Evaluation of lung metastatic tumor using Dextran-DTPA-Mn nanoprobes with ultra-short echo-time imaging

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Introduction Ultra-short echo-time (UTE) imaging [1, 2] has recently been utilized to evaluate signal changes in lung parenchyma for various animal disease models [3, 4]. In addition, quantitative assessment of pulmonary perfusion with dynamic contrast-enhanced MRI has been performed for pulmonary embolism and tumor in humans [5, 6]. In a previous study, we reported that the signal intensity of UTE images in lung parenchyma and liver metastasis increased after conventional MR contrast agent administration [7]. Our group has also developed a multifunctional nanoprobe containing a positive MR contrast agent, a fluorescence dye and an anticancer drug, and succeeded in imaging drug delivery to subcutaneous and deep-seated tumors [8, 9]. As the next step, we applied the nanoprobes to lung tumors and other pulmonary diseases. In the present study, the signal changes in lung parenchyma with metastatic tumor after administration of nanoprobes containing manganese contrast agent were evaluated using UTE imaging.

Materials and Methods Female Balb/c nude mice (Japan SLC Inc., Shizuoka, Japan, n = 7) were used for *in vivo* experiments. Green fluorescence protein-overexpressed Colon 26 cancer cells (Anticancer Japan Inc., Osaka, 2.0×10^5 cells/100 µl) were administered via the tail vein to make metastasis models in the lung area. We confirmed using *ex vivo* fluorescence images that diffuse metastatic tumors developed in the lung area. *In vivo* MR experiments of the model mice were performed more than 7 days after the cell administration.

The nanoprobe consisted of dextran modified with DTPA-chelated residue and bound manganese ions (Dextran-DTPA-Mn) (Figure 1). Binding with dextran-DTPA enables manganese ions to elude capture in the liver and remain in the blood circulation. In this paper, Dextran-DTPA-Mn (0.25mmol/kg, Molecular weight = 40,000) was administered via the tail vein to evaluate changes to the signal intensity of the lung with metastases for periods of at least 24 hours.

MR images were acquired before, immediately, 12 and 24 hours after Dextran-DTPA-Mn administration. To compare the signal changes using conventional contrast agents, Gd-DTPA (Magnevist™, Bayer Healthcare, Germany) (0.25 mmol/kg) was also administered via the tail vein. All MRI acquisitions were performed on a 7.0 Tesla animal MRI (Magnet: Kobelco, Japan; Console: Bruker Biospin, Germany). Measurements were made with a 35 mm inner-diameter transmit/receive volume coil (Rapid Biomedical, Germany). 3D-UTE images were acquired using the following parameters: TR/TE = 8/ 0.02 ms; flip angle = 10º; FOV = 38.4 mm × 38.4 mm × 44.8 mm; Matrix = 128 × 128 × 128; Projection number = 51360. T_2-weighted images using a rapid acquisition with relaxation enhancement (RARE) sequence were also acquired to detect tumors in the lung. Imaging parameters were: TR/effective-TE = 2000/40 ms; FOV = 38.4 mm × 38.4 mm, Matrix = 256 × 256, RARE factor = 4. As an external reference for signal normalization, a tube containing 0.1 mM $MnCl_2$ solution was placed beside the mouse during imaging. After the experiments, regions-of-interest in the lung that excluded blood-rich areas (such as the heart) were selected for the assessment of signal intensity.

Results and Discussion Figure 2 presents normalized 3D-UTE images of the lung before, immediately, 12 and 24 hours after Dextran-DTPA-Mn administration. The normalized signal was calculated by dividing the signal intensity in the lung area by the signal of the external reference. The normalized signal increased immediately after the administration and remained higher than the ratio before administration over 24 hours. Figure 3 compares the normalized signal in lung parenchyma after Dextran-DTPA-Mn (n = 4) and Gd-DTPA (n = 3) administration. The signals were normalized by the signal intensity before the administration. The normalized Dextran-DTPA-Mn signal was significantly higher than that using Gd-DTPA at immediately and 12 hours after the administration. Also, the normalized signal at 12 hours after Dextran-DTPA-Mn administration remained high. These results indicate that Dextran-DTPA-Mn remains in the bloodstream and tissue for long periods.

Figure 4 compares a T_2-weighted and 3D-UTE images in the lung area at 24 hours after Dextran-DTPA-Mn administration to a tumor model mouse at 10 days after tumor cell administration. Although T_2-weighted images can detect the tumor in lung parenchyma (arrow), the signal intensity is poor due to the susceptibility difference with air. On the other hand, 3D-UTE images with Dextran-DTPA-Mn obtained strong signal throughout the entire lung tumor region even for the air-rich parenchyma (arrow). The tumor region became more conspicuous due to the accumulation of Dextran-DTPA-Mn, indicating the future possibility of early-stage disease detection using-3D UTE images combined with multifunctional nanoprobes such as our multimodal nanoprobe or Gd-DTPA/DACHPt-loaded micelles [8-10].

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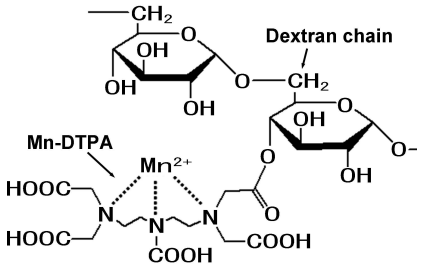

Figure 1: Structure of Dextran-DTPA-Mn. The molecular weight is 40,000.

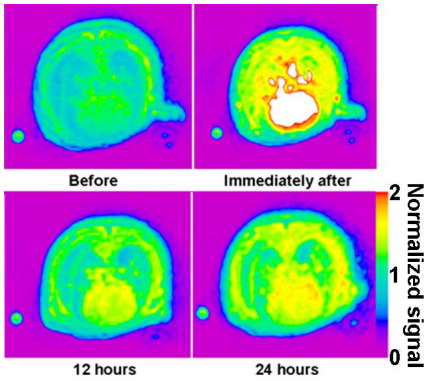

Figure 2: 3D-UTE images of lung with metastases before and after Dextran-DTPA-Mn administration. The signal was normalized by dividing the signal intensity in the lung parenchyma by the signal of the external reference.

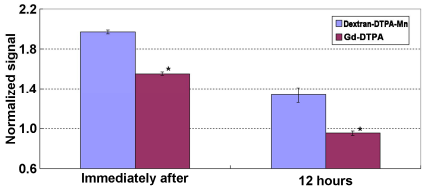

Figure 3: Comparison of the signal changes for Dextran-DTPA-Mn and Gd-DTPA. The signal was normalized by the signal intensity before administration.
*: significant difference, $p<0.05$.

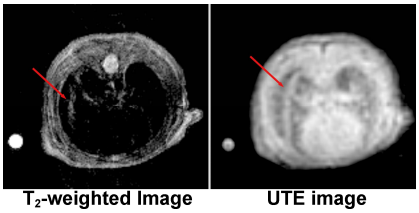

Figure 4: Comparison of typical *in vivo* T_2-weighted and 3D-UTE images at 24 hours after Dextran-DTPA-Mn administration. The metastatic tumor was visualized with 3D-UTE imaging even in the lung parenchyma (arrows).