Decrease In Convective Transport Is Associated With Increase In Voxels Explained By Gadolinium Diffusivity In DCE MRI Of Untreated Human Gastric Cancer Xenografts

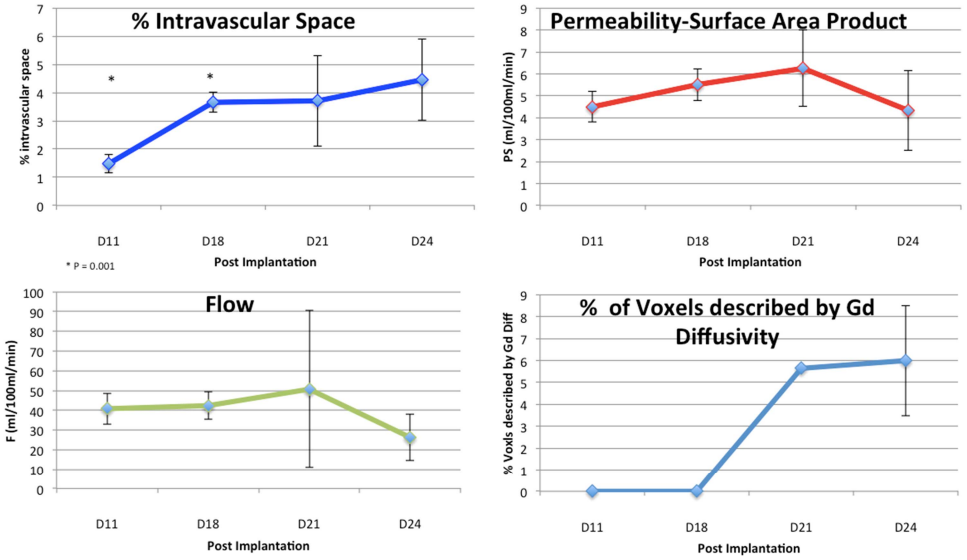
Septian Hartono[1], Tong San Koh[1], Quan Sing Ng[1], Puor Sherng Lee[1], Laurent Martarello[2], The Hung Huynh[1], and Choon Hua Thng[1]
[1]*National Cancer Centre Singapore, Singapore, NA, Singapore,* [2]*Roche Translational Medicine Hub, Singapore, NA, Singapore*

Target Audience: DCE MRI practitioner, Preclinical drug development specialists, Physicists, Radiologists.

Purpose: Growing tumors eventually develop a high interstitial fluid pressure state that shuts down convective interstitial transport and results in central necrotic areas. Gadolinium diffusivity has been reported as a means of characterizing tracer transport where convective transport is absent.[1] We aim to characterize the temporal change of microcirculatory parameters in gastric cancer xenografts with DCE MRI and to determine the time point where gadolinium transport explained by diffusivity is observed.

Methods:
Mice: Four male SCID mice were implanted with human gastric cancer xenografts subcutaneously and formed the control population in a preclinical study. They were scanned at D11, D18, D21 and D24 post implantation. They received a single intraperitoneal dose of sham drug (Xolair (Omalizumab), a human ant-IgE antibody) at 10 mg/kg on D12.

DCE-MRI: MRI was performed on a 7T scanner (Bruker ClinScan, Bruker BioSpin MRI GmbH, Germany). A 3D VIBE sequence was used with following parameters: TR = 3.04 ms, TE = 1.23 ms, FOV = 36 × 36 mm, 128 × 128 matrix, 8 slices with thickness of 1 mm, & temporal resolution 2 s. Five sets of baseline images were acquired with α = 6° & 14°. It was followed by a dynamic sequence of 130 sets of images (α = 14°). A dose of 100 µL of Gd-DOTA (Dotarem, Guerbet SA, France) at 1 mmol/kg was injected through the tail vein after the first set of dynamic images.



Data Processing: Region of interests corresponding to the xenograft and major artery were manually outlined. Microcirculatory parameters such as blood volume were derived from the two-compartment model as described by Hayton/Brix. [2,3]
Poorly perfused and necrotic tumor regions exhibiting delayed and slow enhancement were identified using a k-means clustering algorithm. Tracer behavior in these regions can be described by Fick's diffusion equation from which the gadolinium diffusivity can be estimated. [1] Voxels that exhibit delayed and slow enhancement as described by Fick's diffusion of gadolinium are expressed as a percentage of the total tumor voxels.

Results:
As tumor grows, there is an initial increase in % intravascular volume without increase in blood flow from D11 to D18. Blood flow and permeability begin to show a decreasing trend from D21 to D24. This is accompanied by an increase in the number of voxels explained by gadolinium diffusivity. Between 4.5 to 9.1% (mean 6%) of voxels are explained by gadolinium diffusivity and not by convective transport at D24 compared to zero % at D11 and D18.

Discussion:
Gadolinium diffusivity begins to describe tumor tracer transport from D21 to D24 as convective transport (measured by permeability-surface area product) begins to decrease. Gadolinium diffusivity has potential as new biomarker in tumors with high interstitial fluid pressure and convection transport shutdown.

References:

[1] Koh TS, Hartono S, Thng CH, Lim TKH, Martarello L, Ng QS. In vivo measurement of gadolinium diffusivity by dynamic contrast-enhanced MRI: A preclinical study of human xenografts. Magn. Reson. Med. 2012 Mar 22.
[2] Hayton P, Brady M, Tarassenko L, Moore N. Analysis of dynamic MR breast images using a model of contrast enhancement. Medical Image Analysis. 1997 Apr;1(3):207–24.
[3] Brix G, Bahner ML, Hoffmann U, Horvath A, Schreiber W. Regional blood flow, capillary permeability, and compartmental volumes: measurement with dynamic CT--initial experience. Radiology. 1999;210(1):269–76.