Semi-Parametric Analysis of Gd-DTPA Kinetics in Glioblastoma

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Introduction The kinetics of Gd-DTPA in malignant tumors, as indicated by whole-tumor concentration-time data obtained by DCE-MRI, are typically too complex to be adequately described by a one-compartment tumor model with an additional contribution from blood plasma (Fig. 1a); adding one more tumor compartment usually yields an adequate model fit[1,2] (Fig. 1b). The estimated tumor model parameters (three scale parameters, two rate constants) may depend on any or all of tumor perfusion, vessel permeability, vessel surface area, intratumoral distribution volume[3], transmembrane exchange of water protons[4] and diffusion distances between exchanging vessels. To avoid overinterpretation of the parameter estimates as well as predictions beyond the period of observation, we propose to summarize the compartmental modeling results by calculating non-compartmental descriptors of the fitted tumor impulse-response function (IRF) within the observation period: area under the curve (AUC) and mean residence time (MRT). This analysis has been applied to DCE-MRI data obtained from recurrent glioblastoma patients before and after the first dose of bevacizumab.

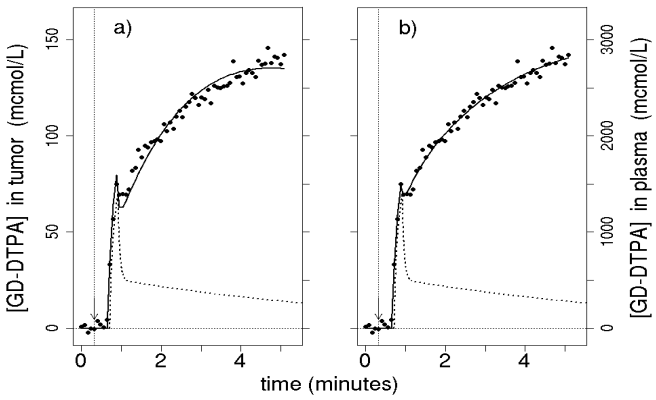

Fig. 1: DCE-MRI in recurrent glioblastoma. Median whole-tumor concentration of Gd-DTPA versus time after bolus injection (arrow). Right y-axis and dotted curve: fitted vascular input function. Left plot: tumor model has one exchanging compartment + plasma compartment. Right plot: tumor model has two exchanging compartments + plasma compartment.

Method and Patients The data came from a phase II study of bevacizumab, followed by bevacizumab + irinotecan, in recurrent glioblastoma patients[5]. DCE-MRI was performed at -72, -24, and +24 hours before and after administration of bevacizumab at a dose of 10 mg/kg. Dynamic images were obtained using 3D FLASH every 4.8 sec for a total of 5 min. The median concentration profiles in the superior sagittal sinus and in the contrast-enhancing tumor volume, respectively, were used as input and output data for compartmental modeling. (Whole-tumor profiles were analyzed rather than single-voxel profiles in order to reduce noise and better detect kinetic complexity.) Tumor models with one or two exchanging compartments, without or with a plasma compartment, were sequentially fitted to each pair of input/output data sets. The most parsimonious model which was not significantly inferior to a more complex model was kept as the final model. The area under the curve (AUC) of the IRF and the mean residence time in tumor (MRT) were then calculated based on the fitted compartmental model parameters using analytical expressions, for the the first 4 min after arrival of contrast agent in tumor,. The AUC was multiplied by the apparent total contrast-enhancing tumor volume (TV), in an effort to obtain a response parameter that reflects the absolute total extent of contrast agent leakage and is unbiased by partial volume effects or necrotic material which may or may not be present within the volume of interest.

Results $AUC_{0\text{-}4}$ x TV showed a drop of 40-60% at 24 hours after bevacizumab in almost all patients, with little inter-patient variability (Fig. 2). Part of the drop seemed to be due to a shrinkage of the apparent contrast-enhancing tumor volume, TV. $MRT_{0\text{-}4}$ did not show a consistent change in either direction.

Discussion In this method, compartmental modeling only serves as a device to derive a tumor impulse-response function. If AUC x TV was known from time zero to infinity, it would represent the total contrast-accessible tumor volume (total accessible volume fraction x TV). Within a limited observation period, it depends both on intratumoral distribution volume and on the speed of contrast agent leakage. MRT reflects the speed of contrast agent exchange. If the predominant drug effect was on vessel permeability and, thus, on the speed contrast agent exchange, then a prolongation of MRT would have been expected which was not apparent. If this finding can be confirmed by extending the DCE-MRI measurements into the washout period (cf. Fig. 1b), then a straightforward explanation for a drop in AUC (and a slight drop in TV) without a change in MRT would be to assume a shrinkage of the intratumoral distribution volume of Gd-DTPA accompanied by a loss of exchanging vessels.

Conclusion The shape of the impulse-response function of malignant tumors can be derived by compartmental modeling. Calculating the summary measures AUC and MRT for the period of observation avoids overinterpretation of the compartmental model and prediction beyond the last measurement time. It still enables hypothesis generating about drug effects on tumor physiology.

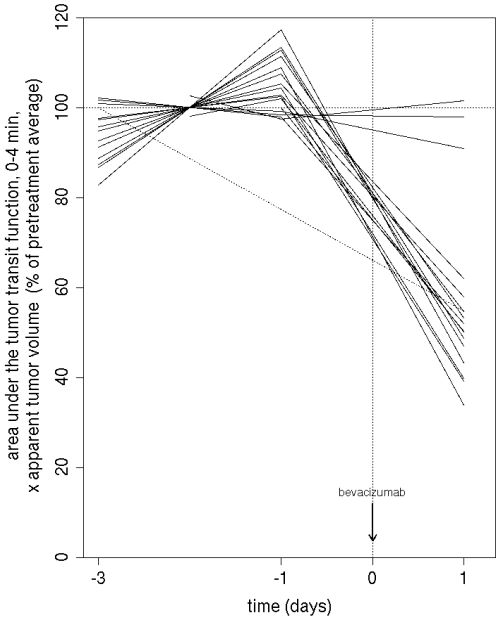

Fig. 2: DCE-MRI in recurrent glioblastoma patients. Area under the tumor transit function of Gd-DTPA before and after the first dose of bevacizumab (10 mg/kg).

References: 1. Port RE et al., JMRI 10, 233-241, 1999. 2. Luedemann L et al., MRM 23, 833-841, 2005. 3. Tofts PS et al., JMRI 10, 223-232, 1999. 4. Yankeelov TE et al., MRM 50, 1151-1169, 2003. 5. Vredenburgh JJ et al., Clin Cancer Res 13, 1253-1259, 2007.