SIMULTANEOUS CHARACTERIZATION OF THE TUMOR VASCULAR PERMEABILITY, VESSEL SIZE AND DENSITY BY USING FIRST-PASS FUNCTION/ STRUCTURE MR IMAGING

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Introduction

Angiogenesis, the formation and development of new vascular network, is essential to tumor growth. Vascular network surrounding tumor tissues, however, exhibits abnormal functional and structural properties distinct from normal blood vessel. Functional abnormalities include higher permeability and altered blood flow, etc. Tumor vascular permeability can be assessed in vivo by using dynamic contrast enhanced–MR imaging (DCE-MRI) based vascular transfer constant (K^{trans}) [1]. Structural changes related to tumor vasculature include blood vessel sizes index (VSI) and vessel densities index (VDI), which can be characterized by steady state contrast enhanced–MR imaging (SSCE-MRI) [2-3]. However, DCE-MRI and SSCE-MRI needed two different MR approaches and two different contrast agents; it was difficult to obtain the imaging for K^{trans}, VSI and VDI at the same time. Simultaneous imaging for both functional and structural properties can greatly contribute to reduce scanning time in clinical diagnosis. Moreover, simultaneous assessment of K^{trans}, VSI and VDI was also helpful to understand the correlation between functional and structural changes. Therefore, this study is aimed to develop First-Pass Function/Structure MR Imaging (First Pass F/S MRI) technique that can simultaneously characterize both functional and structural states of the tumor vascular network.

Material and Method

Rat brain tumor model was created by C6 glioma tumor cell and evaluated weekly (day7, day14, and day21). All images were performed on a 4.7-T Biospec 47/40 MR scanner with an active shielding gradient. Images were acquired by using a 72-mm birdcage transmitter coil and a separate quadrature surface coil for signal detection. First Pass F/S MRI was performed by using an interleaved spin echo and gradient echo echo planar imaging (EPI) sequence and was acquired with TR of 1000 ms, TE_{GE} of 20 ms, TE_{SE} of 50 ms, FOV =3 cm ×3cm × 1.5cm, acquisition matrix = 64×64 (zero-padded to 128×128). The sequence was used to generate both ΔR2 and ΔR2* maps during the first pass of bolus of the contrast agent (USPIO, Resovist). Transverse relaxation rates changes in dynamic imaging will be given by $\triangle R_2$ (=ln (S_{pre} /S_{post})/TE) and $\triangle R_2^*$ (= ln(S_{pre}^*/S_{post}^*)/TE), where S_{pre}, S_{post}, $S_{pre}^*$and S_{post}^* are signal intensities of the pre-contrast and post-contrast (drop to the lowest point in dynamic curve) for spin echo and gradient echo, respectively. The kinetic analysis in VSI and VDI with dynamic signal curve can be estimated from the following equation

$$VSI = \frac{\Delta R_2^*}{\Delta R_2} \qquad VDI = \frac{\Delta R_2}{\left(\Delta R_2^*\right)^{2/3}}$$

And were analyzed for K^{trans} map by using the first pass pharmacokinetic model

$$C_t = v_p C_p + v_e C_e = v_p C_p + K^{trans} \int_0^t C_p\left(t'\right) \exp\left(-\frac{K^{trans}\left(t - t'\right)}{v_e}\right) dt'$$

where Ct is total tissue concentration; Cp and Ce are the contrast agent in the interstitial space and plasma, respectively; vp is the fractional plasma volume and Ve is interstitial space**.** We assume an analytical expression for Cp, such as gamma variate function, can be fitted numerical to the measured tissue concentration time curve. K^{trans} is derived directly from the fit [4]. K^{trans} is production of permeability and vascular surface area [5]. All EPI derived color maps were infused onto T2 weighted imaging (T2WI).

Results and discussion

Tumor region was determined by hyperintensity of T2WI, showing the growth of tumor (Fig.1a). Fig.1b, c, and d showed the changes with time in the K^{trans}, VSI, and VDI, respectively. From day7 to day21, quantitative analysis showed an increase in K^{trans} and VSI (Fig.2a, b) and showed a decrease in VDI (Fig.2c). The simultaneous assessment showed significant positive correlation between K^{trans} and VSI (n=6, r =0.754, p=0.0003, Fig.2d) and negative correlation between K^{trans} and VDI (n=6, r =-0.54, p=0.02, Fig.2e). Tumor growth needed new vessels to exchange more nutrients and oxygen. The characteristics of these vessels were immature, leaky, and highly permeable and resulted in increase in K^{trans}. In addition, VSI increase also contributed to K^{trans} because of increased vascular surface area when vessels are dilated, and K^{trans} is calculated as the product of vascular permeability and vessel surface area [5]. Thus, the changes of permeability and structure showed a strong correlation between VSI and K^{trans}. Moreover, the increased K^{trans} had a negative correlation to vessel density. The decreased vessel density was suggested to regression regulated by growth factors in different tumorgenesis stages [6]. The correlation was also altered by effects on the combination of vascular permeability and surface area. Therefore, the correlations of VSI, VDI, and K^{trans} simultaneously assessed by First Pass F/S MRI technique can provide new insights into the process of tumor angiogenesis.

Conclusion

The current study using proposed First Pass F/S MRI with USPIO can integrate images of K^{trans}, VSI and VDI for imaging multi-facet characteristics of tumor vasculature. This proposed technique featured the advantage of simultaneous measurements of both functional and structural properties. Furthermore, the significantly reduced scan time of this new method and knowledge of correlation between functional and structural change enhance its potential use for clinical diagnosis in the future.

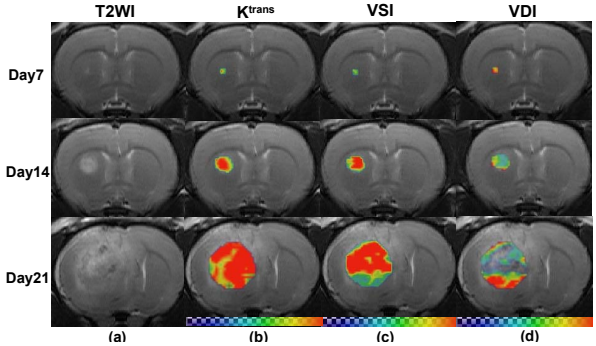

Fig1.In vivo (a)T2WI, (b) K^{trans}, (c)VSI, and (d) VDI of C6 tumor.

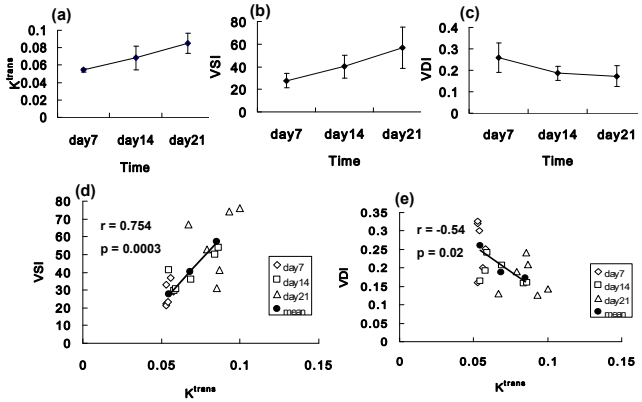

Fig.2 Quantitative analysis of(a) K^{trans}, (b)VSI, and (c) VDI and correlation between (d) K^{trans} and VSI , and (e) K^{trans} and VDI in C6 tumor.

References

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