Transcapillary transport and interstitial fluid pressure in tumors; monitoring by DCE-MRI using instantaneous and slow infusion.

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Introduction

Many solid tumors show an increased interstitial fluid pressure (IFP), which forms a barrier to transcapillary transport. This barrier leads to an inefficient uptake of therapeutic agents and hence, demonstrates a physical resistance to therapy. Currently IFP is measured locally by invasive methods that may damage the tissue and modulate the IFP level. Herein we show the capability of DCE-MRI to non-invasively map the distribution of IFP in tumors and indicate the mechanism of transcapillary transport.

Methods

Studies were performed in two different experimental tumor models: 1. Human H-460 non small cell lung carcinoma cells inoculated subcutaneously in the flank of nude mice. 2. Human MCF7 breast cancer cells inoculated in the mammary gland of nude mice. The mice were anesthetized throughout the experiments by exposure to 1% isoflurane in an O_2/N_20 (3:7) mixture. All animal procedures were approved by IACUC.

DCE measurements were conducted with GdDTPA administered as a bolus at a dose of 0.4 mmol/kg or by slow infusion through the tail vein at a rate of 0.67 mmol/ kg/h.

Images were acquired with a 4.7T Biospec spectrometer (Bruker). The protocols included:

1. Multi slice 2D gradient echo sequence (GE) with TE/TR = 2.8/36.7 msec, flip angle 60º, matrix size 128:128, FOV 3 cm., 2 averages, and temporal resolution of 9 sec.

2. One slice fast SNAP inversion recovery (IR) sequence with a non selective inversion pulse, inversion time, TI, ranging from 50 to 10000 msec and fast low angle GE acquisition with TE/TR=3.5/36.7 msec, matrix size 128:128, and FOV 3 cm.

The data obtained by the GE monitoring was analyzed by a nonlinear curve-fitting of the time courses of signal enhancement to the perfusion equation based on a compartmented model to yield the influx and efflux transcapillary transfer constants k_{in} , and k_{ep} [1]. The T1 measurements served to assess the apparent GdDTPA concentration per pixel [Ct] according to: 1/T1 = 1/T10 + r1[Ct] where r1 is the T1 relaxivity = 4.3 $sec^{-1}mM^{-1}$[2].

The IFP in the tumors relative to that in other normal tissues was measured by the wick-in-needle method [3].

Histological characterization included H&E staining, and CD34 immunostaining of new capillaries.

Results

The time courses of GdDTPA distribution in the tumors during the infusion or after bolus injection were monitored by sequential GE images. After the bolus injection MCF7 tumors showed enhancement throughout the entire tumor, including inner parts, whereas H-460 tumors exhibited rim enhancement and null enhancement in the center. The employment of the slow infusion protocol enabled us to monitor the entrance of the contrast agent to H-460 regions with low transcapillary transfer rates. However, in some regions where no entrance was observed during the slow and long infusion, the presence of high IFP was inferred. Nonlinear curve-fitting of the time-dependent contrast enhancement per pixel yielded parametric images of the influx and efflux transcapillary transfer constants (Figure 1 A and B). The results demonstrated an heterogeneous distribution of the perfusion parameters in the tumor and in the surrounding tissue. The median values of these parameters in H-460 lung cancer tumors, 9-14 days after implantation were: k_{in}= 0.09±0.03 k_{ep} = 0.01 ±0.003 (n=5). Most frequently k_{in} was higher and k_{ep} lower or null in the tissue surrounding the tumor, indicating the presence of convection. Analysis of T1 measurements at steady state concentration of GdDTPA (reached 60 minutes after the start of the infusion) indicated that in the region surrounding the tumor GdDTPA was accumulated to a concentration of ~0.5 mM while in some inner parts the concentration was practically null, in accord with the presence of high IFP (figure 2).

Inspection of the histological and immunostained slices of the tumors, as well as IFP pressure measurements served to confirm the presence of high IFP in the lung tumors as compared to those in the breast.

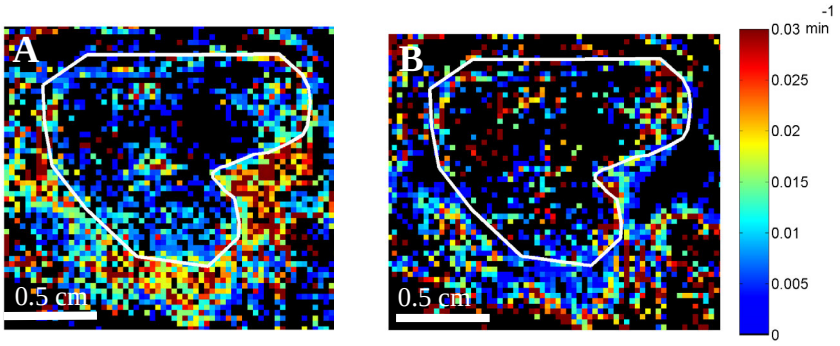

Figure 1: Parametric images of the transcapillary transfer constants in H-460 tumor implanted in the flank of a nude mouse. The parametric k_{in} (A) and k_{ep} (B) revealed heterogeneous distribution. Note the high k_{in} and low k_{ep} values outwards compared to the tumor, which indicates on convection.

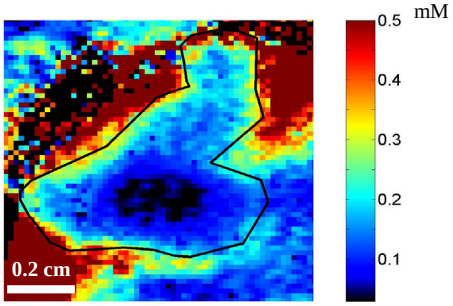

Figure 2: Steady state apparent GdDTPA concentration map of H-460 tumor implanted in the flank of a nude mouse.

Conclusion

DCE-MRI using slow infusion administration provides a means to explore tumors with highly impaired and slow perfusion, and detect regions with high IFP. Moreover, tumor regions with capillaries of low permeability that were not identified by the bolus protocol could be monitored using the slow infusion protocol. In addition, the steady state GdDTPA T1 measurements could map the distribution of the contrast agent in the tumor and hence, assess the presence of regions with barriers for drug delivery.

References

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