DCE-MRI reveals increased peritumoral fluid flow in brain metastases after SRS

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Target audience: The method presented in this communication for investigating peritumoral fluid flow in brain tumors could be of interest for radiologist, oncologists, and basic researchers within the field of cancer imaging and radiation biology.

Purpose: To study interstitial fluid pressure (IFP) driven peritumoral interstitial fluid flow, its relation to peritumoral edema, and its changes following stereotactic radiosurgery (SRS).

Method: 9 patients were imaged using dynamic contrast enhanced MRI (DCE-MRI) before (i.e day 0) and at days 2 and day 7 after SRS. DCE-MRI images were acquired with a 3D FLASH sequence (3T, slice thickness: 1.5 mm, In-plane resolution 1.15 mm X 1.15 mm) with a temporal resolution of 5 seconds. Total scan time for the DCE-MRI sequence was ~4 minutes. Magnevist™ was used as the contrast agent. The imaging protocol also included high-resolution pre-contrast T2-weighted images and post-contrast T1-weighted images. Tumor and edema volume was determined using the Osirix image analysis tool from manually outlined regions of interest in the high-resolution post-contrast T1-weighted and pre-contrast T2-weighted image series.

Peritumoral fluid flow measurements performed on the DCE-MRI images were analyzed on the basis of a finding by Hompland et al. (1). They observed a contrast agent rim enhancement surrounding tumors in mice at the first image after contrast agent, and that this rim moved radially outward with time. This rim motion is hypothesized to be the result of contrast agent being carried outward by an interstitial fluid flow from the tumor into the surrounding tissue, and furthermore that this fluid flow is driven by the magnitude of the tumor IFP. The phenomenon of the moving rim was also observed in the metastatic lesions investigated here. A program was developed in Matlab to measure the rim motion of the contrast agent with time. The program measured the rim motion of the contrast agent at intervals of 0.3 mm along the tumor periphery. By fitting a 6th degree polynomial to the rim we were able to record sub-pixel movements. However, with the spatial resolution of the DCE-MRI sequence we where were not able to accurately determine the initial velocity of the RIM, although the distance that the rim moved within the total scan-time (S_{rim}) could be accurately determined. By summing up all the rim movement measurements along the periphery we could quantified the total rim movement for each tumor (S_{total}). To address issue of patient motion, we developed a frame-by-frame 3D rigid registration to correct for displacements over the course of the DCE analysis.

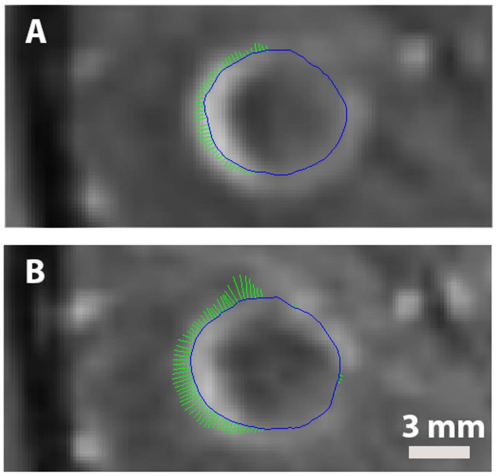

Figure 1 Illustration of S_{rim} calculated along the tumor periphery (blue line) for a tumor at A) day 0 and B) day 2. The length of the green lines corresponds to the calculated S_{rim} value.

Results: 12 tumor metastases were available for DCE-MRI assessment at day 0, 10 at day 2 and 11 at day 7. Tumor size at day 0 ranged from 0.5-4.9 cm^3 with a mean value of 2.0 cm^3. Somewhat unexpectedly, tumor volume increased from day 0 to day 2 (mean=2.6 cm^3) ($p<0.05$) and decreased towards baseline values at day 7 (mean=2.3 cm^3). As reported by others, edema increased significantly from day 0 (mean=1.7 cm^3) to day 2 (mean=4.2 cm^3) and remained elevated at day 7 (mean=5.9 cm^3).

The distance the rim moved (S_{rim}) varied around the tumor periphery of each tumor, ranging from 0 to 2.3 mm, with large heterogeneity seen within most tumors. S_{rim} also varied significantly between individual tumors, some tumors showed little or no rim movement, while others displayed a large rim motion around most of its periphery. S_{total} increased significantly from day 0 (median=13.8 mm) to day 2 (median=23.8 mm) ($p<0.05$) and decreased 7 days post treatment (median=3.8 mm).

The brain does not have a lymphatic system and if the observed rim motion were caused by an interstitial fluid flow from the tumor into the normal brain tissue one would expect an association between rim movement and edema. Indeed a strong correlation was found between S_{total} and edema for the baseline and day 2 values ($p<0.001$, $R^2=0.90$). Furthermore, increase in S_{total} (S_{total} day 2 - S_{total} day 0) correlated with increase in edema (edema day 2 – edema day 0) for the individual tumors ($p<0.001$, $R^2=0.85$).

Interestingly, the increase in S_{total} correlated with the increase in tumor volume from day 0 to day 2 ($p<0.001$ $R^2=0.76$). Thus, the increase in tumor volume observed at day 2, determined by contrast enhancing volume, is most likely an effect of an increased contrast agent transport from the tumor periphery into the surrounding normal tissue, as opposed to changes in tumor boundary location.

Discussion: Interstitial fluid pressure is elevated in tumors and has been shown to correlate with patient prognosis in cervical cancer patients treated with radiation therapy. However, IFP measurements in brain tumors are rare, mainly due to the fact that there is currently no noninvasive method available for its assessment. Here we communicate a method for measuring interstitial fluid flow in brain metastases, a potential tool to noninvasively measure changes in IFP. With this method we are able to show an increased peritumoral fluid flow after SRS most likely caused by an increase in tumor vasculature permeability and subsequent increase in IFP. The observed fluid flow was found to correlate with an increase in peritumoral edema. Interestingly, we also show that the fluid flow induced contrast agent transport can lead to misinterpretations of tumor volume measured by DCE-MRI depending on the time interval between injection and contrast-enhanced image acquisition.

References:

1) Hompland T, et al. Cancer Res 2012;72(19):4899-4908,