

Improved Contrast Enhancement of Experimentally Induced Rat Hepatocellular Carcinoma Using New Blood Pool Contrast Agent Dendrimers DTPA-D1Glc(OH)

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INTRODUCTION: Hepatocellular carcinoma (HCC) is the fifth most common liver neoplasm causing one million cancer deaths annually worldwide. MR diagnosis of HCC has been traditionally made by whole liver dynamic study using fast gradient echo sequence with non-specific extravascular extracellular gadolinium chelates. **PURPOSE:** In this study, we have tested if our newly developed blood pool contrast agent, dendrimers DTPA-D1Glc (OH) can show improved and sustained contrast enhancement of the hypervascular hepatocellular carcinoma with less amount of gadolinium chelate as compared to conventional Gd-DTPA.

MATERIALS AND METHODS: Dendrimers DTPA-D1Glc (OH) functionalized ligand for a lanthanide ion based on dendric architecture was synthesized by our group. Dendric frameworks were applied as a paramagnetic metal support. These ligands are composed of diethylenetriaminepentaacetic acid (DTPA) and glycodendrimers. The molecular weight of the contrast agent is 1448.45D. Six male F344/N Slc rats (age 5 weeks, 80g BW) were housed in animal quarters with free access to standard pellet diet and distilled water containing 100ppm diethylnitrosamine (DEN). After three months, HCCs and hyperplastic or dysplastic nodules were induced in the cirrhotic liver of the rats. All procedures were carried out with the approval of our institutional ethical committee for the care and use of laboratory animals which is consistent with standards required by the UKCCCR guidelines. Six tumor bearing rats with were used for the contrast enhanced MRI. All rats were examined with two contrast media consecutively [i.e.: Gd-DTPA (0.1 mmol/kg, Magnevist, Bayer Pharma.) first, and more than 6 hours later, dendrimers DTPA-D1Glc (OH) (0.0125mmol/kg) was given]. A 3.0T imager (Magnetom Allegra 3.0T, Siemens Medical Solutions, Erlangen, Germany) together with a homemade surface coils were used for imaging. Under general anesthesia induced by an intraperitoneal injection of sodium pentobarbital (50 mg/kg), axial and coronal T1-weighted conventional spin-echo images and T2-weighted fast spin-echo images were acquired before contrast administration. T1-weighted coronal fat saturated 3 dimensional fast spoiled GRASS (3D-VIBE) was repeated before and 30s, 60s, 90s, 30 min, 1 hr, and 2 hr following the contrast administration. The parameters used for T1-weighted imaging were: TR(ms)/TE(ms) ; 4.5/1.8, NEX; 1, FOV(mm);120. Matrix; 256x208, partition(mm) ; 0.7. For T2-weighted imaging, the parameters were TR (ms) / TE (ms) of 2000 / 86, image matrix of 256 x 128, slice thickness (mm) of 2 , and slice gap (mm) of 0.6. Rats were injected intravenously with 0.1 mmol/kg of Gd-DTPA and 0.0125 mmol/kg of dendrimers DTPA-D1Glc (OH) via the tail vein consecutively with an interval of more than 6 hours. After completion of image acquisitions, the rats were sacrificed with intraperitoneal injection of an overdose of sodium pentobarbital, and the livers were excised from the rats, and then, fixed in the 10% formaldehyde solution for two days. The livers were embedded in paraffin, and then sliced identically to the axial or coronal planes of the MR imaging planes. The axial histological sections were stained with hematoxylin and eosin (H-E) for photomicroscopic investigations. The histological sections were correlated with MR images and the hypervascular HCCs more than 5 mm in diameter were picked out and numbered. The lesions were histopathologically diagnosed based on the general rules for the clinical and pathological study of primary liver cancer. On photomicroscopic images, HCCs were diagnosed when the nodules were composed of hepatocytic lesions exhibiting advanced atypia and structural derangements. Mean signal intensities and standard deviations (SD) were measured by focusing circular regions of interest on the each tumor, adjacent liver parenchyma, and the background air. The contrast to noise ratio (CNR) was then calculated for each HCCs. A total of 25 hypervascular HCCs were identified in the liver of the 6 rats. All tumors were extremely hypervascular both on contrast enhanced MR imaging and subsequent histopathological photomicroscopic images. **RESULTS:** All HCCs were clearly identified as strongly enhanced tumors with use of T1-weighted 3D-VIBE sequence after administration of dendrimers DTPA-D1Glc (OH). The CNR of the tumor at 30s after injection of dendrimers DTPA-D1Glc(OH) was 13.1+/-6.4 as compared to Gd-DTPA (5.3+/-4.5) ($p<0.01$). The lesions were only enhanced at 30s after injection of Gd-DTPA, and no significant contrast was created thereafter. Whereas, dendrimers DTPA-D1Glc (OH) continued to reveal stronger and sustained contrast enhancement, which were reflected by the time-course changes of the CNR. **CONCLUSION:** Newly developed blood pool contrast agent dendrimers DTPA-D1Glc (OH) can show improved and sustained contrast enhancement of hypervascular HCC using 1/8 amount of gadolinium chelate at molecular basis as compared to Gd-DTPA.