SUPPLEMENTARY MATERIALS 1

Quantitative Analysis Method

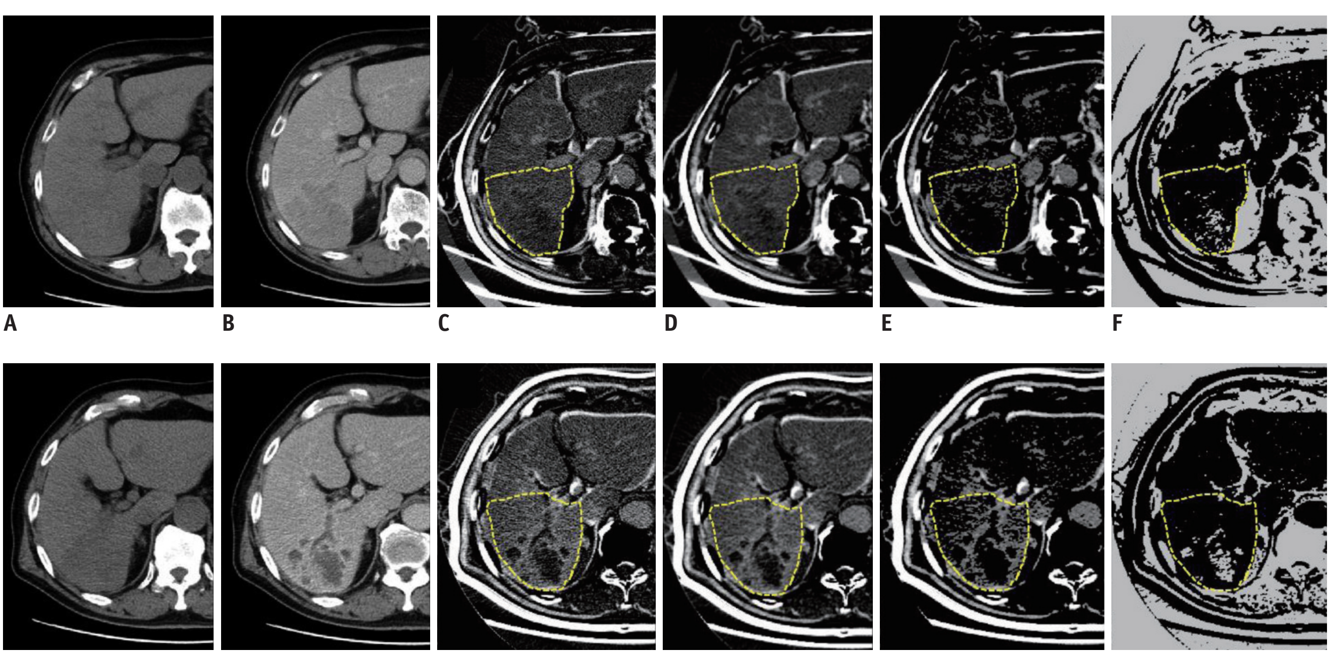
A regional radiation reaction after radioembolization is often observed in the form of delayed-phase enhancement during early follow-up. However, visual assessment is not suitable for differentiation of the delayed-enhancement area, due to the innate low contrast of this area and the heterogeneous enhancement of the baseline cirrhotic liver. Therefore, we devised a quantitative method for measuring the combined delayed-enhancing area and necrotic area (DN) in the tumor-containing segment. The quantitative method for calculating the percentage increase in the DN (pD + N) before and after transarterial radioembolization (TARE), consist of a series of steps: digital imaging and communications in medicine (DICOM) loading, image registration between phases, subtraction, noise reduction, segmentation by threshold, and area measurement.

The contrast-enhanced dynamic computed tomography (CT) studies were retrieved from the institutional archive and loaded onto a standard workstation in DICOM format for further quantitative analysis. Two phases of dynamic liver CT–pre-contrast and delayed phase–were used for creating an enhancement map of the delayed phase. Delayed-phase images are typically taken 3 minutes after the contrast media injection. Delayed-enhancement maps were made by subtracting the pre-contrast images from the delayed-phase images. When the positions of the liver in the 2 phases were different, subtraction was performed after three-dimensional image registration. The registration method used rigid transformation, which allows movement and rotation of coordinate axes of 2 images, but does not allow scaling. This method was chosen because it does not allow a change in the measured length. If small mis-registration due to breathing was observed after automatic registration, additional manual registration was performed to minimize mis-registration. Manual registration included three-dimensionally 6-directional movement and rotation of the postcontrast image based on the precontrast image.

Subtraction between images involved a process of subtracting the HU of the pre-contrast image (Fig. 1A, G) from the delayed-phase image (Fig. 1B, H), and as a result, a map composed of the absolute values of the delayed-phase contrast enhancement was obtained (Fig. 1C, I).

CT images basically contain noise. This noise appears as multiple dot-like enhancing foci at a location where there is no enhancement, which could lead to errors in automatic area measurement. Thus, we applied a denoising process (Fig. 1D, J) to the enhancement map. The denoising method was used with a pixel-wise adaptive Wiener method, based on statistics estimated from the local neighborhood of each pixel (1).

A circular region of interest (ROI) was placed on the portion of the underlying liver parenchyma (mean area: 2.36 cm^2; range: 2.12–2.83 cm^2), while avoiding focal lesions, vessels, and ducts, to measure the mean and standard deviation (SD)



A B C D E F
G H I J K L

Fig. 1. Process of quantitative image analysis.
Liver CT images of 70-year-old man with HCC with portal vein invasion before TARE **(A-F)** and 4 weeks after treatment **(G-L)**. Measured value of percentage increase in the combined delayed-enhancing area and necrotic area was 373.6%. Tumor did not recur until 38 months. CT = computed tomography, HCC = hepatocellular carcinoma, TARE = transarterial radioembolization

of the delayed enhancement of baseline liver parenchyma. This is because most patients had chronic liver disease or liver cirrhosis and the liver enhancement was heterogeneous; thus, the threshold value for adequate suppression of baseline liver enhancement should be obtained. Removal of the enhancement region, which is smaller than the mean value + 2 times the SD of the underlying liver, can remove 97.5% of the underlying liver signal; hence, the delayed enhancement from the radiation reaction was distinguished from the surroundings.

Next, the image slice was selected at the position with the largest observed cross-sectional area of the target tumor. A freehand-drawn ROI was placed along the border of the tumor-containing hepatic segment in the subtraction enhancement map (Fig. 1C, I), for automatic measurement of the DN. The software automatically selected the same regions in the other processed images, then converted the number of pixels remaining in the delayed-enhancement map inside the ROI into an area value (Fig. 1E, K). Additionally, the number of pixels with enhancement of 20 or less within the same region was automatically counted and converted into an area value (Fig. 1F, L). These 2 values were measured in the images before and after TARE, respectively, and the pD + N and pNI were calculated.

All processes were performed using in-house software written in Matlab (version 2017a, MathWorks Inc., Natick, MA, USA) and all image processing methods were implemented using the standard functions provided by Matlab.

REFERENCE

1. Lim JS. *Two-dimensional signal and image processing*. Englewood Cliffs, NJ: Prentice Hall, 1990