MR perfusion of non-small cell lung cancer in transgenic SCID mice overexpressing VEGF

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Purpose:
This study is to evaluate the feasibility of dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) in subcutaneously transplanted vascular endothelial growth factor (VEGF) overexpressing NSCLC in a severe combined immunodeficiency (SCID) mice model.

Introduction:
VEGF is an endothelial cell-specific growth factor and the principal regulator of angiogenesis under both normal and pathological conditions such as tumor growth. VEGF can stimulate endothelial cell proliferation, migration, and suppress endothelial cell apoptosis (surviving signal). In vivo, VEGF can induce sprouting angiogenesis, increases vessel permeability, and controls vasculature remodeling and integrity. VEGF is expressed in many types of tissues and is up-regulated during development, tissue remodeling, wound healing and in vast majority of human tumors including lung cancers. The VEGF189 mRNA isoform expression ratio correlates with tumor angiogenesis, postoperative relapse time, and survival in patients with non–small-cell lung cancers (NSCLC) (1). Using DCE MRI with kinetic modeling, parametric mapping for heterogeneous internal tumor composition and parametric histogram analysis are valuable information. DCE MRI with the use of nonspecific gadolinium-chelate contrast agent has been demonstrated to be an important biomarker to correlate in vivo tumor angiogenesis, such as microvessel density (MVD) and VEGF (2).

Materials and methods:
We used established transgenic SCID mice model which received subcutaneous implantation of VEGF isoform 189 overexpression (VEGF-189) NSCLC. MRI perfusion through intravenous contrast injection via neck vein was performed in 50 SCID mice, including 25 mice with VEGF-189 and 25 mock, at the age of implanted tumor 4th, 5th, 6th, 7th and 8th weeks. All studies were performed in a 3T MR scanner (Biospec, Bruker, Germany) equipped with small animal coil (microimaging system) and a surface coil (Rapid Biomedical GmbH, Germany). DCE MRI with T1-weighted sequence (FLASH, TR/TE/FA, 100/3.661/30) was used (NEX 1, 9 slices, FOV: 4 x 2 cm, slice thickness 2mm, matrix size 256 x 128, resolution156.25 µm, scan time 12.8 sec/acquisition, total 60 acquisitions). Arterial input function was obtained for a prominent major arterial enhancement in the pelvis. Pixel-based mappings of MR derived parameter K^{trans}, $K_{ep,}$ V_e and V_p were obtained. Haematoxyline & Eosin stain and immunohistochemical stain with CD31 were performed for resected tumors.

Results:
Tumor growth was observed from the 4th to 8th weeks associated with increased microvessel count in both VEGF-189 and mock groups. Larger tumor size in VEGF-189 has been observed (Figure 1). Tumor growth accompanied with increased vascularity characterized with higher K^{trans} and $K_{ep,}$ values indicating increased transfer constant due to vascular permeability (Figure 2).Implanted tumor with VEGF -189 overexpression has heterogeneous distribution of tumor vascularity which was prominent at the periphery of the tumor and decreased tumor perfusion at the central portion. Parametric histogram analysis of VEGF-189 group shows more prominent Kep and Ktrans.

Discussion:
According to the results of this study, perfusion MRI study is feasible for evaluating NSCLC with VEGF overexpressing transgenic SCID mice model. This study enables the future implementation of DCE perfusion MRI study in SCID mice model of lung cancer.

Figure 1

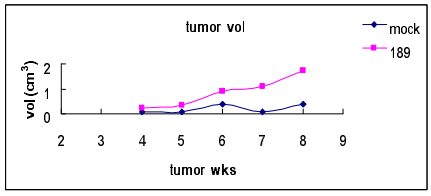


Figure 1. Interval change of tumor growth between SCID mice implanted with mock and VEGF-189 shows larger tumor volume of VEGF-189 group (pink curve).

Figure 2. DCE MRI of SCID mice implanted with mock (left column) and VEGF isoform-189 overexpression (right column) shows much larger tumor size, more prominent heterogeneous distribution of K^{trans} (B) and K_{ep} in the tumors of VEGF-189 group (right column), which corresponds to the findings of immunohistochemical stain (D).

Figure 3.Parametric histograms of (A) k_{ep} of VEGF-189, (B) K^{trans} of VEGF-189. There is higher Kep and Ktrans in VEGF-189 group, indicating more prominent angiogenetic permeability.

Figure 2

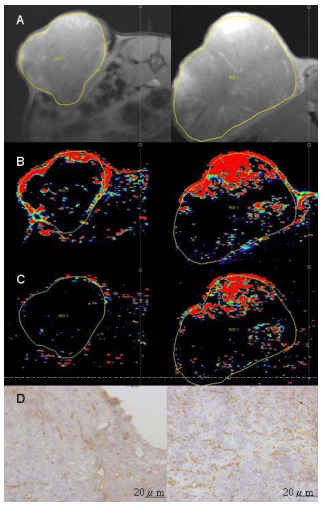
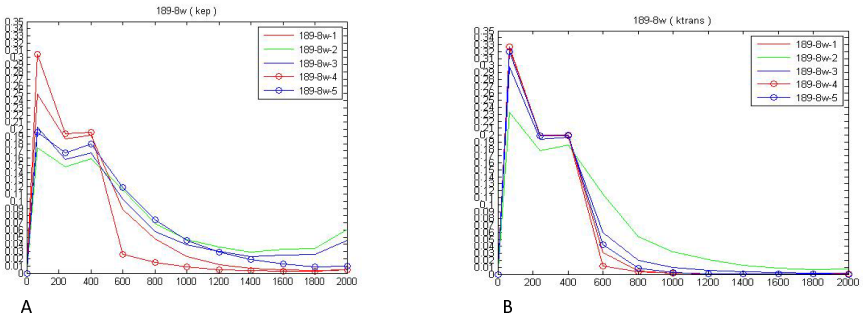


Figure 3



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1) Yuan A, Yu CJ, Kuo SH, Chen WJ, et al. J Clin Oncol 2001; 19: 432-441.
2) Knopp MV, Weiss E, Sinn HP, et al. J Magn Reson Imag 1999;10:260-266.

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