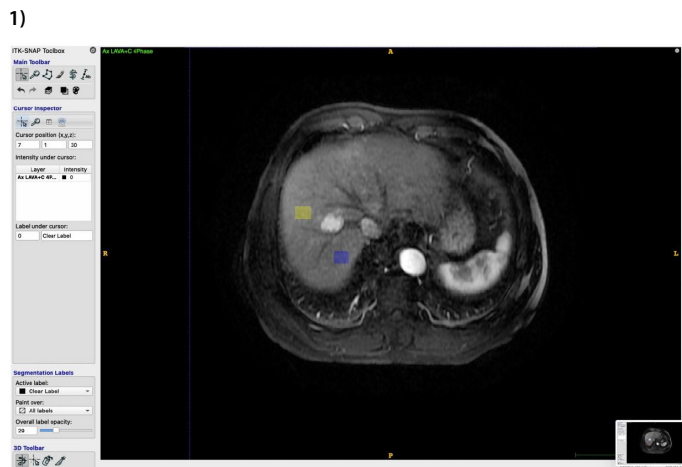placed in which the largest tumor area was emerging. The signal intensity of each ROI region is the average value of the signal intensity of the voxels in the corresponding region. The final threshold, namely the mean intensity value (MIV), is the average value of the four ROI regions.

2) When the segment tool was set up, a region including the index tumor was chosen manually using a square frame.
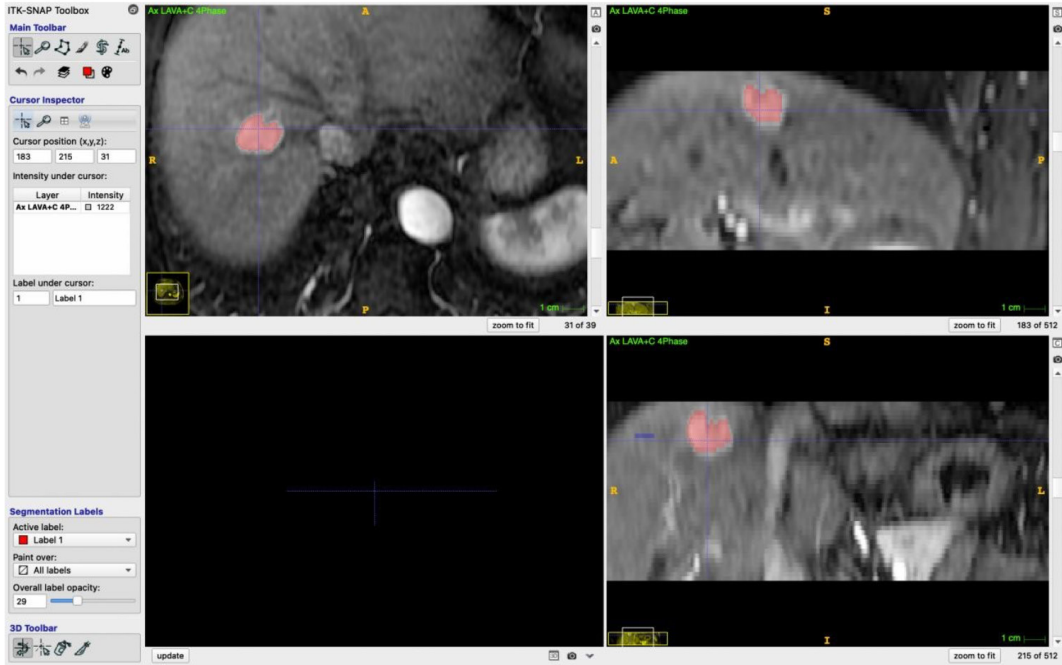
3) The seed points were set in the hyperenhancement part of the tumor visually based on the hepatocellular carcinoma (HCC) enhanced characteristic. The necrotic areas, cysts, and vessels related to each lesion at the certain slice were also avoided, as identified on T2-weighted imaging (T2WI) or arterial early phase images. Meanwhile, the pre-enhanced T1WI image was scrutinized to distinguish high signal intensity, like hemorrhage, so as to avoid overestimate enhanced tumor volume value. Using the "color map editor" function to adjust the signal intensity contrast between the tumor and liver background with aim of easier bubble placement. The exterior delineated bubbles were placed inside the edge of the enhanced part of lesion with being tangent to the inner margin in principle, and the interior delineated bubbles were placed randomly. The bubble radius was adjustable to accommodate tumors of different sizes. In addition, the cross-referencing with coronal and sagittal reconstructed MRI images were used for an accurate supplement of bubble.

4) After placing the bubbles, the number of iterations of the bubble evolution needs to be set, which is determined the tumor size, region competition force and smoothing force. The latter two parameters can be adjusted, with reference to the animation presentation. In this study, the region competition force was set as 0.8, and smoothing force value was set as default value. In regard to the small HCC diameter in this study, the numbers of iterations of the bubble evolution were set as 8-12. The voxel inside or peripheral of the seed was clustered if the signal intensity was distributed within the threshold interval, ranging from the MIV+2 standard deviations to abdominal aorta signal intensity. In this step, tumor enhanced volume was obtained. Considering the presence of low or delayed enhancement components, such as fibrotic scarring within the tumor, the brush tool was used to cover the unmasked components in the tumor. Then, the total tumor volume was calculated.

1)

1)

2)

2)

2)

2. X-tile software