In vivo visualization of mouse sciatic nerves involved with a pancreatic cancer cells using manganese enhanced MR imaging technique.

H. Mieno[1,2], M. Yamaguchi[3], S. Mitsunaga[1,4], A. Imoto[1], T. Ikumoto[1,2], A. Hirayama[3,5], A. Nabetani[5], A. Nozaki[5], T. Kinoshita[2], H. Fujii[3], and A. Ochiai[1]

[1]Pathology Division, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [2]Upper Abdominal Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [3]Functional Imaging Division, National Cancer Center Hospital East, [4]Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, [5]GE Yokogawa Medical Systems,Ltd., Tokyo, Japan

Introduction: Nerve invasion is frequently seen in patients with pancreatic cancer and is widely recognized as a strong predictor of poor prognosis. Since accurate imaging diagnosis of nerve invasion can be made by clear discrimination between minute cancerous tissues from the surrounding nerve plexus, manganese enhanced MR imaging (MEMRI) [1] is a reasonable approach for this purpose, because it provides a high contrast between peripheral nerve and non-neural tissue [2]. Usefulness of MEMRI to visualize nerve invasion, however, has yet to be determined. We therefore carried out an MEMRI study of a mouse model (N-Inv model) [3], in which nerve invasion of human pancreatic cancer cells (Capan-1) was experimentally produced in murine sciatic nerves. The purpose of this study was to explore MEMRI technique to visualize mouse sciatic nerves under normal conditions and those with tumors in our N-inv model.

Materials and Methods: All MR images were taken using a 3T whole-body scanner equipped with an in-house build solenoid coil (35mm in diameter) for signal reception. We attempted to visualize bilateral sciatic nerves in mice by intra-spinal administration of $MnCl_2$. First, a pilot study was conducted using 6 male C57Bl/6 mice to determine the optimum dose of $MnCl_2$. Under barbiturate anesthesia (50mg/kg BW i.p.), 0.5 μl of $MnCl_2$ was directly injected into the mouse spinal cord at the lower thoracic level using a 30 G needle and a 25-μl Hamilton syringe. MR scans were performed 1 day after the intra-spinal administration of 300mM concentration $MnCl_2$ in 6 normal C57Bl/6 mice, another 4 C57 Bl/6 mice whose sciatic nerve was lightly injured by forceps crushing, and 4 SCID mice whose sciatic nerve with introduced Capan-1 tumor (N-inv model). In this model, 2.5×10^4 Capan-1 cells were inoculated into the left sciatic nerve 5wks before the MR scan. T_1-weighted SE images (TR/TE = 600/12 ms, 40mm FOV, 512x256 matrix, 1mm slice thickness) were obtained in the transverse plane.

Results and discussions: T_1-weighted images 24 hrs after intra-spinal injection of $MnCl_2$ clearly demonstrated bilateral sciatic nerves as hyperintence cord-like structures running from the spinal canal down to the mid-thigh (Fig. 1) in all cases, whereas T_1-weighted images without $MnCl_2$ failed to demonstrate sciatic nerves because they were nearly isointense compared with the surrounding muscle tissue. In the cases of nerve injury produced by forceps crushing, hyperintense signals from sciatic nerves disappeared at the injury site where $MnCl_2$ transportation by axonal flow was possibly disrupted. In 2 of 4 cases of N-Inv model, a hyperintence sciatic nerve engulfed by Capan-1 tumor was observed in the proximal part (Fig. 2), while it disappeared in the central part of the tumor, suggesting the presence of a residual nerve in the tumor invasion front. In the other two cases, the enhanced sciatic nerve disappeared at the proximal edge of the Capan-1 tumor where the sciatic nerve could be completely destructed. Six of 14 mice (43%) examined showed paraparesis or paraplesia after the intraspinal injection of $MnCl_2$,

Conclusion: For the first time we succeeded in visualizing mouse sciatic nerves under normal condition and with invasive tumors using MEMRI with intraspinal $MnCl_2$ administration. Despite the considerable complication rate, this technique is promising to evaluate nerve invasion in the experimental model of human pancreatic cancer.

References: [1] Magn Reson Med 2006;55(5):1124-31. [2] NMR Biomed. 2004;17(8):532-43 [3] Mitsunaga et al. Clin Cancer Res; under revision.

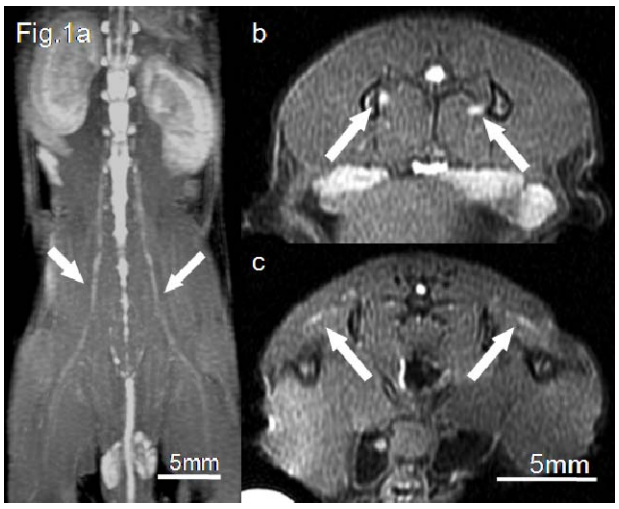

Figure 1: MEMRI of normal sciatic nerves 24hrs after spinal cord injection of $MnCl_2$. A T1-weighted coronal MIP image (a), axial T1W images in the pelvis (b), and in upper thigh (c) clearly demonstrate Mn-enhanced sciatic nerves.

Figure 2: Axial T_1-weighted images of the N-Inv model 24hrs after spinal cord injection of $MnCl_2$ with (b) or without (a) systemic administration of Gadoteridol (0.01 mol/kgBW). An Mn-enhanced sciatic nerve with a tumor, which is inhomogeneously enhanced by Gadoteridol (arrowheads).