Dynamic contrast-enhanced magnetic resonance imaging of high-grade gliomas - methodological aspects and error estimations

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Summary

High-grade gliomas (HGG) are the most common type of primary brain tumor in adults and affect around 300 Norwegian patients each year. This is a very aggressive form of cancer, and the median survival is 14 months. Standard treatment for HGG consists of surgical removal of as much of the tumor as possible followed by radiation therapy and chemotherapy. Because this entails a significant extra strain for the patient, it is desirable to be able to detect as early as possible during treatment whether it has the desired effect.

Dynamic contrast-enhanced MRI (DCE-MRI) is one of the techniques used to assess the treatment response by providing a description of the vascular environment in the tumor. By making frequent repeated image shots during and after contrast agent injection, we can use pharmacokinetic models to calculate interesting physiological parameters that give quantitative measures of the tumor's condition. This presupposes a calculation of absolute concentration curves in both tumor and an artery, which places a number of requirements on the acquisition technique and the analysis methods which are not yet sufficiently elucidated. We have sought to remedy this by doing both simulations and analysis of clinical data from a treatment monitoring study that was conducted at Oslo University Hospital from 2010 to 2014 with 23 HGG patients.

One of the conditions for quantitative analysis of DCE-MRI is a precise measurement of the contrast agent concentration in a supplying artery to the tumor, called the arterial input function (AIF). The highest concentration occurs at the first passage of the contrast agent through the arteries, and we hypothesized that it may be higher than conventional DCE-MRI is able to detect. We found that the hypothesis was correct in our data and

defined which conditions must be met to avoid this. We also examined whether the results depend on who performs the measurement of the AIF. This showed that there is a significant operator dependence, and that the reproducibility can be increased by performing a normalization of the measured AIFs.

We then examined what temporal resolution is needed in the dynamic acquisitions to obtain sufficient information in the concentration curves. The prevailing assumption is that high time resolution is essential, which gives less time for each dynamic timepoint and thus limits the image quality that is possible to achieve. By downsampling the image series and using simulations, we found no significant change in the results for lower than 20 s sampling duration. This is significantly longer than normal acquisition time (1-3 s), and allows for higher spatial resolution and/or better signal-to-noise ratio.

To determine the contrast agent concentration in DCE-MRI, it is necessary to relate the signal change it causes to the reduction in T_1 relaxation. This requires a separate T_1 measurement before the DCE-MRI acquisition, which introduces more noise in the analysis chain and means that the total examination time increases. We examined the effect on the results of using a fixed T_1 value rather than measured values and found a linear relationship between errors in $1/T_1$ and errors in the results. On the other hand, there was no difference in change over time for each individual patient, which means that the analysis can be considerably simplified if the purpose is to observe development over time.

Several aspects of DCE-MRI have been identified in this dissertation that can be used to make the method more applicable and reproducible. These are at the expense of quantifiable results, but do not prevent monitoring of disease development in individual patients.

Sammendrag (summary in Norwegian)

Høygradige gliomer (HGG) er den hyppigst forekommende typen av primær hjernesvulst hos voksne, og rammer rundt 300 norske pasienter hvert år. Dette er en svært aggressiv kreftform og median overlevelse er 14 måneder. Standard behandling av HGG består av kirurgisk fjerning av så mye som mulig av svulsten etterfulgt av stråleterapi og cellegiftbehandling. Fordi dette medfører en vesentlig ekstra påkjenning for pasienten er det ønskelig å kunne oppdage så tidlig som mulig i behandlingsforløpet om det har ønsket virkning.

Dynamisk kontrastforsterket MR-avbildning (DCE-MRI) er en av teknikkene som benyttes for å vurdere behandlingsresponsen ved å gi en beskrivelse av det vaskulære miljøet i tumor. Ved å gjøre hyppige gjentatte bildeopptak under og etter kontrastmiddelinjeksjon kan vi ved bruk av farmakokinetiske modeller beregne interessante fysiologiske parametere som gir i utgangspunktet kvantitative mål på svulstens tilstand. Dette forutsetter en beregning av absolutte konsentrasjonskurver i svulst og arterie, hvilket setter en del krav til opptaksteknikken og analysemetodene som ikke er tilstrekkelig belyst. Dette har vi søkt å bøte på ved å gjøre både simuleringer og analyse av kliniske data fra en studie på behandlingsmonitorering som ble gjennomført ved Oslo universitetssykehus fra 2010 til 2014 med 23 HGG-pasienter.

En av betingelsene for kvantitativ analyse av DCE-MRI er en presis måling av kontrastmiddelkonsentrasjonen i en tilførende arterie til svulsten, kalt den arterielle inputfunksjonen (AIF). Den høyeste konsentrasjonen forekommer ved kontrastmidelets første passasje gjennom arteriene, og vi fremsatte en hypotese om at den kan være høyere enn konvensjonell DCE-MRI klarer å registrere. Vi fant at hypotesen stemte i våre data og kom fram til hvilke betingelser som må oppfylles for å

unngå dette. Vi undersøkte også om resultatene avhenger av hvem som utfører målingen av AIFen. Dette viste at det er en signifikant operatørvhengighet, og at reproduserbarheten kan økes ved å gjøre en normalisering av de målte AIFene.

Vi undersøkte deretter hvilken tidsoppløsning som er nødvendig i de dynamiske opptakene for å oppnå tilstrekkelig informasjon i konsentrasjonskurvene. Den gjeldende antagelsen er at høy tidsoppløsning er essensielt, noe som gir mindre tid til hvert enkelt dynamiske tidspunkt og dermed begrenser bildekvaliteten som er mulig å oppnå. Ved å nedskalere bildeseriene og bruk av simuleringer fant vi ingen signifikant endring i resultatene for lavere enn 20 s dynamisk opptakstid. Dette er vesentlig lenger enn vanlig opptakstid som er 1-3 s, og åpner for at man kan benytte høyere romlig oppløsning.

For å bestemme kontrastmiddelkonsentrasjon i DCE-MRI er det nødvendig å relatere signalendringen den forårsaker til reduksjon i T_1 -relaksasjon. Dette krever en egen T_1 -måling før DCE-MRI-opptaket, noe som introduserer mer støy i analysekjeden og medfører at total undersøkelsestid øker. Vi undersøkte effekten på resultatene av å bruke en fast T_1 -verdi fremfor målte verdier, og fant en lineær sammenheng mellom feil i $1/T_1$ og feil i resultatene. Det var derimot ingen forskjell i endring over tid for hver enkelt pasient, hvilket betyr at analysen kan forenkles betraktelig hvis formålet er å observere utvikling over tid.

Det er i denne avhandlingen identifisert flere aspekter ved DCE-MRI som kan utnyttes til å gjøre metoden mer anvendbar og reproduserbar. Disse går på bekostning av absolutt kvantifiserbare resultater, men er ikke til hinder for å følge sykdomsutvikling hos individuelle pasienter.

List of abbreviations

2CXM	Two-compartment exchange model
AIF	Arterial input function
ANOVA	Analysis of variance
AUC	Area under the curve
BBB	Blood-brain barrier
CA	Contrast agent
C_a	CA concentration in arterial blood
CI	Confidence interval
C_t	CA concentration in tissue
DCE	Dynamic contrast-enhanced
DE	Domain expert
DSC	Dynamic susceptibility contrast
DTI	Diffusion tensor imaging
EES	Extravascular, extracellular space
ETM	Extended Tofts model
FA	Flip angle
FLAIR	Fluid attenuated inversion recovery
Gd	Gadolinium
GRE	Gradient echo
HGG	High-grade glioma
ICC	Intraclass correlation coefficient
IR	Inversion recovery
κ	Fleiss' kappa
k_{ep}	Rate constant for contrast agent reflux from EES to plasma space
K^{trans}	Contrast agent transfer constant from the plasma space to EES
LL	Look-Locker

MR	Magnetic resonance
MRI	MR imaging
MTT	Mean transit time
NMR	Nuclear magnetic resonance
PKP	Pharmacokinetic parameter
Pop-AIF	Population-averaged AIF
PS	Permeability surface area
PV	Partial volume
R_1	Longitudinal relaxation rate ($= 1/T_1$)
R_2	Transverse relaxation rate ($= 1/T_2$)
R_2^*	Effective transverse relaxation rate in GRE sequences ($= 1/T_2^*$)
RANO	Response Assessment in Neuro-Oncology Working Group
RF	Radio frequency
ROI	Region of interest
SE	Spin echo
SNR	Signal to noise ratio
SR	Saturation recovery
SR-SPGR	Saturation recovery spoiled gradient echo
SSS	Superior sagittal sinus
T	Tesla
T_1	Longitudinal relaxation time
$T_1(0)$	T_1 in absence of CA
T_1 -LL	T_1 Look-Locker
T_2	Transverse relaxation time
T_2^*	Effective transverse relaxation time in GRE sequences
T_{acq}	Total acquisition time
TE	Echo time
T_s	Sampling interval
TD	Saturation delay (trigger delay)

TI	Inversion time
VFA	Variable FA
v_e	Fractional EES
v_p	Fractional tissue plasma volume
WSR	Wilcoxon signed-rank test

List of papers included

Paper I:

T₂*-Correction in Dynamic Contrast-Enhanced MRI From Double-Echo Acquisitions.

Kleppestø M*, Larsson C, Groote IR, Salo R, Vardal J, Courivaud F, Bjørnerud A.

Journal of Magnetic Resonance Imaging, 2014;39:1314–1319, doi:10.1002/jmri.24268

Paper II:

Sampling Requirements in DCE-MRI Based Analysis of High Grade Gliomas: Simulations and Clinical Results.

Larsson C*, **Kleppestø M**, Rasmussen I, Salo R, Vardal J, Brandal P, Bjørnerud A.

Journal of Magnetic Resonance Imaging, 2013;37:818-829, doi:10.1002/jmri.23866

Paper III:

T₁ in High-Grade Glioma and the Influence of Different Measurement Strategies on Parameter Estimations in DCE-MRI.

Larsson C*, **Kleppestø M***, Grothe IR, Vardal J, Bjørnerud A.

Journal of Magnetic Resonance Imaging, 2015;42:97-104, doi:10.1002/jmri.24772

Paper IV:

Operator Dependency of Arterial Input Function in Dynamic Contrast-Enhanced MRI.

Kleppestø M*, Bjørnerud A, Groote IR, Kim M, Vardal J, Larsson C.

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1 Introduction

High-grade gliomas (HGGs) are the most common of primary malignant brain tumors in adults¹. Around 300 cases are diagnosed in Norway each year, and incidence increases with age². Despite several advances in both diagnostics and treatment over the last decades, median survival for this particularly aggressive disease is little more than one year³. Some patients survive significantly longer, but currently there exists no established biomarker to predict individual patients' response to therapy. As treatment further reduces quality of life for the patient, there is a need for a means to determine the expected effect of treatment as early as possible after diagnosis.

Magnetic resonance (MR) imaging (MRI) is the primary imaging modality used for diagnosis and staging of HGGs as well as monitoring during treatment. The present evaluation of treatment response is by changes in tumor volume using structural T₁-weighted and fluid-attenuated inversion recovery (FLAIR) weighted images. While the morphological information extracted from these images provide useful indications on tumor status, they reflect not only treatment induced changes, but also recurrent disease. This has led to the development of several sophisticated imaging techniques in recent decades, including dynamic perfusion and permeability MRI⁴. These methods seek to provide information on the microvasculature of the tumor and surrounding tissue that may improve characterization of disease status. This thesis will address the method known as dynamic contrast-enhanced (DCE) MRI, which provides estimates of vascular permeability-related parameters in the tumor.

2 Background

2.1 MRI

MRI is based on the nuclear magnetic resonance (NMR) phenomenon, which describes the interaction between the spin of atomic nuclei and a magnetic field^{5,6}. NMR is inherently a quantum mechanical concept, but as imaging involves measurement of large collections of nuclei, most of the physics of MRI is sufficiently described using classical terminology.

2.1.1 The MR signal

Atomic nuclei with an odd number of nucleons (protons and/or neutrons) possess a net magnetic moment called spin that will respond to an external magnetic field by precessing around the field's direction. The angular velocity vector ω_0 of the magnetization in an external magnetic field $\mathbf{B}_0$ is given by the Larmor equation:

$$\omega_0 = -\gamma \mathbf{B}_0, \quad [1]$$

where γ is the gyromagnetic ratio, which is a constant unique to each isotope. The corresponding frequency - the Larmor frequency - is therefore proportional to the external field strength. In clinical MRI, the nucleus of interest is primarily that of hydrogen (^1H), which consists of a single proton and is omnipresent in human tissue as a component of water and lipids. The most common type of clinical MRI scanners today utilizes a cylindrical superconducting electromagnet in which the static $\mathbf{B}_0$ -field is directed along the magnet bore. When a hydrogen-containing object is placed in this field, the sum of the magnetic moments of the protons will be directed in what is

commonly defined as the z-direction in a xyz coordinate system. In order to measure the magnetization, it needs to have a component in the transverse plane perpendicular to $\mathbf{B}_0$. This is achieved by exciting the proton spins by way of a magnetic field $\mathbf{B}_1$ that is orthogonal to $\mathbf{B}_0$, in the form of a transient electromagnetic wave at the Larmor frequency. Because the gyromagnetic ratio of protons puts their Larmor frequency in the radiofrequency (RF) range at clinical field strengths, $\mathbf{B}_1$ is commonly called an RF-pulse. The amount of magnetization transferred to the transverse plane depends on the amplitude and duration of the pulse and is reported as the angle of the resulting magnetization vector sum with the z-axis, so that a 90° -pulse completely flips the magnetization to the transverse plane. This is known as the flip angle (FA) of the RF-pulse. For the duration of the RF-pulse the magnetization vectors of the individual spins remain in phase. While the magnetization is precessing in the transverse plane, it will induce an electromotive force in a receiving coil that may be measured.

2.1.2 Relaxation

When the RF-pulse is switched off, the system will gradually revert towards equilibrium. The processes that facilitates this are known as relaxation, which occurs by the magnetization realigning with the $\mathbf{B}_0$ -field, termed T_1 -relaxation, and disappearing from the transverse plane, known as T_2 -/ T_2^* -relaxation.

T_1 -relaxation

Excited spins will exchange energy with its surroundings to restore thermal equilibrium. The recovery of magnetization in the z-direction is exponential and is characterized by the time constant T_1 , which is the time required for the longitudinal magnetization to regain 63 % ($= 1 - e^{-1}$) of its initial value. The inverse of T_1 is referred to

as the longitudinal relaxation rate, R_1 . In humans at body temperature at clinical field strengths, T_1 ranges from 100-200 milliseconds in fatty tissue to several seconds in fluids. T_1 is generally increasing with field strength. So-called *T_1 -weighted* images are the result of tailoring an imaging sequence to be sensitive to the tissue-specific variation in T_1 . This is achieved by using a TR in the range of T_1 of the imaged tissue to differentiate the relevant tissues based on their T_1 , and shortest possible TE ($\ll T_2$) to minimize the amount of transverse relaxation before signal acquisition. In these images the signal intensity in each voxel will depend on the cumulative T_1 of the spins in that voxel, such that shorter T_1 gives rise to a higher signal intensity and vice versa.

T_2 - and T_2^* -relaxation

The loss of phase coherence in the transverse plane is also an exponential process and its characterizing time constant is termed T_2 . While this includes the transfer of magnetization back to the z-direction, the dominating mechanism is by local effects. Small field inhomogeneities from interactions with nearby spins (chemical shift) cause differences in precession frequency, which leads to dephasing. The T_2 value is tissue-specific and is not much affected by field strength. Equivalently to the definition of T_1 , T_2 is the time after which 63 % of the transverse magnetization is *lost*, and the transverse relaxation rate is referred to as R_2 . T_2 in tissue is generally significantly shorter than T_1 .

Static macroscopic field inhomogeneities caused by imperfections in the external $\mathbf{B}_0$ field and disruptions from the object placed in the field leads to additional dephasing in the transverse plane. This is termed T_2' relaxation and adds to the transverse relaxation rate giving the effective relaxation rate $R_2^* = R_2 + R_2'$. R_2' -relaxation rates increase with increasing field strength.

2.1.3 Image formation and MRI signal behavior

To reconstruct an image from the recorded signal, the signal must be encoded with spatial information. This is achieved by applying carefully timed magnetic field gradients in all three orthogonal directions, which results in position dependent Larmor frequencies and phase shifts. There exists a plethora of ways to organize RF-pulses and field gradients into what is known as pulse sequences, each aiming to provide a certain image contrast. Clinically employed pulse sequences are almost always based on either the spin-echo (SE) or the gradient-echo (GRE) techniques.

In a SE pulse sequence, the longitudinal magnetization is first flipped to the transverse xy-plane with a 90° -pulse, after which the spins are left to dephase for a time $TE/2$, where TE is the echo time at which the peak of the signal is sampled. Then, a 180° refocusing pulse flips the dephased spins to the opposite quadrant of the xy-plane, where they rephase and converge to form an echo at time TE. The initial dephasing due to static field inhomogeneity is reversed following the refocusing pulse, and the measured signal will reflect T_2 relaxation.

In a GRE sequence, the excitation FA may be lower than 90° , and refocusing is done with a bipolar gradient pair. The gradients do not revert dephasing caused by static field inhomogeneity, and so the signal intensity will be attenuated by T_2^* relaxation. By not employing a 180° pulse and the possibility of lower FAs allow GRE sequences to employ shorter TE and overall faster acquisition than a SE sequence.

The relation between sequence parameters, relaxation times and MR signal intensity S of a GRE sequence is:

$$S(TE, TR, FA, T_1, T_2^*) \propto \frac{\sin(FA) (1 - e^{-TR/T_1})}{1 - (e^{-TR/T_1}) \cos(FA)} e^{-TE/T_2^*} \quad [2]$$

Equation [2] is valid under the assumption that any remaining transverse magnetization is eliminated between excitations. Equation [2] reduces to the standard SE signal equation when FA=90 deg and replacing T_2^* by T_2 .

2.1.4 Contrast agent in MRI

The relaxation rates of tissues can be greatly increased in the presence of paramagnetic metal ions. Unpaired electrons in the outer orbital shells of the ion create strong magnetic dipoles when exposed to a magnetic field. Because the electron has a vastly smaller mass than the proton, the magnetic moment of an unpaired electron is about 700 times larger than in a proton. This exposes nearby protons to large fluctuating magnetic fields which prolong their relaxation rates if these fluctuations are at, or close to, the Larmor frequency. The most common paramagnetic metal ion used in MRI contrast agents (CA) is gadolinium (Gd) because of several favorable properties⁷. Because the Gd ion itself is toxic, it is chelated into a biocompatible small molecular weight ligand. The relationship between CA concentration C and R_1 - and R_2 -relaxation rates is assumed to be linear⁸:

$$R_{1,2}(C) = R_{1,2}(0) + r_{1,2} \cdot C, \quad [3]$$

where r_1 and r_2 are the longitudinal and transverse relaxivity of the CA, respectively. The linearity depends on fast water exchange between tissue compartments such as the vasculature and interstitium, which entails that all water protons contributing to the signal have equal and unrestricted access to the paramagnetic ion within a time frame

in the order of the T_1 relaxation time of the medium. The linear assumption is considered reasonable in most clinical settings^{9,10}.

In addition to T_1 - and T_2 -shortening due to dipole-dipole interactions, the presence of paramagnetic ions also produces a shortening of T_2^* times from what is referred to as the susceptibility effect^{11,12}. This is not dependent on direct interaction with the paramagnetic ion but arises from the susceptibility difference caused by the CA not being uniformly distributed. Unlike direct dipole interactions, this is a long-range effect.

2.1.5 DCE-MRI

DCE-MRI is an imaging technique where T_1 -weighted images are serially acquired before, during and after the intravenous administration of CA into the patient. By observing the dynamic distribution of CA in tissue, information about the vascular environment can be obtained¹³. Because the T_1 -effect is dependent on direct interaction between the CA and water protons, the signal enhancement will occur only in the immediate vicinity of where the CA is distributed⁹. Conventional CAs are extracellular and restricted to the vasculature and the interstitium. These two compartments will in the following be referred to as the (blood) plasma space and the extravascular, extracellular space (EES), respectively.

In order to extract quantitative information from DCE-MRI, the CA concentration in the tissue of interest $C(t)$ must be determined at each time point t in the series. This is achieved by estimating $T_1(t)$ from the voxel signal intensity and combining with equation [3]. Because a precise, direct T_1 measurement requires a prohibitive amount of time to be feasible in a dynamic study, DCE sequences exploits the proportionality of

change in R_1 (ΔR_1) to CA concentration, as ΔR_1 can be estimated without explicitly measuring R_1 at each time-point, as described below.

The DCE pulse sequence used in this thesis is a saturation recovery spoiled GRE (SR-SPGR) sequence. This technique employs short TE and TR times to rapidly read out the MR signal following a saturation pulse and uses crusher gradients to remove any remaining transverse relaxation between excitations. The general signal equation for a SR-SPGR sequence is¹⁴:

$$S = M_0 \sin \alpha (1 - e^{-TD \cdot R_1}) e^{-TE \cdot R_2^*}, \quad [4]$$

where M_0 is the longitudinal magnetization before the excitation RF-pulse, α is the FA and TD is the trigger delay. TD is also referred to as *saturation delay* and is the time between the saturation pulse and acquisition of the first echo.

The signal intensity $S(t)$ at time t after the injection of CA is then related to the signal intensity $S(0)$ before the presence of CA as:

$$\frac{S(t)}{S(0)} = \frac{(1 - e^{-TD \cdot R_1(t)})}{(1 - e^{-TD \cdot R_1(0)})} e^{-TE(R_2^*(t) - R_2^*(0))} \quad [5]$$

Solving equation [5] for $R_1(t)$, and thus $C(t)$, is possible if $R_1(0)$ is known. It is customary to assume that the T_2^* -effect of the CA at 3.0 T is negligible at sufficiently low TE:

$$e^{-TE(R_2^*(t) - R_2^*(0))} \approx 1, \quad [6]$$

thereby eliminating the need to obtain R_2^* -measurements. This also means that the signal intensity of the SR-SPGR sequence is mainly defined by TD , although it is also to some extent influenced by the method used to rapidly read out the signal following the TD delay.

2.1.6 Quantitative relaxometry

In order to obtain $R_1(0)$ -estimates for Equation [5] and to test the validity of equation [6], measurements of T_1 and T_2^* are needed. This is called relaxometry and is achieved in this thesis by a dedicated sequence for T_1 relaxometry and a double-echo DCE sequence for T_2^* -relaxometry.

T_1 -relaxometry

T_1 is measured by indirectly sampling the longitudinal magnetization M_z following an excitation to reconstruct the relaxation curve. In this thesis we used a 3D inversion recovery (IR) sequence based on the Look-Locker method^{15,16} that samples M_z at N evenly spaced time points τ following an initial inversion pulse. Using a low FA and assuming the duration of the excitation pulses to be negligible, the recorded signal intensity will be proportional to M_z at the time of each excitation, and M_z is assumed to

Figure 1: Simulation of longitudinal magnetization M_z following an inversion pulse in a Look-Locker experiment using $FA = 20^\circ$, measurement interval $\tau = 300$ ms and $T_1 = 1000$ ms. The dashed line shows the recovery of longitudinal magnetization in the absence of any manipulation, while the solid line shows the magnetization course when excitation pulses (red crosses) are applied.

recover by T_1 -relaxation between the excitations. A simulated experiment using exaggerated parameters for illustrative purposes is shown in figure 1.

In the unperturbed situation, the signal recovery following a perfect 180° inversion pulse is given by:

$$S(t) = S_0 \left(1 - 2e^{-t/T_1}\right), \quad [7]$$

and T_1 can thus be estimated by non-linear curve fitting to the measured signal at multiple time-points t along the magnetization recovery trajectory. In practice, each measurement will cause a slight perturbation of the magnetization trajectory and the

magnetization thus approaches a steady state with an apparent relaxation time T_1^* that is dependent on the sequence parameters:

$$T_1^* = \frac{T_1}{1 - \frac{T_1}{\tau} \ln(\cos FA)}. \quad [8]$$

After fitting the signal points to obtain T_1^* , the perturbations to the magnetization caused by each measurement can be removed using equation [8] to get an estimate of T_1 .

T_2^* -relaxometry

One of the objectives of this thesis was to evaluate potential errors in DCE-derived metrics by assuming T_2^* -effects to be negligible (equation [6]), and for this purpose a double-echo DCE-sequence was used for estimation of $T_2^*(t) / R_2^*(t)$ by assuming a mono-exponential T_2^* -decay between the first (TE_1) and second (TE_2) echoes:

$$\frac{S(t, TE_2)}{S(t, TE_1)} = \frac{1 - e^{-TE_2 \cdot R_2^*(t)}}{1 - e^{-TE_1 \cdot R_2^*(t)}}$$

$$R_2^*(t) = \frac{\ln \left[\frac{S(t, TE_1)}{S(t, TE_2)} \right]}{TE_2 - TE_1}. \quad [9]$$

2.2 Tracer kinetic modeling for DCE-MRI

To extract pharmacokinetic parameters (PKPs) from the CA concentration time curves, a suitable kinetic model must be chosen. The objective of such models is to describe the pharmacokinetics of the CA in tissue of interest and thereby gain insight into the state of the tissue.

2.2.1 Two-compartment exchange model

The two-compartment exchange model (2CXM) is a four-parameter model that was first adopted for DCE-MRI for the breast¹⁷, and has since been used in other anatomies including the brain^{14,18,19}. It models the tissue as two compartments: the vascular plasma space of fractional volume v_p , and the EES of fractional volume v_e . CA enters the plasma space via arterial blood at concentration C_a , referred to as the arterial input function (AIF), and may from there diffuse into the EES in absence of an intact BBB. The rate at which CA enters the EES and returns to the plasma space is dependent on the plasma blood flow F and the permeability-surface product PS . The CA concentrations in

Figure 2: Illustration of the 2CXM. C_a , C_p and C_e is the CA concentrations in incoming arterial blood, the tissue plasma space v_p and tissue EES, respectively. F is blood flow and PS is the permeability surface product. The dotted line represents the BBB.

the two compartments are denoted C_e and C_p , respectively. An illustration of the model is shown in figure 2. Mass conservation for the two compartments gives the following two coupled differential equations:

$$v_p \frac{d}{dt} C_p = FC_a + PSC_e - (F + PS)C_p \quad [10]$$

$$v_e \frac{d}{dt} C_e = PSC_p - PSC_e \quad [11]$$

A thorough solution to this problem is given in Sourbron et al.²⁰ and yields estimates for F , v_p , v_e and the transfer constant $K_i = PS$ describing transfer from plasma space to EES. The transfer in the opposite direction is given by K_i/v_e .

2.2.2 Kety/Tofts model

The model proposed in 1951 by Kety²¹ describing gas exchange in the lungs has served as the basis for several models applied to CA kinetics²²⁻²⁴ that are of the same general form²⁵:

$$\frac{dC_t(t)}{dt} = K^{\text{trans}} (C_p(t) - C_t(t)/v_e) \quad [12]$$

This model assumes that v_p is negligible, which corresponds to reducing the 2CXM to only equation [11]. The notation used in equation [12] is referred to as the Tofts or Kety/Tofts model, and $C_t(t)$ is used in place of $C_e(t)$ to denote tissue CA concentration and $C_p(t)$ becomes the AIF. The K^{trans} in equation [12] is the volume transfer constant describing the flux of CA between blood plasma and EES and is defined under different assumptions in the referenced models. The physiological interpretation of K^{trans} is dependent on whether blood flow or permeability is the limiting factor in CA exchange

between the two compartments²⁶. In the former case $K^{\text{trans}} = F$, while in the latter it represents PS .

2.2.3 Extended Tofts model

The model used in this thesis is commonly referred to as the extended Tofts model (ETM), which accounts for a non-negligible plasma space and describes tissue CA concentration C_t as a function of time t by adding a vascular term to equation [12]¹⁰:

$$\frac{dC_t(t)}{dt} - v_p \frac{dC_p(t)}{dt} = K^{\text{trans}} C_p(t) - k_{\text{ep}} (C_t(t) - v_p C_p(t)), \quad [13]$$

where $C_t = v_p C_p + v_e C_e$ with C_e being the CA concentration in EES. K^{trans} and k_{ep} (both in min^{-1}) are the unidirectional volume transfer constants between plasma space and EES and the reverse, respectively and v_p is the fractional plasma space volume. k_{ep} is defined as the ratio of K^{trans} to v_e . Solving equation [13] with initial conditions $C_t(0) = C_p(0) = 0$ yields the convolution integral:

$$C_t(t) = K^{\text{trans}} \int_0^t C_p(\tau) e^{-k_{\text{ep}} \tau} d\tau + v_p C_p(t) \quad [14]$$

A graphical illustration of the model is shown in figure 3. The use of ETM in this thesis assumes the highly perfused permeability limited case, in which CA is readily available in the vasculature to diffuse to the EES²⁶. Equation [14] may be solved numerically for K^{trans} , k_{ep} and v_p from measurements of the voxel-wise $C_t(t)$ and the AIF. An example of tumor CA concentration time curve and AIF together with DCE-images is shown in figure 4. From Equation [14] it follows that the accuracy of K^{trans} and v_p estimations is very

Figure 3: Graphic representation of the ETM. Shown here is the vascular plasma space of fractional volume v_p and the extravascular, extracellular space (EES) of fractional volume v_e . The flux of the contrast agent, illustrated as black dots, between the two compartments is described by the rate constants K^{trans} and k_{ep} .

sensitive to correct determination of the AIF ($C_p(t)$). Given the limited spatial resolution of current DCE-MRI methods, AIF determination is challenged by partial volume effects^{30–34}, T_2^* -contamination and inter-observer variability in AIF selection, posing major limitations in the current ability to obtain reproducible parameter estimations in DCE-MRI in clinical routine^{35,36}.

Figure 4: Top: CA concentration curves of $C_t(t)$ in tumor tissue (black) and $C_p(t)$ (red) from DCE-MRI. Bottom: corresponding DCE images at selected time points; (a) prior to CA arrival, (b) CA peak, (c) one minute following CA peak and (d) three minutes following CA peak.

2.2.4 Patlak model

The Patlak model²⁷ is similar to ETM in that it describes a highly perfused system, but with the assumption that CA entering the EES is trapped for the duration of the acquisition. This makes the model suitable for cases where CA reflux from the EES is negligible, either due to tissue characteristics or because T_{acq} is limited. By setting $k_{\text{ep}} = 0$ in equation [13] and solving for initial conditions $C_t(0) = C_p(0) = 0$, we get:

$$C_t(t) = K^{\text{trans}} \int_0^t C_p(\tau) d\tau + v_p C_p(t) \quad [15]$$

By dividing each side of equation [15] by $C_p(t)$, a linearized form is obtained:

$$\frac{C_t(t)}{C_p(t)} = K^{\text{trans}} \frac{\int_0^t C_p(\tau) d\tau}{C_p(t)} + v_p \quad [16]$$

Thus, a plot of $C_t(t)/C_p(t)$ versus $\int_0^t C_p(\tau) d\tau/C_p(t)$ will, given that the Patlak model is valid for the data, provide a straight line with slope K^{trans} and intercept v_p in what is known as a *Patlak plot*^{28,29}. This allows for quick determination of whether the model is appropriate for the data by visual inspection, and easy fitting of the model to obtain the two KPEs.

Temporal requirements of ETM

Sampling duration (T_s) is the primary limiting factor of spatial resolution and signal-to-noise ratio (SNR) in DCE-MRI, which makes high image quality and rapid sampling of the concentration curves mutually exclusive requirements. In the interest of clinical throughput and patient comfort and compliance it is desirable to keep to the total acquisition time (T_{acq}) as short as possible. The optimal compromise between these competing factors is the longest T_s and shortest T_{acq} that provide adequate sampling of

the concentration curves. To approach this problem, the requirements on the sampling scheme of $C_p(t)$ and $C_t(t)$ in Equation [14] will be considered in the frequency domain. Fourier transform of equation [14] yields the system transfer function³⁷:

$$H(\omega) = \frac{C_t(\omega)}{C_p(\omega)} = v_p + \frac{K^{\text{trans}}}{i\omega + k_{\text{ep}}} \quad [17]$$

where ω is the angular frequency and the system input $C_p(\omega)$ and output $C_t(\omega)$ are the Fourier transforms of $C_p(t)$ and $C_t(t)$, respectively. It is seen that this system has a pole (3 dB input-output attenuation) at $i\omega = -k_{\text{ep}}$ which makes $e^{-k_{\text{ep}}\tau}$ in equation [14] act as a low-pass filter between C_p and C_t with cutoff frequency given by $\omega = 2\pi k_{\text{ep}}$. The highest frequency that can be identified in $H(\omega)$ for a given T_s is: $\omega_{\text{max}} = \frac{\pi}{T_s}$, while the lower limit is dependent on T_{acq} : $\omega_{\text{min}} = \frac{2\pi}{T_{\text{acq}}}$. The Nyquist-Shannon sampling theorem dictates that the sampling frequency $\frac{1}{T_s}$ must be at least twice that of the highest k_{ep} to be measured³⁸:

$$T_s \leq \frac{1}{2 \cdot k_{\text{ep}}^{\text{max}}}. \quad [18]$$

In order to detect the lowest k_{ep} , T_{acq} must satisfy:

$$T_{\text{acq}} \gg \frac{1}{k_{\text{ep}}^{\text{min}}}. \quad [19]$$

It follows that one should ideally use the longest T_s possible for the expected range of k_{ep} *in vivo*, while T_{acq} should be sufficiently long to achieve a reliable representation of the lowest k_{ep} (and K^{trans}) values.

2.2.5 Importance of the AIF

The AIF is an essential component in quantitative pharmacokinetic modeling, but accurate AIF measurement has been a consistent challenge in DCE-MRI³⁹. The preferred

approach is to estimate the CA concentration in an artery directly upstream of the tissue of interest¹⁰. This imposes several requirements on the DCE-MRI acquisition: the image volume must contain an appropriate artery; the spatial resolution must allow for measurement within this artery without suffering partial volume (PV) effects^{33,40} and the temporal resolution must be sufficient to capture the shape of the AIF. One common way of avoiding this problem is to use a population-averaged AIF (pop-AIF) from a collection of measurements in a study population⁴¹. This method is most commonly used outside the brain where locating a suitable vessel is often not feasible⁴². While pop-AIF does not reflect the individual hemodynamics of each subject, studies have found it to produce KPEs comparable to those obtained using individually measured AIFs when SNR and/or temporal resolution was low^{43–46}.

AIF measurements in the brain are most commonly made in the larger arteries such as the middle cerebral artery^{47–49}. The superior sagittal sinus (SSS) has also been proposed due to its prominent presence in almost any brain imaging volume, despite representing a venous signal^{50–54}. Keil et al.⁵² reported a significant impact on KPEs from measuring the AIF in the SSS compared to the internal carotid artery, while Filice and Crisi⁵³ and Jia et al.⁵⁵ found no significant difference when comparing AIFs from the SSS with arterial signal, and from four different arteries, respectively. Prostate studies have shown substantial variation in KPEs when different imaging centers measure AIFs in the same datasets^{35,56}.

2.3 HGG

Gliomas are a family of primary brain tumors that originate in the glial cells. They make up 30 % of all primary tumors in the brain, and as much as 70 % of the malignant ones⁵⁷. The WHO grading system for gliomas defines four subdivisions with increasing tumor aggressiveness. Grades I and II are classified as LGGs, while grades III and IV are termed HGGs. 55 % of gliomas are glioblastomas (WHO astrocytoma grade IV), and of these the majority (80-85 %) are primary glioblastomas⁵⁷. These tumors develop rapidly, as diagnosis is usually preceded by only six months of presenting symptoms⁵⁷. The grading system used in this thesis is the 2007 WHO classification⁵⁸, which has since been updated in 2016 to include genetic markers⁵⁹.

2.3.1 Treatment of HGGs

The standard treatment of HGG is radical surgery followed by radiotherapy and concomitant and adjuvant chemotherapy in the Stupp protocol³. Due to the infiltrative nature of gliomas, a complete removal by surgery is not feasible. However, maximum surgical resection while preserving eloquent neurologic functions serves to increase overall survival and provide symptom relief, as well as allowing for histological diagnosis⁶⁰. Radiotherapy localized to the margins of the original tumor increases median survival from 4-5 months with surgery as the only therapy to about one year⁶¹. Radiation is delivered in fractions of 2.0 Gy per day, five times a week for six weeks, to a total of 60 Gy. A further two months median survival is gained by adding chemotherapy with the alkylating agent temozolomide administered daily for the duration of the radiation therapy, and then in six cycles of five days followed by 23 days of pause starting four weeks after completion of radiotherapy.

2.3.2 MRI of HGGs

International guidelines suggest MRI follow-ups every 3-4 month after treatment completion^{62,63}. The standard guideline in Norway dictates that MRI should be performed every three months following treatment in addition to immediately before and after surgery. The current gold standard for response criteria in gliomas was introduced in 2010 by the Response Assessment in Neuro-Oncology (RANO) working group, and is primarily based on tumor appearance on structural FLAIR, T₂-weighted and contrast-enhanced T₁-weighted images⁶⁴. A standard imaging protocol additionally contains T₁-weighted imaging before CA administration, and these two series are referred to as pre- and post-contrast T₁-images. An example of structural images from a standard glioma MRI protocol is shown in figure 5. In the healthy brain the exchange of molecules between the vasculature and tissue is strictly regulated by the blood-brain-barrier (BBB), which makes conventional CAs behave as intravascular agents in the central neural system. HGG is accompanied by a compromised BBB, which permits the CA to leak into the cancerous tissue.

Figure 5: Structural images in a grade IV glioma patient. From left to right: pre-contrast T₁-weighted (A), post-contrast T₁-weighted (B), FLAIR (C) and T₂-weighted (D).

2.3.3 DCE-MRI in HGGs

Malignant tumors are dependent on a constant supply of oxygen and nutrients to maintain growth. Passive diffusion from the existing blood system allows for a tumor volume of 2-3 mm³ before the cells furthest away from microvasculature are starved, and in order to advance past this stage the tumor must grow new blood vessels connected to the pre-existing capillaries through angiogenesis⁶⁵. This process generates vessels that are generally fragile and prone to leakage compared to those of healthy tissue, and has been found to be particularly predominant in HGG^{66,67}. The dependence of tumor growth on the presence of an active and highly permeable vasculature makes DCE-MRI an attractive method in disease assessments. It is useful in distinguishing gliomas from other other brain tumors^{68,69}, as CA enhancement patterns and visual features in structural MRI alone do not provide sufficient information for differentiation⁷⁰. Elevated K^{trans} and v_e have been shown to be associated with higher tumor grade and can be used to aid in glioma grading by allowing for better targeted biopsy^{54,69,71}. Several studies have shown a correlation between pre-treatment K^{trans} and v_e and outcome in HGG, with increasing K^{trans} and v_e being associated with worse prognosis⁷²⁻⁷⁴.

A promising application of DCE-MRI in HGGs is in treatment response assessment. Up to 50 % of patients treated with the Stupp protocol develop areas with increased CA enhancement or edema around the tumor during the first three months of treatment, which is not easily distinguished from tumor growth in structural images^{75,76}. This is termed pseudoprogression and is considered to be a result of treatment induced vascular damage or inflammation⁷⁷. Because pseudoprogression is associated with increased survival, the ability to differentiate it from true progression is important to

facilitate the best treatment outcome⁷⁸. K^{trans} , v_p and v_e have been found to be lower in areas with pseudoprogression compared to tumor tissue^{79,80}.

Despite great effort to standardize the DCE imaging technique, different methodology across imaging sites and small study cohorts have so far prevented the materialization of a definitive gold standard that would encourage widespread adaption in clinical use^{13,25,81,82}.

3 *Aim of this thesis*

The aim of this thesis was to investigate several aspects of DCE-MRI in HGG in order to improve the understanding of their impact on the diagnostic value of the method.

Specific aims:

Paper I: To evaluate the effect of the T2*-relaxation on AIF measurements in DCE-MRI of HGG, and its effect on PKP estimates.

Paper II: To investigate the effect of variation in sampling interval and total measurement time on PKP estimates in DCE-MRI of HGG, using *in silico* simulations and clinical data.

Paper III: To investigate the temporal evolution of tumor T_1 and to evaluate the importance of acquiring baseline T_1 measurements in DCE-MRI PKP estimation.

Paper IV: To assess the effect of inter-operator variability in AIF definition on PKP estimates from DCE-MRI.

4 Methods

4.1 Study design

The works described in this thesis is part of a prospective HGG treatment monitoring study carried out at The Intervention Centre at Oslo University Hospital, Rikshospitalet in Oslo, Norway. The study included an extended MRI protocol for the purpose of investigating the treatment monitoring potential of several advanced imaging techniques. Imaging was performed before the start of radiochemotherapy, every 14 days during and once after 6 weeks of treatment, and then every third month for the remainder of follow-up time.

4.2 Ethical approval

The study of which this thesis is part was performed in accordance with the Declaration of Helsinki⁸³ and informed consent was signed by all participating patients. Approval was obtained by the Regional Ethical Committee with reference ID 2009/1867b.

4.3 Patients

The study was carried out between 2010 and 2014 and included 23 HGG patients. Papers I and II were written while patient recruitment was ongoing and include seven and 15 patients with a total of 50 and 101 examinations, respectively. Papers III and IV were written after the inclusion of all patients and includes the full material of 196 examinations and the first six imaging time-points ($N = 118$) of all patients, respectively.

4.4 MRI protocol

All MRI was performed using a Philips Achieva 3.0 T system (Philips Healthcare, Best, The Netherlands) with an eight-channel head coil (InVivo, Gainesville, FL, USA). The imaging protocol consisted of the following structural sequences: 3D FLAIR, pre- and post-contrast 3D T₁-weighted images, 2D T₂-weighted images, diffusion tensor imaging (DTI) and Look Locker (LL) T₁ relaxometry (T₁-LL). The dynamic series included was DCE-MRI and dynamic susceptibility contrast (DSC)-MRI, which included injection of 0.1 mmol/kg of gadobutrol (Gadovist®, Bayer Schering Pharma AG, Berlin, Germany) into the right cubital vein at a rate of 3 mL/s and 5 mL/s, respectively.

The T₁-LL sequence was acquired before CA injection with identical geometry as the DCE-sequence and allows for a reliable measurement of tissue T₁(0). The implementation used here was a 3D IR GRE sequence with an initial 180° inversion pulse followed by $N = 38$ excitation pulses with $\alpha = 4^\circ$ at an interval of $\tau = 69$ ms and initial inversion time (TI) 38 ms.

A summary of key sequence parameters of the protocol is given in table 1, with the DCE sequence receiving a more detailed description below.

Table 1: Key sequence parameters of the MRI protocol. The sequences are listed in order.

Sequence	Technique	Voxel size (mm ³)	Matrix size	slices	TE/TR (ms)	T _{acq} (min:s)
DTI	2D SE-EPI	2.5x2.5x2.5	96x96	50	60/9686	5:52
FLAIR	3D IR TSE	1.07x1.07x0.6	224x224	300	424/8000	8:40
T ₁ -w	3D FFE	1.0x1.0x1.0	256x232	190	2.3/5.1	6:40
T ₂ -w	2D TSE	0.45x0.45x2.5	400x255	28	80/3000	3:30
T ₁ -LL	3D IR FFE	1.88x1.88x4.0	120x109	11	1.4/2.7	2:48
DCE	3D SR-SPGR	1.88x1.88x4.0	120x120	11	2.5/5.1	5:15
T ₁ -w	3D FFE	1.0x1.0x1.0	256x232	190	2.3/5.1	6:40
DSC	2D SE-EPI	1.88x1.88x4.0	120x120	190	70/1349	1:52

Abbreviations: DTI – diffusion tensor imaging; FLAIR – fluid attenuated inversion recovery; T₁-w – T₁-weighted image series; T₂-w – T₂ weighted image series; T₁-LL – Look-Locker T₁ relaxometry; DCE – dynamic contrast enhanced; DSC – dynamic susceptibility contrast; IR – inversion recovery; [T]SE – [turbo] spin echo; FFE – fast field echo*; EPI – echo planar imaging; TE – echo time; TR – repetition time; T_{acq} – acquisition time. *Field echo is the manufacturer's trade name for gradient echo.

4.4.1 DCE sequence

The DCE sequence used in this study was a 3D SR-SPGR with centric reordering based on a previously described method⁸⁴. In order to facilitate T₂*-estimation, patients 1-7 were imaged with a double-echo sequence (Sequence 1), while patients 8-23 were imaged using a single-echo variant (Sequence 2). Both sequences had the following parameters in common: acquisition matrix: 120x120; voxel size 1.88 x 1.88 x 4.0 mm³; partial Fourier: 5/8; pixel bandwidth: 434 Hz; FA: 26° and sensitivity encoding factor 2.3 in the anterior-posterior phase encoding direction. The differing parameters TD, number of frames, T_s, T_{acq}, TR and TE can be found in table 2. The initial saturation pulse (a 90° RF-pulse) was applied non-selectively to the complete volume followed by

Table 2: List of differing parameters in DCE Sequence 1 and Sequence 2.

	Sequence 1	Sequence 2
Echo time (ms)	2.5 / 5.6	2.5
Repetition time (ms)	8.2	5.1
Saturation delay (ms)	80	50
Sampling interval (s)	3.4	2.1
Number of frames	100	150
Total acquisition time (min:s)	5:40	5:15

spoiling gradients, effectively eliminating both transverse and longitudinal magnetization. T₁-Relaxation takes place until the signal readout portion of the sequence starts at TD. A short TD is desirable because it limits the effect of water exchange that would allow CA-affected water protons to travel further from the CA distribution site⁸⁵. CA injection was initiated after six dynamic time-points had been acquired. The mean of these images served as the reference signal intensity $S(0)$ of the DCE series without contrast-enhancement. The relative signal equation for the SR-SPGR DCE-sequence is given by equation [5] assuming $e^{-TD(R_2^*(t)-R_2^*(0))} \approx 1$:

$$\frac{S(t)}{S(0)} = \frac{1 - e^{-TD \cdot R_1(t)}}{1 - e^{-TD \cdot R_1(0)}}, \quad [20]$$

from which $R_1(t)$ is calculated as:

$$R_1(t) = \frac{1}{-TD} \ln \left[1 - \frac{S(t)}{S(0)} (1 - e^{-TD \cdot R_1(0)}) \right] \quad [21]$$

$R_1(0)$ must be determined beforehand, either by measurement or by choosing a fixed value. In the present work the T₁-LL sequence provided measured values.

4.5 Analysis software

Analysis was done using the software packages nordicICE (NordicNeuroLab AS, Bergen, Norway), MATLAB (versions 7.14 (paper I), 7.11 (paper II), 8.2 (paper III) and 9.6 (paper IV), The MathWorks, Natick, MA, USA), SPM8 (The Wellcome Centre for Human Neuroimaging, London, UK), Minitab 16 (Minitab Inc, PA, USA) and Stata SE 16.1 (StataCorp LLC, College Station, TX, USA).

4.6 Image pre-processing

4.6.1 Co-registration and tumor delineation

Images were exported from the scanner in DICOM format and anonymized by removing identifying DICOM-tags before being stored in a central database. Rigid motion correction was applied to the DCE-series to account for any patient movement of the head during acquisition⁸⁶. The pre-contrast T_1 -images of each patients' first examination was used as the reference for co-registration of the structural images. The DCE series of each examination was co-registered to the corresponding post-contrast

Figure 6: Co-registration and tumor delineation workflow. FLAIR- and post-contrast T_1 -images (T_1 -post) are co-registered to pre-contrast T_1 -images (T_1 -pre), and the DCE-images are co-registered to the T_1 -post-images. The tumor mask created from FLAIR and T_1 -post is then applied to the DCE-images.

T₁-images, which had already been registered to the pre-contrast T₁-images⁸⁷. An overview of the workflow is shown in figure 6.

DCE analysis in this thesis was performed in regions-of-interest (ROIs) containing only tumor tissue as defined by contrast-enhancement. Tumor delineation was performed in each examination using a semi-automatic method where initially B₁-inhomogeneities were removed from FLAIR and post-contrast T₁-weighted images by entropy minimization^{87,88}. Regions with both high FLAIR intensity and post contrast T₁-enhancement was identified using second order relative entropy thresholding and used as a starting point for manual finalizing by an experienced neuroscientist⁸⁹.

4.6.2 AIF generation

AIFs were defined in each examination by manually selecting an area likely to contain large arteries and extracting the pixels that best demonstrated the characteristics of an AIF using an automatic k-means clustering based algorithm⁹⁰. Up to five pixels were averaged together to form the final AIF after manual inspection. Visual acceptance criteria were a high well-defined first pass peak followed by a lower second pass and a smooth tail. The signal intensity was converted to CA concentration via ΔR_1 using equation [21] with T₁(0) set to 1664 ms, as reported for blood at 3.0 T⁹¹. As the DCE image slices covered only 44 mm centered on the tumor, it was not possible to choose the same artery in all patients. When present in the image volume, the middle cerebral artery was preferred. PV correction was performed by defining a venous output function from the superior sagittal sinus or transverse sinus, using the same detection method as for the AIF. The PV-corrected AIF was obtained by multiplying the measured AIF with

Figure 7: Outline of the AIF extraction process. Top right: the search area (yellow rectangle) is placed in an area likely to contain arterial signal, and the algorithm selects the best pixels (red squares). The AIF is the mean signal of the selected pixels and is plotted in red. The venous output function is detected similarly and is plotted in blue along with mean tumor signal in green.

the ratio of the venous and arterial area-under-the-curve(AUC)⁹². AIFs were created using nordicICE. An illustration of the procedure is shown in figure 7.

4.7 Image analysis

DCE analysis was performed using in-house algorithms in MATLAB. PKPs were estimated in the tumor ROIs using the extended Tofts model as described in section 2.2. CA concentration time curves $C_t(t)$ were obtained from DCE signal intensities by equations [21] and [3], using $r_1 = 4.4 \text{ s}^{-1}\text{mM}^{-1}$ as reported from literature⁹³. Deconvolution of the AIF with $C_t(t)$ (equation [14]) by singular value decomposition was performed using the linear least squares method described by Murase, in which both sides of equation [13] is integrated to give the following form of equation [14]⁹⁴:

$$\begin{aligned}
C_t(t_k) = & (K^{\text{trans}} + k_{\text{ep}} \cdot v_p) \int_0^{t_k} C_p(\tau) d\tau - k_{\text{ep}} \int_0^{t_k} C_t(\tau) d\tau \\
& + v_p C_p(t_k) \quad (k = 1, 2, \dots, n)
\end{aligned} \tag{22}$$

where t_k is time at dynamic time point k . Expressing equation [22] in matrix form gives a system that is readily solvable for the PKPs:

$$\vec{C} = \vec{A} \cdot \vec{B} \tag{23}$$

where

$$\vec{A} = \begin{pmatrix} \int_0^{t_1} C_p(\tau) d\tau & - \int_0^{t_1} C_t(\tau) d\tau & C_p(t_1) \\ \int_0^{t_2} C_p(\tau) d\tau & - \int_0^{t_2} C_t(\tau) d\tau & C_p(t_2) \\ \vdots & \vdots & \vdots \\ \int_0^{t_n} C_p(\tau) d\tau & - \int_0^{t_n} C_t(\tau) d\tau & C_p(t_n) \end{pmatrix}, \tag{24}$$

$$\vec{B} = \begin{pmatrix} K^{\text{trans}} + k_{\text{ep}} \cdot v_p \\ k_{\text{ep}} \\ v_p \end{pmatrix} \tag{25}$$

and

$$\vec{C} = \begin{pmatrix} C_t(t_1) \\ C_t(t_2) \\ \vdots \\ C_t(t_n) \end{pmatrix} \tag{26}$$

In this thesis, equation [23] was solved for $\vec{B}$ using the MATLAB routine *mldivide*.

Paper I, II and IV used a fixed $T_1(0)$ value in tumor corresponding to the median obtained from the T_1 -LL-sequence in all examinations at the time of analysis. In paper III both fixed and estimated $T_1(0)$ were utilized.

4.7.1 T_2^* -correction of AIF (paper I)

The double-echo DCE Sequence 1 was used to correct for T_2^* -effects in the first pass of the AIF in 50 DCE examinations of seven HGG patients. Using equation [9], the correction factor $e^{TE \cdot R_2^*(t)}$ was applied to the uncorrected AIFs in the first pass, and kinetic analysis was performed in each examination using both AIFs. A fixed tumor $T_1(0)$ of 1200 ms was used for $R_1(t)$ -estimation. Median tumor PKPs estimated using the uncorrected and corrected AIFs were compared.

4.7.2 Sampling interval and total acquisition time (paper II)

The effect of sampling interval and sampling duration on kinetic parameter estimation was investigated by down-sampling and truncating the original data sets. From this, DCE-series with different T_s and total T_{acq} were created. Down-sampling factors between 2 and 20 were used to achieve T_s from 3.4-68 s (Sequence 1) and 2.1-42 s (Sequence 2) by averaging consecutive images. The images acquired before CA arrival were not included in the down-sampling to avoid temporal jittering⁹⁵. The original series was truncated by removing images from the end, resulting in T_{acq} of 1, 2, 3, 4 and

Figure 8: Example of temporal resolution down-sampling (A, left) and truncation (B, right) of AIF and tumor time curves showing CA-induced change in R_1 . The original curves are shown in the top row. Reproduced from paper II with kind permission.

5 min. The AIFs were extracted from the original image series and subjected to the same treatment in both operations. An example of down-sampled and truncated tumor CA concentration curves and AIFs can be seen in figure 8.

4.7.3 $T_1(0)$ sensitivity (paper III)

$T_1(0)$ -maps was generated from the T_1 -LL sequence in each examination and DCE-analysis was performed using both the T_1 -maps (Method 1) and a fixed value corresponding to the median of all $T_1(0)$ -maps (Method 2). Voxel-wise errors in PKP

estimates using Method 2 as a function of deviation from the $T_1(0)$ -map was assessed, and the change in median tumor PKPs in consecutive examinations was compared using the two methods. The temporal evolution of median $T_1(0)$ in HGG during treatment was investigated by testing for differences between consecutive exams and between the first and any later exam.

4.7.4 Operator dependency of AIF (paper IV)

AIFs were generated independently by three domain experts (DEs) in 118 DCE-MRI examinations. A total of 243 AIFs from Sequence 2 were used to generate a pop-AIF from brain DCE data on the same functional form as previously published from abdominal data⁴¹:

$$C_b(t) = \sum_{n=1}^2 \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp\left(-\frac{(t - T_n)^2}{2\sigma_n^2}\right) + \frac{\alpha \exp(-\beta t)}{1 + \exp(-s(t - \tau))}, \quad [27]$$

where A_n are scaling factors, T_n are centers and σ_n are widths of the n th Gaussian; α and β describe the amplitude and slope of the exponential function, respectively, and s and τ are the width and center of the sigmoid.

To assess the effect of different peak values in the DE-measured AIFs, they were normalized to a common AUC. Pharmacokinetic analysis was performed with the three DE-AIFs, the pop-AIF and the AUC-normalized DE-AIFs. Median tumor values of estimated PKPs using all AIFs was used for comparison.

4.8 Simulations

Simulations were performed in papers I-III using in-house developed algorithms in MATLAB. All simulations used a reference AIF generated in JSim⁹⁶

(<http://physiome.org/jsim>) using the dispersion model described by Barboriak et. al⁹⁷ combined with PKPs covering the range of values found in clinical data to create $C_t(t)$ -curves using equation [14]. The generated reference AIF used in the simulations is shown in figure 9.

Figure 9: Original form of the JSim-generated AIF used for simulations. Time resolution is 0.05 s, and the full AIF has been truncated here from 10 to 5 min for clarity.

4.8.1 T_2^* -correction of AIF (paper I)

Simulations were performed to assess the effect of first-pass attenuation in the AIF for a continuous range of PKPs and attenuation factors. Tissue CA concentration curves were constructed using equation [14] with K^{trans} between 0.02 and 0.15 min^{-1} , v_p between 0.5 and 5 %, $k_{ep} = K^{\text{trans}}/v_e$ with $v_e = 30$ %, and the JSim-generated AIF

multiplied with a global scaling factor between 0.1 and 1 and then attenuated using the relationship between CA concentration and T_2^* as published elsewhere³¹. A sampling interval of 1.0 s was used and TE was set to 2.5 ms in calculation of T_2^* . Noise was added individually to the attenuated AIF and tissue concentration curve to achieve a SNR of 60 in both curves.

4.8.2 Sampling interval and total acquisition time (paper II)

Simulations were used to investigate the effect of sampling interval and total acquisition time on the precision and accuracy of PKP estimates, with emphasis on k_{ep} , v_e and v_p were kept fixed at 25 % and 2 %, respectively, while k_{ep} was varied to cover the range of values seen in the clinical data. For the T_s analysis k_{ep} was stepped from 0.4 to 4 min^{-1} in steps of 0.4 min^{-1} , T_s from 3.4 s to 68 s in steps of 3.4 s and synthetic tissue concentration curves were generated with $T_{acq} = 10$ min. T_{acq} analysis was performed with k_{ep} ranging from 0.04 min^{-1} to 0.4 min^{-1} in steps of 0.04 min^{-1} and T_s was set to 0.1 s. The simulations were repeated 1000 times for each k_{ep} -value with noise added to the tissue concentration curve and AIF to reach an SNR of 100, defined as the ratio of peak AIF concentration and baseline standard deviation.

4.8.3 $T_1(0)$ sensitivity (paper III)

In paper III, simulations were performed to assess how estimates of PKPs are affected by using a fixed $T_1(0)$ of 1490 ms when the true $T_1(0)$ ranges from 600 to 2200 ms, which covers all observed tumor $T_1(0)$ in the clinical data. The synthetic time series was created with $TD = 50$ ms, $T_s = 3$ s and $T_{acq} = 5$ min to resemble the two clinical DCE sequences. 10,000 iterations were executed with $C_t(t)$ generated using PKPs randomly selected from the following ranges: $0.01 \text{ min}^{-1} \leq K^{trans} \leq 0.9 \text{ min}^{-1}$, $0 \% \leq v_e \leq 40 \%$ and

$1 \% \leq v_p \leq 4 \%$. Relative signal curves (equation [14]) were generated from $C_t(t)$ using $R_1(t)$ calculated using equation [3] with a randomly selected $R_1(0)$ from the range mentioned above, and noise was added to give $SNR = 40$. A new estimation of $R_1(t)$ using equation [20] with $R_1(0) = 1490$ ms was then used to estimate the final $C_t(t)$ used for kinetic analysis. This gave a large pool of PKP estimates with known errors both in the PKPs themselves and $T_1(0)$.

4.9 *Statistical analysis*

The threshold for statistical significance was defined as $P < 0.05$ in all tests in this thesis.

4.9.1 Wilcoxon signed-rank test (papers I-IV)

The Wilcoxon signed-rank test (WSR) is a non-parametric equivalent to the parametric paired t-test that is appropriate for evaluating repeated measurements⁹⁸. Several cases in this study involves comparing exam-wise measurements, which does not constitute a large enough sample size to assume a normal distribution. The WSR requires no such assumption and was therefore preferred throughout this thesis.

In paper I, WSR was used to test for significance in the difference between PKPs estimated with T2*-corrected AIFs and uncorrected AIFs.

In paper II, the median of PKPs estimated from the original DCE series was tested against estimates from the down-sampled and truncated series using WSR.

In paper III, the difference in median tumor $T_1(0)$ between consecutive examinations and between the first examination and all following examinations in all patients was tested for significance using WSR with Holm-Bonferroni correction.

In paper IV, the difference in peak and AUC between each pair of DE-AIFs was tested for significance using WSR.

4.9.2 Mann-Whitney U test (paper II)

Also known as Wilcoxon rank-sum test, the Mann-Whitney U test is the WSR for independent measurements. It was used in paper II to test for difference between errors in PKP estimates from Sequence 1 and Sequence 2.

4.9.3 Analysis of variance (paper II)

One-way analysis of variance (ANOVA) was used to investigate T_s - and T_{acq} -dependence of the PKPs.

4.9.4 Multiple linear regression (paper III)

The dependency of errors in PKP estimates on $R_1(0)$ error was assessed by multiple linear regression, using the magnitude of the PKPs estimated with $T_1(0)$ -maps as the second regressor.

To assess the effect of $T_1(0)$ error and $T_1(0)$ -map distribution on K^{trans} heterogeneity, the ratios of normalized K^{trans} histogram peaks estimated using $T_1(0)$ -maps and fixed $T_1(0)$ was calculated in each tumor. The peak of a histogram normalized to have an AUC of unity will be higher in narrower distributions, indicating a homogenous distribution and vice versa. The ratio of K^{trans} histogram peaks was included in multiple linear regression with error in $T_1(0)$ and the histogram width of the $T_1(0)$ -map as predictors.

4.9.5 Inter-operator agreement (paper IV)

Agreement between PKPs estimated using different AIFs was assessed by the intraclass correlation coefficient (ICC) using the absolute-agreement, two-way random effects model. Change in median tumor K^{trans} from the first to the sixth examination (three months after the end of treatment) defined by ± 10 % difference or status quo was estimated using each AIF source, and the results was tested for agreement using Fleiss' kappa with linear weights (κ). Both ICC and κ was reported with 95 % confidence intervals (CI), and was interpreted according to the Landis & Koch benchmarking scale (table 3)⁹⁹. The Stata program *kappaetc* was used for estimation of both metrics¹⁰⁰.

Table 3: The Landis and Koch benchmarking scale⁹⁹ used for interpreting ICC and κ .

κ	Interpretation
≤ 0.00	Poor
0.00 - 0.20	Slight
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Substantial
0.81 - 1.00	Almost perfect

5 Results

5.1 Paper I

Paper I investigated the validity of assuming a negligible contribution from CA-induced T_2^* -effects in AIF determination on estimated PKPs using ETM in DCE-MRI.

There was a significant overestimation in all PKPs except v_e when not correcting for T_2^* -effects in the AIF using a TE of 2.5 ms (K^{trans} : $P < 10^{-5}$, k_{ep} : $P < 10^{-6}$, v_p : $P < 10^{-8}$). Figure 10 shows a box-plot of relative error in PKP medians. The error in PKP estimates was found to increase with more severe underestimation of the AIF peak. Higher nominal K^{trans} led to larger overestimation, while lower nominal v_p was the most affected. Simulation results agreed with findings from patient data.

Figure 10: Box-plot of relative error in 50 tumor median estimates of PKPs when using uncorrected AIF. The boxes are bounded by the 25th and 75th percentiles and the horizontal line represents the median. The whiskers extend to the most extreme values within 1.5 heights of the box below and over the 25th and 75th percentiles, respectively. Values outside this range are considered outliers and marked as crosses. A cutoff was made on the y-axis at 350 % for readability, the outliers beyond this value are k_{ep} : 357 %, v_p = 434 % and v_e = 380 %. Reproduced with permission from paper 1.

5.2 Paper II

A significant dependence of all PKPs on T_s was found in the clinical data (ANOVA: $P < 0.001$), however error in K^{trans} , k_{ep} and v_e were below 15 % for $T_s < 20$ s (figure 11). The most T_s -dependent trend was seen in K^{trans} and v_p , for which the decrease and increase, respectively, was significant at $T_s > 20$ s. Simulations showed increasing T_s -dependent error in all KPKs with increasing k_{ep} . The relative error in v_e and v_p as a function of T_s was larger ($P = 0.004$ and $P = 0.03$, respectively) using Sequence 1 compared to Sequence 2.

Shorter T_{acq} was seen to underestimate K^{trans} and k_{ep} and overestimate v_e and v_p in both clinical data and simulations. All PKPs exhibited a dependence on T_{acq} ($P < 0.001$) in clinical data, and the simulations showed increasing error in all PKPs for all T_{acq} with

Figure 11: Median tumor PKP estimates at different T_s relative to original (Sequence 1: 3.4 s; Sequence 2: 2.1 s) with error bars showing the 5-95 percentile range. Sequence 1 and Sequence 2 data are plotted separately as circles and triangles, respectively. The dotted lines indicate $\pm 15\%$ error. Reprinted with permission from paper II.

Figure 12: K^{trans} -maps from a sample patient generated from different T_s (top row) and T_{acq} (bottom row). A contrast-enhanced T_1 image is shown at the far right for tumor reference. Underestimation and loss of heterogeneity can be seen at higher T_s , while lower T_{acq} leads to overestimation and broader distribution. Figure adapted from paper II with permission.

decreasing values of k_{ep} . K^{trans} maps obtained from a sample patient with different T_s and T_{acq} are shown in figure 12.

Figure 13: K^{trans} -maps overlaid on structural images in two sample patients estimated using estimated $T_1(0)$ map (left column) and fixed $T_1(0) = 1490$ ms (middle column). The right column shows the voxel-wise T_1 error when using fixed $T_1(0)$ (error map = $T_1(0)$ -map - 1490 ms). The top row patient has regions of both under- and overestimation of $T_1(0)$ when using fixed value, while the bottom row patient exhibits underestimation throughout. Neither K^{trans} -map in the middle row has an appearance substantially different compared to that to the left, however a too high or too low fixed $T_1(0)$ is seen to slightly under- or overestimate K^{trans} , respectively. This can potentially obscure hot-spots (arrow) or cause artificial heterogeneity (circles). Figure adapted from paper III with permission.

5.3 Paper III

The median $T_1(0)$ in all tumors was 1490 ms, which was used as the fixed $T_1(0)$ in Method 2. A linear relationship between error in $R_1(0)$ and error in all estimated PKPs except k_{ep} was found in both simulations and clinical data. Using a fixed $T_1(0)$ higher than the true median $T_1(0)$ of the tumor caused a broadening of the PKP distributions. Visual examples of K^{trans} -estimates in the presence of over- and underestimation of $T_1(0)$ are shown in figure 13.

Table 4: Change in median $T_1(0)$ compared to first and previous exam. Columns show weeks since start of radiochemotherapy, number of exams and Holm-Bonferroni-corrected Wilcoxon P-values. Significant change ($P < 0.05$) is shown in bold typeface. Table reprinted from paper III with permission.

From first exam				From previous exam			
Weeks	N (exams)	P-value	Estimated median change (ms)	Weeks	N (exams)	P-value	Estimated median change (ms)
2	15	0.410	25.34	2	14	0.209	36.12
4	14	0.802	-16.16	4	18	0.760	6.939
6	15	0.244	56.24	6	16	0.394	24.31
8	15	0.038	97.47	8	16	0.028	61.81
20	13	0.012	215.2	20	15	0.018	95.21
32	11	0.023	202.1	32	14	0.268	32.89
44	9	0.097	149.3	44	12	0.666	-6.57
56	9	0.097	29.47	56	10	1.000	3.04
68	7	0.800	99.96	68	8	0.107	-48.40

Results from the temporal evolution of $T_1(0)$ is shown in table 4 and a box-plot is presented in figure 14. A significant increase in median tumor $T_1(0)$ was seen at 8, 20 and 32 weeks compared with the start of radiochemotherapy, and there was also a significant increase from the previous exam at weeks 8 and 20. The intra-patient change in PKPs during treatment was however not affected, with a significant linear

Figure 14: Box-plot of median $T_1(0)$ in tumor from all patients at each imaging time-point. The boxes encompass the middle percentile of values while the whiskers indicate the complete range of values. The horizontal line in each box marks the median. Outliers are not included in the box-plots and are shown as crosses. The number of patients at each time-point is indicated along the top. Significant change in $T_1(0)$ from the previous time-point is marked with an asterisk, and significant change from the first time-point is marked with a hashtag. The stapled line shows the median off all examinations (1490 ms).

Figure 15: Mean AIF across all domain expert-measured AIFs in individual subjects at all timepoints represented with crosses, and error bars showing ± 1 standard deviation. The fitted population AIF is shown in red.

relationship found for change in all PKPs ($P < 0.001$) estimated using Method 1 and Method 2 (R^2 : 0.93 (K^{trans}), 0.84 (v_e) and 0.97 (v_p)).

5.4 Paper IV

The resulting function parameters from fitting the mean AIF to equation [27] is given in table 5, and a plot of the pop-AIF is shown in figure 15.

There was a significant difference in AIF peaks between all DEs ($P = 0.03$ for all combinations) and in AUC only between DE 2 and DE 3 ($P < 10^{-8}$). Agreement in PKP estimates was moderate to substantial ($0.51 < \text{ICC} < 0.76$) between DE-AIFs, and substantial to almost perfect ($0.70 < \text{ICC} < 0.95$) between the AUC-normalized DE-AIFs.

Table 5: Parameter values and their standard deviation (SD) for the fitted population AIF.

Parameter	A_1	A_2	T_1	T_2	σ_1	σ_2	α	β	s	τ
Value	2.092	0.118	0.696	1.051	0.059	0.067	3.161	0.200	818.4	0.66
SD	0.028	0.032	0.0009	0.016	0.0008	0.0178	0.0982	0.011	0.000	0.00
Units	mmol·min	min	min	min	min	min	mmol	min ⁻¹	min ⁻¹	min

Inclusion of the pop-AIF in both sets of DE-AIFs caused a slight but non-significant decrease in agreement.

Agreement in median K^{trans} -change between first and sixth examination was found to be fair to moderate (κ (CI) = 0.60 (0.36, 0.83)) when using the DE-AIFs, and substantial to almost perfect (κ (CI) = 0.81 (0.62, 0.96)) when using the AUC-normalized DE-AIFs.

6 *Discussion*

This thesis is focused on gaining methodological insight to DCE-MRI applied in treatment monitoring of HGG patients. The primary goal has been to investigate how sequence parameters and analysis approaches affect the resulting kinetic parameter maps. By identifying constraining factors, it is possible to make better informed choices when designing a DCE-experiment. The main findings of the thesis are:

- The common assumption of negligible T_2^* -effects in DCE-MRI may be violated for $TE \geq 2.5$ ms when using a standard CA dose and injection rate, potentially leading to over-estimation of all PKPs except v_e .
- The sampling interval should be less than 20 s, and the total dynamic measurement time should at least be five minutes in order to minimize measurement errors in DCE-MRI-derived metrics in HGG.
- A per-examination T_1 -map is not necessary if a representative estimate of tumor T_1 values can be found.
- AIF selection is largely operator-dependent even when semi-automatic AIF detection algorithms are used, and quantitative results should only be compared if they are produced by the same operator or with the same AIF normalization approach.

6.1 *T_2^* -effect on AIF (paper I)*

Most approaches to DCE-MRI do not consider the reduction in T_2^* from CA because it is assumed to not have a significant effect on signal intensity when using heavily T_1 -weighted sequences with TE in the range of a few milliseconds. In paper I we

hypothesized that this assumption is invalid when measuring the first pass of the AIF in the brain. By using a double-echo sequence we were able to estimate T_2^* at each dynamic time point and found that the signal attenuation at $TE = 2.5$ ms significantly affected the estimated PKPs. We used a standard CA injection rate of 3 mL/s and a commercially available CA and therefore believe that this finding is universally valid in DCE-MRI of the brain.

The overestimation of K^{trans} that we see in our results is in agreement with other works on non-brain data¹⁰¹, animal studies^{102,103} and simulations^{36,104}. In our data, estimation of T_2^* was only feasible in the first pass of the AIF, and the results reflect the effect of underestimating the AIF peak. The effect seen on v_p is particularly large because this parameter is directly dependent on the AIF amplitude, while K^{trans} is related to the integral of the whole AIF which is affected by a lesser degree by the first pass amplitude.

Our results suggest that when using a single-echo DCE sequence, TE needs to be close to 1 ms in order to keep T_2^* -induced errors in both K^{trans} and v_p below 10 % when AIF concentration peaks similar to those found in our patient material is expected.

6.2 Temporal requirements (paper II)

Paper II investigated the effect of sampling interval, T_s , and total sampling time, T_{acq} , on the estimated PKPs. Higher T_s and shorter T_{acq} leads to increasingly lower accuracy and precision of PKP estimates, however median tumor estimates of K^{trans} , v_e and v_p were not significantly affected for $T_s < 20$ s. A longer T_s fails to correctly sample the highest frequency components of the concentration curves, causing higher K^{trans} and k_{ep} to be more underestimated. The proportion of affected voxels is <5 % for T_s lower than 20 s, and while this has little impact on the tumor median PKP estimates, heterogeneity is

reduced. As can be seen in figure 12, this runs the risk of concealing hot-spots that are prevalent in HGGs due to a highly disorganized vessel structure¹⁰⁵. A T_s closer to 10 s should therefore be considered if hot-spot analysis is required. Similar results have been reported in previous simulation studies^{36,95} and in breast tumors¹⁰⁶.

Shorter T_{acq} than the ~ 5 min used in the clinical series was seen to cause over-estimation of K^{trans} and k_{ep} and under-estimation of v_e and v_p , and the simulation results suggest that 5 min is too short for the highest k_{ep} found in the clinical material. Artzi et al found that error in k_{ep} could be kept below 3 % if the 5 min continuous acquisition was followed by two measurements at 7 and 9 minutes¹⁰⁷. This approach allows for structural images to be obtained between the delayed acquisitions, thus not extending total imaging time by much. Vidarsson et al. used the Patlak model in acute ischemic stroke patients and similarly observed overestimation in K^{trans} at shorter T_{acq} ¹⁰⁸. They concluded that a T_{acq} of 3.5 min was sufficient to identify patients with hemorrhagic transformation. Abe et al. also performed DCE-MRI with T_{acq} of 3.5 min in the interest of saving time¹⁰⁹. They successfully distinguished LGG and lymphoma from HGG and metastasis using v_e , and LGG from other brain tumors using K^{trans} . The shorter T_{acq} may improve adaption of DCE-MRI in clinical use for cases where coarser KPEs suffice¹⁰⁹.

In conclusion, T_s should be lower than 20 s and T_{acq} should be at least 5 min in DCE-MRI of HGGs to ensure an acceptable level of tumor heterogeneity is reflected in the results.

6.3 T_1 in tumor and need for T_1 -maps (paper III)

The main finding of paper III was that longitudinal changes in DCE-derived PKPs in HGG patients undergoing treatment can be reliably assessed using a fixed $T_1(0)$. It is however of importance that the fixed $T_1(0)$ is reasonably close to the median tumor $T_1(0)$. In this

study, we had $T_1(0)$ -measurements from all examinations and were able to choose the median from all examinations as the fixed value. The results show that the error in estimated PKPs scales linearly with the error in $R_1(0) = 1/T_1(0)$, so that an overestimation of $T_1(0)$ will lead to smaller PKP errors than an underestimation of the same magnitude. There was a significant increase in $T_1(0)$ in all patients from the first exam, however the change in median PKPs estimated using fixed $T_1(0)$ correlated strongly with those estimated with $T_1(0)$ -measurements. This aligns well with studies that have found the use of a fixed $T_1(0)$ to be acceptable for glioma grading^{110,111}.

The most widely adopted technique for obtaining $T_1(0)$ -estimates is the variable FA (VFA) method, which is able to achieve a mapping of a typical brain volume in less than 30 s¹¹². This method is sensitive to noise and B_1 -inhomogeneities, and it has been shown to be a major contributor to PKP estimate errors^{110,113}. The IR-based LL-method used in our study was not investigated for reliability, but it has been previously validated¹¹⁴. Its main drawback is the longer acquisition time (2:48 minutes in our study) which adds to the duration of the DCE protocol, making it less feasible to include in a clinical setting.

This study shows that using a fixed $T_1(0)$ for kinetic analysis of DCE data is a valid approach if the selected value is reasonably close to the true values in the tissue of interest. Such a value can be obtained quickly and without the need for co-registration.

6.4 Operator dependency of AIF (paper IV)

In this work, AIFs were generated independently by three DEs, and a population-averaged-AIF was constructed from a pool of measured AIFs. These four AIFs, in addition to AUC-normalized versions of the measured AIFs were used in kinetic analysis of 118 DCE examinations to assess the operator-dependence on estimated PKPs. It was

seen that agreement in K^{trans} , v_e and v_p from the DEs was improved when the AIFs were normalized to a common AUC, while k_{ep} was not significantly affected. This is in good agreement with previous work showing that k_{ep} is insensitive to AIF scaling¹¹⁵. Including the pop-AIF in the two groups of DE-AIFs had a non-significant effect on PKP estimates, suggesting that this AIF is not an unreasonable replacement for the per-examination measured AIFs. In a study comparing KPE repeatability using measured AIF, pop-AIF and pop-AIF scaled to the maximum CA concentration in each patient in a prostate cohort, it was reported that the scaled pop-AIF was the best choice for K^{trans} and v_e ¹¹⁶. While not directly comparable, this harmonizes well with the higher ICC with AUC-normalized AIF in our study.

The relatively low agreement between PKP estimates from the measured DE-AIFs emphasizes the difficulty in obtaining reproducible results from DCE-MRI. However, the normalized AIFs yield better agreement in PKP estimates and perhaps most importantly, in the relative change over time in a single patient. While normalized AIFs do not produce quantitative results that may be used for comparison to literature values, a reliable measure of change over time is valuable information when assessing treatment response.

6.5 Limitations

This study has several limitations. One general limitation of the work presented in this thesis is the limited number of HGG patients included, and ideally the results should be replicated in larger patient cohorts. Patient inclusion was limited by the (fortunately) low incidence of HGG and a study protocol deemed too demanding for many patients.

However, our study design included a large number of serial MRI examinations both during and after radiochemotherapy, adding valuable insight into the treatment- and disease progression-dependent variation in the study of DCE-MRI derived metrics.

The ETM was chosen as the kinetic model in all papers because it is a widely used model in DCE-MRI and is often applied in HGG. The limitations of this model are well known²⁶, and in this thesis we assumed that the validity requirements were met. One requirement is that CA MTT in tissue is negligible, which may not hold true in our data. The lowest T_s in this work is 2.1 s, while MTT in HGG has been reported to be >5 s¹¹⁷. A more general model such as the 2CXM with fewer assumptions about the modeled tissue would eliminate many uncertainties of this nature, but has been shown to require a higher temporal resolution than used here¹¹⁸.

7 Concluding remarks

7.1 Conclusions

The work presented in this thesis suggests that DCE-MRI of HGGs at present has a better potential as a semi-quantitative rather than fully quantitative method. It was also seen that relative changes in DCE-MRI derived metrics in individual patients receiving treatment appear reliable when analyzed by a single operator, demonstrating that DCE-MRI is a valuable tool for monitoring HGG progression.

Both simulations and results from clinical data in HGG patients indicate that the DCE sampling interval may be significantly longer (lower temporal resolution) than what is conventional without loss of reliability. This opens the possibility for higher spatial resolution and/or SNR, which may add further to the clinical quality than what was possible to obtain in our work. That a detailed pre-contrast measurement of T_1 is not essential for producing useful results reduces the total time needed for a DCE examination and allows for removing one source of noise from the analysis chain.

The most sobering insight from this thesis is the operator-dependence on AIF-selection and its impact on the results. Optimistically, it is possible that higher spatial resolution made possible with a longer sampling duration could lead to images that more readily allows for identification of arterial voxels.

7.2 *Future perspectives*

Although several studies, including the work in this thesis have shown the diagnostic potential of DCE-MRI in the workup of brain tumor patients, lack of standardization of both acquisition methods and kinetic analysis approach, combined with poor spatial resolution and has limited the clinical impact of the method to date. Ideally, the DCE-MRI protocol should provide similar spatial resolution to that obtained by standard volumetric T1-weighted post contrast MRI. If this was possible, DCE-MRI could replace the current standard post contrast MRI, adding temporal kinetic information without loss of spatial detail. Recent advancements in MRI whereby high-quality images are reconstructed from heavily under-sampled data (sparse sampling of k-space), either based on deep learning or compressed sensing hold great promise for significantly faster MRI acquisitions¹¹⁹⁻¹²¹. The goal of acquiring DCE-MRI data with sufficient temporal resolution and with spatial resolution and brain coverage matching current standard post contrast MRI is thus within reach. Combining this advancement with a standardized kinetic analysis approach, like those initiated by The Quantitative Imaging Biomarkers Alliance¹²² (rsna.org/QIBA) and The American Society of Functional Neuroradiology (asfnr.org) may be what is needed to bring DCE-MRI into widespread clinical acceptance in the diagnosis and follow-up of brain tumor patients.

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Papers I-IV

Technical Note

T₂*-Correction in Dynamic Contrast-Enhanced MRI From Double-Echo Acquisitions

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Purpose: To evaluate the importance of T₂*-effects on the arterial input function (AIF) and on the resulting dynamic parameter estimation in dynamic contrast-enhanced (DCE) MRI of high-grade gliomas.

Materials and Methods: Seven patients with high-grade gliomas were imaged in total 50 times using a double-echo DCE sequence. Kinetic analysis using the extended Tofts model was performed using AIFs with and without correction for T₂*-effects, and the resulting estimates of the transfer constant (K^{trans}), blood plasma volume (v_p), and the rate constant (k_{ep}) were compared. Numerical simulations were done for comparison with clinical results as well as to further investigate the dependency of parameter values on the magnitude of T₂*-induced errors.

Results: All kinetic parameters were found to be overestimated if T₂*-effects in the AIF were not accounted for; with v_p being most severely affected. The relative error in each parameter was dependent on the absolute parameter magnitude, resulting in incorrect parametric tumor distributions in the presence of uncorrected AIF T₂*-effects.

Conclusion: In DCE, a sufficiently short echo time should be used or corrections for T₂*-effects based on double-echo acquisition should be made for correct quantification of kinetic parameters.

Key Words: dynamic contrast-enhanced MRI; DCE-MRI; glioma; AIF; T₂* correction; T₂*-effect

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DYNAMIC CONTRAST-ENHANCED (DCE) MRI is increasingly used as a method to assess progression and treatment response in oncology (1–3). Model

choice and model assumptions have been shown to significantly affect the accuracy and interpretation of kinetic parameter estimations in DCE-MRI. For quantitative analysis in particular, several elements have been identified that warrant attention, including the importance of baseline T₁-estimation (4), proper model selection (5,6), and correct interpretation of the results under different physiological conditions (7).

It is customary to use heavily T₁-weighted sequences in conventional DCE-MRI to minimize T₂*-relaxation effects under the assumption that contrast agent (CA) concentration does not reach sufficient levels to cause significant T₂* signal loss before echo acquisition. Using a standard single echo acquisition, T₂*-effects need to be negligible to relate signal intensity changes in blood to the underlying CA concentration. We hypothesize that this assumption is violated in the brain and consequently that the arterial first pass CA concentration may be miscalculated because of significant T₂*-decay, leading to errors in the subsequent pharmacokinetic analysis. Others have investigated the feasibility of bypassing this problem by deriving the arterial input function (AIF) from phase measurements (8), and by modeling the true peak of the AIF using postprocessing methods (9,10). Here, we present an approach in which these errors are corrected by the use of a double echo DCE sequence.

The purpose of the present work is to quantify, through simulations and in clinical data, the error in kinetic parameter estimations in DCE imaging of high-grade gliomas due to CA-induced arterial T₂*-effects.

METHODS

Patient Study

Subjects

Seven patients (six males; mean age, 59 years) with histologically verified WHO grade IV glioma were imaged a total of 50 times (between 4 and 9 examinations per patient) as part of an ongoing longitudinal treatment response study. Six of the patients had surgical debulking procedure before baseline imaging, whereas one had biopsy performed. The study was

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approved by the Regional Medical Ethics Committee and signed informed consent was obtained from all included patients.

MRI

All imaging was performed on a 3 Tesla (T) Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) using an eight-channel head coil. DCE series was acquired using a three-dimensional (3D) saturation recovery (SR) double-echo gradient-echo sequence adapted from (11), thereby allowing dynamic estimation of T₂*-relaxation. By using a saturation preparation pulse, T₁-contrast is improved and inflow effects are reduced (12). Key sequence parameters were: repetition time (TR) = 8.2 ms, echo time (TE) = 2.5 ms and 5.6 ms, saturation delay 80 ms, acquisition matrix of 120 × 120, voxel size 1.9 × 1.9 × 4 mm³, pixel bandwidth 434 Hz and temporal resolution 3.4 s. Each series included 100 images, covering a time frame of 5 min and 40 s. After five baseline images, the patient was injected with 0.1 mmol/kg of gadobutrol (Gadovist[®], Bayer Schering Pharma AG, Berlin, Germany) at 3 mL/s using a power injector, followed by a 20-mL saline flush. A high-resolution 3D sagittal T₁-weighted gradient-echo sequence was run before and directly after the DCE sequence yielding comparable pre- and postcontrast images, in addition to a high-resolution 3D sagittal fluid-attenuated inversion-recovery (FLAIR) sequence run at the start of the imaging protocol. Baseline T₁ maps were generated using a Look-Locker inversion recovery sequence with TE = 1.3 ms, TR = 2.6 ms, flip angle = 4°, 38 inversion times (TI), TI(0) = 43 ms and ΔTI = 69 ms.

Data Analysis

For pharmacokinetic analysis, we used the extended Tofts model (13), in which the dynamic CA concentration in tissue is given as:

$$C_t(t) = K^{\text{trans}} \int_0^t C_p(\tau) \exp\left(-\frac{K^{\text{trans}}(t-\tau)}{v_e}\right) d\tau + v_p C_p(t), \quad [1]$$

where C_t and C_p are the CA concentrations in tissue and blood plasma, respectively, K^{trans} is the rate constant of CA exchange between blood plasma and the extracellular, extravascular space (EES), and the fractional compartment volumes of blood plasma and EES are denoted v_e and v_p , respectively. The ratio K^{trans}/v_e is commonly denoted as the rate constant, k_{ep} . We used a constant baseline T₁(0) of 1670 ms in arterial blood (14) and 1200 ms in tissue (the median value in the present study's tumors). Fixed baseline T₁ values were used to avoid additional noise from pixel-wise T₁(0) analysis (4), further justified by the fact that the relative effects of AIF T₂*-effects on kinetic parameter estimations is expected to be minimally influenced by small variations in baseline T₁. The temporal DCE data were subjected to rigid body motion correction (15) to remove the effects of patient head movement during acquisition. In arterial blood,

we estimated the change in R₁ relaxation rate both by assuming negligible T₂*-effects (i.e., TE < ΔR₂*(t)) and from the full expression, including ΔR₂*(t) as estimated from the double-echo data.

The CA concentration in blood plasma $C_p(\tau)$ (i.e., the AIF) was estimated using a semi-automatic AIF-detection algorithm (16). The algorithm was applied to an area likely to contain a tumor-feeding artery, and the resulting voxels were manually inspected to ensure plausible dynamic AIF characteristics.

Time-dependent 1/T₂*-curves were estimated in the AIF voxels by assuming a mono-exponential signal decay as function of TE. The AIF curves were corrected to account for this signal loss up to and including the first pass of the CA. By assuming blood hematocrit to be constant at 0.45, $C_p(\tau)$ -curves were obtained with and without T₂*-correction. Kinetic analysis was performed by deconvolution of Eq. [1] using established techniques (17).

Region of Interest Analysis

Tumor regions of interest (ROIs) were generated in a process where B₁ field inhomogeneities were first removed from FLAIR and contrast-enhanced T₁-weighted (T₁-CE) images using an entropy based method (18), after which ROIs representing FLAIR hyperintensity and T₁-CE regions were produced using a second-order entropy thresholding method (19). ROIs assumed to represent active tumor were obtained by identifying voxels with both contrast enhancement on T₁-CE and hyperintensities in FLAIR images after applying slight dilation to the FLAIR ROIs. Finally, the ROIs were checked and fine-tuned by an experienced neuroscientist (I.G.). K^{trans} , k_{ep} , v_e , and v_p were estimated using uncorrected and T₂*-corrected AIFs, and the results were compared pixel-wise and on a tumor-median basis.

Statistical Analysis

Median values for K^{trans} , k_{ep} , v_e , and v_p were calculated in all ROIs using both uncorrected and corrected AIF. Differences between parameters estimated with the two AIFs were tested using Wilcoxon signed rank test.

Simulations

Computer simulations were performed to systematically investigate the echo time dependent error in K^{trans} estimates due to T₂*-induced AIF signal loss. Reference AIFs were generated in Jsim (www.physio-me.org) and convolved according to Eq. [1] using typical parameter values previously obtained in the present patient material (20), yielding a reference tissue response. The reference AIF was then attenuated by T₂*-decay as postulated in (21). Noise was added to the tissue curve and AIF to give an SNR of 60, corresponding to that of a typical exam series. Subsequent deconvolution of the tissue curve with the modified AIF then provided parameter estimates directly relatable to the reduction of the AIF peak as well as actual parameter values. This procedure was

Figure 1. a: Boxplot of distribution of percent error in median parameter values from 50 DCE measurements using uncorrected AIFs, compared with double echo T_2^* corrected AIFs. b: Relative error in parameter estimates as a function of actual peak T_2^* -induced AIF attenuation in 50 DCE examinations. The striped lines indicate 10% error. The numbered circles indicate corresponding estimates from two examinations.

repeated 10^6 times with v_e kept constant at 30%, K^{trans} ranging from 0.02 to 0.15 min^{-1} , and v_p ranging from 0.3 to 3.0%. Finally, the single echo TE required to keep AIF T_2^* -induced errors in the kinetic parameters below 10% was estimated. Here, we used peak concentration values from the corrected AIFs and a previously published relationship between concentration of Gd-DTPA and change in T_2^* (21). In the current study, a different gadolinium-chelate was used, but their T_2^* relaxivity is expected to be almost identical because it is determined by the susceptibility of the gadolinium ion itself, and not the carrier molecule. Furthermore, we make the assumption that this relationship is not significantly different at 3T, although this has only been verified for CA

concentrations up to 6 mM (22). To validate this relationship, the difference in concentration estimates from the first pass of the CA from the two AIFs were compared with the difference predicted by van Osch et al (21).

RESULTS

Figure 1a shows a box-plot of the resulting error in the median of the estimated parameters in each tumor due to uncorrected T_2^* -effects in the AIFs. There was a significant difference in the corrected and uncorrected values for all parameters except v_e (K^{trans} : $P < 10^{-5}$, k_{ep} : $P < 10^{-6}$, v_p : $P < 10^{-8}$). The same data points are plotted in Figure 1b as a function of the

Figure 2. a: Relative error in K^{trans} - and (b) v_p -estimates from simulated data due to T_2^* -induced AIF attenuation. The colors indicate the nominal value of K^{trans} and v_p according to the color-bar scale.

Figure 3. First pass AIF concentration before ($TE = 2.5$ ms) and after double echo correction from patient data compared with the results from simulations using reference values for T_2^* -relaxivity of gadolinium in blood (14).

percent reduction in the uncorrected AIF peak amplitude relative to the T_2^* -corrected peak amplitude. As expected, the error in the parameter estimates increase with increasing underestimation in the peak AIF amplitude. The same trend is observed for simulated data for K^{trans} and v_p as shown in Figure 2. In the simulations the impact of nominal parameter values is also taken into account, showing larger

overestimations in K^{trans} for higher nominal K^{trans} values and conversely lower overestimation of v_p for higher nominal values of v_p . Figure 3 shows the correlation between estimated first pass concentrations (estimated at each dynamic time-point) in corrected versus uncorrected AIFs obtained from patient data. As expected, increasing AIF concentrations leads to increasing amplitude underestimation in the

Figure 4. (Top) K^{trans} and (bottom) v_p tumor maps before (a) and after (b) T_2^* -correction and the corresponding tumor histogram distributions (c). The uncorrected images exhibit broader value distributions.

Figure 5. The highest TE required in single-echo acquisitions to achieve a minimum of 75% and 85% of the true peak AIF amplitude, thus giving less than 10% error in K^{trans} and v_p estimates, respectively. For k_{ep} the requirement is the same as for K^{trans} .

uncorrected AIF. The results from patient data are seen to be in good agreement with the simulated data obtained using TE = 2.5 ms and previously published dose-dependent change in $1/T_2^*$ for Gd-DTPA in blood (21).

The effect on parameter estimates is evident in the example shown in Figure 4, where K^{trans} - and v_p -maps are shown along with histograms of their distributions in tumor. Increased heterogeneity in the uncorrected images is evident.

Figure 5 shows simulations of the required TE to produce less than 10 % T_2^* -induced error in K^{trans} and v_p from a single echo acquisition. The results indicate that when using TE = 2.5 ms, the AIF concentration should not exceed approximately 8 mM or 6 mM to keep errors below 10 % in K^{trans} and v_p , respectively.

DISCUSSION

The aim of the present work was to investigate the validity of the assumption that T_2^* -effects are negligible in DCE-MRI in a relevant patient group using a double-echo DCE-MRI protocol. The results show that, using a DCE sequence with TE = 2.5 ms and a power injector for CA administration, the CA-induced reduction in T_2^* during the first pass of the CA bolus in an artery is not negligible and will result in incorrect AIF estimates and consequently significant errors in the estimated kinetic parameters. The resulting overestimation of K^{trans} is in line with previous work done on nonbrain tumors (23).

The presence of uncorrected T_2^* -effects results in an underestimation of the AIF peak amplitude which in turn result in a significant overestimation of all kinetic parameters except v_e . The effect is particularly dramatic for v_p because AIF amplitude errors are directly reflected in the magnitude of the v_p estimate. For K^{trans} , the effect is less pronounced because this

parameter is related to the time integral of the AIF and thus to a larger extent depends on the “tail” part of the AIF, where no arterial T_2^* -effects is identified due to the much lower steady state arterial CA concentration.

In the present study, a TE value of 2.5 ms was used, as this was the shortest TE value obtainable with the DCE sequence used. T_2^* -effects can be reduced further by using shorter TE values or by reducing the peak CA concentration in blood through reduced injection rates. Although the mean error in K^{trans} due to AIF T_2^* -effects are expected to be modest at short TE values, these effects may inevitably lead to a bias in the distribution of tumor K^{trans} values. As seen from the simulations (Fig. 2), larger K^{trans} values are more affected by AIF errors, and the larger the uncorrected T_2^* -attenuation in the AIF, the larger the erroneous effect in the resulting K^{trans} values. This may lead to tumors being interpreted as more heterogeneous than is the case, with resulting artificial “hotspots” due to increasing overestimation of higher parameter values as exemplified in Figure 4.

The presence of T_2^* -effects in the AIF should be recognized as a potential source of error in DCE-MRI, affecting both the median tumor kinetic values, but more importantly leading to a bias in the distribution of kinetic parameter estimates in tumor, which should be corrected for. Potential weaknesses of the proposed method includes some added analysis complexity, the need to acquire double echo data and possible errors in the dynamic T_2^* -measurements used for AIF corrections. The method is, however, readily implementable on most standard MR systems, and the analysis can to a large extent be automated, resulting in little processing overhead in practice.

In conclusion, the presence of uncorrected T_2^* -effects in blood leads to overestimation of kinetic parameter estimations in DCE-MRI, and the effect is particularly large for estimations of plasma volume fraction. The error is dependent on the nominal value of the parameter, which may result in a bias in the estimation of parameter tumor distribution. The error due to T_2^* -effects can be reduced by lowering the TE value or can be eliminated completely by acquiring double-echo data.

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Original Research

Sampling Requirements in DCE-MRI Based Analysis of High Grade Gliomas: Simulations and Clinical Results

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Purpose: To investigate the effect of variations in temporal resolution and total measurement times on the estimations of kinetic parameters derived from dynamic contrast-enhanced (DCE) MRI in patients with high-grade gliomas (HGGs).

Materials and Methods: DCE-MRI with high temporal resolution (dynamic sampling time (T_s) = 2.1 s and 3.4 s) and total sampling time (T_{acq}) of 5.2 min was acquired in 101 examinations from 15 patients. Using the modified Tofts model K^{trans} , k_{ep} , v_e and v_p were estimated. The effects of increasing T_s and reducing T_{acq} on the estimated kinetic parameters were estimated through down-sampling and data truncation, and the results were compared with numerical simulations.

Results: There was an overall dependence of all four kinetic parameters on T_s and T_{acq} . Increasing T_s resulted in under-estimation of K^{trans} and over-estimation of V_p , whereas k_{ep} and V_e varied in a less predictable manner. Reducing T_{acq} resulted in over-estimation of K^{trans} and k_{ep} and under-estimation of v_p and v_e . Increasing T_s and reducing T_{acq} resulted in increased relative error for all four parameters.

Conclusion: Estimated K^{trans} , K_{ep} , and V_e in HGGs were within 15% of the high sampling rate reference values for $T_s < 20$ s. Increasing T_s and reducing T_{acq} leads to reduced precision of the estimated values.

Key Words: DCE-MRI; DCE sequence optimization; glioma; temporal resolution; Tofts model

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DYNAMIC CONTRAST-ENHANCED (DCE) MRI is an established technique for the assessment of brain hemodynamics and blood–brain barrier (BBB) integrity. In DCE-MRI, dynamic changes in signal intensity (SI) are measured following an intravenous bolus injection of a paramagnetic contrast agent (CA). Given that the SI change can be measured with sufficient temporal resolution and is related to tissue CA concentration, established tracer kinetic models can be used to estimate the volume CA transfer constant across the capillaries and CA distribution volume fractions in the extravascular extracellular space (EES) and plasma (1–3). In the brain, parameters derived from DCE-MRI have primarily been used to evaluate treatment effects in primary brain tumors (4), glioma grading (5), differential diagnosis (6), and to differentiate recurrent tumor from radiation injury (7). The clinical interpretation and utility of DCE-MRI in the diagnosis and management of primary brain tumor patients is, however, limited by a lack of standardization, both in terms of acquisition protocol and analysis approach (8). Therefore, despite many individual studies indicating diagnostic efficacy of DCE-MRI in the brain, a recent proposal for updated treatment response assessment criteria for high grade gliomas (HGGs) still only includes conventional CE MRI as the basis for assessment of treatment response in HGG patients (9). A broad range of studies have addressed factors affecting the accuracy and reproducibility of metrics derived from DCE-MRI, including effects of acquisition parameters, applied kinetic model, and analysis approach (10–13). Most of these studies are of a theoretical nature and the results are typically not clearly linked to clinical relevance in a defined patient population.

To this end, the main objective of the current study was to systematically investigate, both through simulations and in clinical DCE data, the effect of varying temporal resolution and total sampling duration on the ability to estimate standard kinetic parameters using the most established kinetic model combined with robust deconvolution and arterial input function (AIF) detection methods. By acquiring DCE data with

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high temporal resolution it was possible to simulate the effect of reduced time resolution by successive averaging of images, thereby providing directly comparable DCE time series with a range of different temporal resolutions. Furthermore, by truncation of the dynamic time series, the effect of different total dynamic measurement times was systematically investigated.

To ensure clinical relevance in a well-defined patient population, the analysis was performed in patients with histologically confirmed HGG undergoing a standard combined radiation therapy (RT) and chemotherapy regimen (14), where each patient was imaged multiple times, before, during- and after therapy, thereby capturing the full range of tumor kinetic parameters to be expected in these patients during the course of treatment and disease progression. Temporal resolution was chosen as the test parameter because of its direct impact on achievable spatial resolution, brain coverage and signal-to-noise ratio (SNR). Temporal resolution is considered one of the most important parameters to optimize both from an analysis and a clinical point of view. Total dynamic measurement time was evaluated because this parameter is a major determinant for patient throughput, patient compliance and motion-induced image artifacts.

THEORY

Kinetic Modeling and Sampling Requirements

The permeability dependent evolution of total tissue tracer concentration following the bolus injection of a small molecular weight gadolinium (Gd) based CA can be described in terms of the bidirectional CA flux across the capillary wall (1,2):

$$C_t(t) = K^{trans} \int_0^t C_p(\tau) \exp\left(-\frac{K^{trans}(t-\tau)}{v_e}\right) d\tau + v_p C_p(t), \quad [1]$$

Where $C_t(t)$ is the CA in tissue, $C_p(t)$ is the plasma CA concentration in a feeding artery (i.e., the AIF), v_p , is fractional tissue plasma volume, K^{trans} is the CA transfer constant and v_e is the CA distribution volume fraction in the EES. The ratio $k_{ep} = K^{trans}/v_e$ is conventionally denoted the rate constant. K^{trans} is a function of tissue perfusion and the permeability surface area (PS) product (3). C_p is related to the total blood concentration, C_b , by: $C_p(t) = C_b(t)/(1-Hct)$, where Hct is the hematocrit. Sampling considerations are more readily analyzed in the frequency domain and Fourier transformation of Eq. [1], yields the following system transfer function (15):

$$H(\omega) = \frac{C_t(\omega)}{C_p(\omega)} = v_p + \frac{K^{trans}}{i\omega + k_{ep}} \quad [2]$$

where ω is the angular frequency and $C_p(\omega)$, $C_t(\omega)$ are the Fourier transformed AIF (system input)- and tissue concentration time curves (CTCs, system output), respectively. The exponential term in Eq. [1] thus acts

Table 1

Median (Interquartile Range) Values for Tumor Median and 95 Percentile Values for the Kinetic Parameters Obtained From 101 Exams in 15 Patients

Parameter	Median	95 percentile
K^{trans} (min^{-1})	0.04 (0.03-0.07)	0.14 (0.08-0.20)
K_{ep} (min^{-1})	0.30 (0.22-0.40)	0.80 (0.55-1.02)
V_e (percent)	15.9 (8.5-25.0)	41.8 (28.6-58.6)
V_p (percent)	1.1 (0.52-1.66)	3.9 (2.0-6.2)

as a low-pass filter between C_p and C_t with a pole frequency (3 dB input-output attenuation) given by $\omega_p = 2\pi k_{ep}$, whereas the plasma fraction v_p gives rise to a frequency-independent input-output attenuation. For a given sampling interval, T_s , the highest (ω_{max}) and lowest (ω_{min}) frequencies that can be correctly identified in $H(\omega)$ are given by $\omega_{max} = \pi/T_s$ and $\omega_{min} = 2\pi/T_{acq}$, where $T_{acq} = NT_s$ and N is the number of data points. Assuming negligible frequency components in the output signal above the transfer function pole frequency, the minimum required sampling frequency according to the Nyquist criterion is given by $2\omega_p = 4\pi k_{ep}$ and the corresponding maximum sampling interval is $T_s^{max} = 1/(2k_{ep})$. Given that the experimental data are well described by the extended Tofts model according to Eq. [1] with sampling interval T_s , the highest k_{ep} that can correctly be determined is then $k_{ep}^{max} = 1/(2T_s)$. The sampling duration requirement is similarly given by $\omega_{min}/(2\pi) \ll k_{ep}$ or $T_{acq} \gg 1/k_{ep}$.

MATERIALS AND METHODS

Patients

A total of 101 DCE-MRI studies from 15 patients (11 males; mean age, 53.7 years; range, 32 to 66 years) with histologically confirmed HGG (1 grade III and 14 grade IV) were included in the study. Individual patients were imaged one time before, three times during-, and up to five times for a maximum of 15 months after initiation of standard treatment regimen (14). Study approval was obtained from the Regional Medical Ethics Committee and patients were included only if informed consent was signed.

Magnetic Resonance Imaging

All imaging was performed at 3 Tesla (T) (Philips Achieva, Philips Medical Systems, Best, The Netherlands), using an eight-channel head coil. DCE images were acquired using a 3D- saturation-recovery (SR) based gradient echo (GRE) sequence. Using a short saturation delay (TD), this sequence has been shown to be relatively insensitive to water exchange effects (16). Eleven slices covering the tumor volume were acquired with the following sequence parameters: acquisition matrix 120×120 with partial Fourier (half-scan), voxel size $2 \times 2 \times 4 \text{ mm}^3$, pixel bandwidth 434 Hz, repetition time/echo time/flip angle (TR/TE/flip angle) = 8.2 ms/2.5 ms/26°. TD/ T_s were either: 80 ms/3.4 s (patients 1-7) or 50 ms/2.1 s (patients 8-

15). A total of 100 dynamic images (patients 1–7) or 150 images (patients 8–15) were acquired, giving a total dynamic measurement time (T_{acq}) of 330s or 340s. Parallel imaging was applied with a sensitivity encoding (SENSE) factor of 2.3 in the phase-encoding direction. After five time-points, 0.1 mmol/kg of gadobutrol (Gadovist®, Bayer Schering Pharma AG, Berlin, Germany) was injected using a power injector at a rate of 3 mL/s, immediately followed by a 20-mL bolus of saline. The imaging protocol included the following structural image series: 3D sagittal fluid-attenuated inversion-recovery (FLAIR) images, 2D axial T2-weighted images and 3D sagittal T1-weighted GRE images acquired before- and after CA administration. All image series were acquired before the DCE series except the CA-enhanced T1-weighted images which were acquired directly after. The two different DCE-sequences will be referred to as Sequence 1 (patients 1–7) and Sequence 2 (patients 8–15).

Data Analysis

DCE Analysis in Patient Data

The DCE time series were analyzed using the extended Tofts model according to Eq. [1]. Hct was set to 0.45 and $C_a(t)$ was estimated using an automated AIF detection algorithm (17). All AIFs were visually inspected for location in appropriate arterial territory. Rigid body motion correction (18) was applied to the DCE data before AIF detection and kinetic analysis. For the SR sequence, using a 90° saturation pulse, the SI response can be approximated by:

$$S(C) \propto M_0[1 - \exp(-TD \cdot R_1(C))] \quad [3]$$

where $R_1 = 1/T_1$, C is the CA concentration, M_0 is the equilibrium magnetization and TD is the delay time between the saturation pulse and the centre of K-space of the acquisition. The CA induced change in R_1 is then given by:

$$\Delta R_1(t) = -\frac{1}{TD} \ln \left[1 - E_0 \frac{S(t)}{S(0)} \right] - R_1(0) \quad [4]$$

where $R_1(0)$ is the baseline (precontrast) $1/T_1$, $E_0 = 1 - \exp(-TD \cdot R_1(0))$, and $S(t)$ is the measured SI at time t . ΔR_1 was assumed to be proportional to CA concentration (with equal CA relaxivity) in both blood and tissue. Because CA concentration is estimated indirectly through ΔR_1 (in units of s^{-1}), K^{trans} and k_{ep} in Eq. [1] are given in units of inverse time (min^{-1}) whereas v_e and v_p are given as fractions (in percent) of total tissue volume.

Correction for partial volume (PV) effects in the AIF was done by detection of a venous output function (VOF) comprising five venous voxels, automatically selected in the region of the superior sagittal sinus based on large area under curve (AUC) and late CA arrival time. A PV correction factor was then estimated as the ratio of the AUC for the VOF versus AIF and the AIF was scaled by this factor before further kinetic analysis (19). The PV corrected AIF was deconvolved with the pixel-wise tissue response curve (20)

using singular value decomposition (21) following conversion of SI to ΔR_1 without further preprocessing. Estimation of ΔR_1 from SI was performed using a fixed baseline T1 of 1700 ms and the T1 relaxivity of the CA was assumed to be the same in blood and tissue.

Temporal Resolution Analysis

The image series were temporally down-sampled between two and twenty times, resulting in an effective temporal resolution ranging from $T_s = 3.4$ s to 68 s (patients 1–7) and 2.1 s to 42 s (patients 8–15). Down-sampling by a factor of n was performed by averaging the dynamic images from n consecutive time-points. This approach was chosen rather than selecting individual images to account for the higher SNR achievable for lower time-resolutions using the same spatial resolution and geometric coverage. The CA arrival time was determined individually for each DCE series and the baseline images were excluded from the down-sampling procedure, thereby reducing potential errors in the analysis of the down-sampled series due to temporal jittering (22). The original AIFs were subject to the same down-sampling scheme, providing AIFs with identical variations in temporal characteristics and SNR properties as the down-sampled DCE images. The CA arrival time was determined based on the AIF, and any delay between the AIF and tissue response were corrected for using the bolus arrival time method (23).

Total Measurement Time Analysis

The effect of variations in T_{acq} , was investigated by truncation of the tail of the dynamic time-series for both the pixel-wise tissue response and the AIF, to give resulting dynamic time series with $T_{\text{acq}} = 1, 2, 3, 4$, and 5 min.

Region-of-Interest Analysis

Initial regions of interest (ROIs) were automatically generated from FLAIR and post contrast GRE images. First, B1-effects resulting in SI variations across the field of view (FOV) were corrected for using entropy minimization (24). Tumor masks were then automatically defined from the high intensity clusters common to both the FLAIR and post contrast GRE images using a second order relative entropy thresholding method (25). All tumor masks were reviewed by an experienced neuroscientist and manually edited to remove nontumor pixels where present. The structural images and corresponding tumor masks were co-registered to the DCE images using a normalized mutual information algorithm (26) and tumor ROI values could then be extracted from the parametric images representing K^{trans} , v_e , v_p , and k_{ep} obtained both for the original DCE images and for the down-sampled and truncated series. ROI statistics was performed both in terms of whole tumor median and 95 percentile values as well as pixel-wise correlation as function of down-sampling- and truncation factor, because median values for the whole tumor would be

expected to mask out effects affecting a small number of tumor pixels. Finally, the average number of tumor pixels under-sampled (i.e., pixels with $k_{ep} \geq 1/2T_s$) was estimated across all examinations as a function of T_s .

Image analysis was performed in nordicICE (Nordic NeuroLab AS, Norway) and in Matlab R2011A (The MathWorks Inc, Natick, MA).

Simulations

Numerical simulations were performed to systematically investigate the effect of temporal resolution and total sampling time using predefined values for the kinetic parameters. This was done to specifically investigate the dependence of errors due to under-sampling and truncation on the value of k_{ep} . First, a reference AIF was generated in JSim (<http://physiome.org/jsim>) by applying the dispersion model developed by Barboriak et al (27). The corresponding reference tissue response curves $C_t(t)$ were then generated from Eq. [1] using a range of kinetic parameters randomly chosen from intervals representing clinically observed values. Gaussian noise was added to the AIF and reference curves to give a SNR of 100 at minimum T_s (defined as ratio of peak AIF amplitude to standard deviation of baseline variation), the typical value observed in the clinical DCE images. Both the synthetic tissue response curves and the AIF were then down-sampled or truncated as described above for the clinical data. For each temporal resolution or truncation level, the kinetic parameters were estimated by deconvolution of Eq. [1] using the same methodology as for the clinical data analysis. Because the sampling theory predicts that under-sampling affects high k_{ep} values and truncation low k_{ep} values, under-sampling effects were investigated for $0.4 \text{ min}^{-1} < k_{ep} < 4 \text{ min}^{-1}$ and truncation effects were investigated for $0.025 \text{ min}^{-1} < k_{ep} < 0.25 \text{ min}^{-1}$. The k_{ep} -range used was selected to cover the entire range of values observed in the clinical data. The value of v_p and v_e were fixed at 2% and 25%, respectively. A total of 1000 simulations were run for at each value of k_{ep} . The simulations were performed in Matlab R2011A.

Statistical Analysis

For each tumor ROI, median and 95 percentile values were calculated for all kinetic parameter and the median and inter-quartile range (IQR) of tumor ROI kinetic values across all patients and all time-points were determined. The relative error (RE) in the four kinetic parameters was estimated in terms of the ratio IQR/median and was plotted as a function of T_s and T_{acq} . The response to variations in T_s and T_{acq} was plotted in terms of the median relative change in each parameter compared with the values at $T_s^{\min}$. Data for the two different DCE sequence parameter groups were plotted separately to detect possible sequence dependence differences in response. One-way analysis of variance (ANOVA) was used to investigate any overall dependence of K^{trans} , k_{ep} , v_e , and v_p on T_s and T_{acq} . Difference between reference tumor kinetic val-

ues (obtained at $T_s^{\min}$ and $T_{acq}^{\max}$) and the values obtained at each T_s and T_{acq} was tested using Wilcoxon signed rank test. Possible group differences in metrics obtained with DCE Sequence 1 versus Sequence 2 were tested using Mann-Whitney test. Probability values of $P < 0.05$ were considered significant for all tests. Statistical analysis was performed in Minitab 16 (Minitab Inc, Pennsylvania, USA).

RESULTS

Figure 1 shows the distribution of the kinetic parameters for all patients. The median (IQR) of the tumor median and 95 percentile values for the four metrics across the 101 examinations in 15 patients are summarized in Table 1. The median value of K^{trans} differed ($P = 0.03$) between the patients scanned with Sequence 1 versus Sequence 2. There were no group differences for the other three kinetic parameters.

Effects of Varying Temporal Resolution

Simulations

As shown in Figure 2, all four kinetic parameters were found to exhibit an oscillating dependence on sampling time up to approximately $T_s = 20$ followed by a distinct reduction in K^{trans} , k_{ep} , and v_e and an increase in v_p at higher T_s -values. The error in all four parameters increased with increasing k_{ep} . At $k_{ep} = 0.4 \text{ min}^{-1}$ the error in K^{trans} was $<15\%$ for the entire range of T_s -values whereas $k_{ep} = 4 \text{ min}^{-1}$ (a value exceeding all clinical data in the present study) resulted in $>15\%$ under-estimation of K^{trans} even at a temporal resolution of $T_s = 3.4 \text{ s}$.

Clinical Data

There was an overall significant dependence on T_s of mean tumor K^{trans} , k_{ep} , v_e , and v_p (ANOVA, $P \leq 0.001$). Figure 3 shows the relative change in the median value of the four kinetic parameters with increasing T_s compared with the values at $T_s^{\min}$. All parameters except v_p were within $\pm 15\%$ of the reference values for T_s less than 20 s. A T_s -dependent trend was most clearly observed for K^{trans} and v_p with a decrease in K^{trans} and an increase in v_p with increasing T_s ; the change being significant for $T_s > 20 \text{ s}$ for both parameters. The effect of down-sampling showed similar trends for data obtained with Sequence 1 and Sequence 2, but the relative error as function of T_s was larger in Sequence 1 compared with Sequence 2 for v_e ($P = 0.004$) and v_p ($P = 0.03$). For all four parameters, the relative error across all examinations increased with increasing T_s (Fig. 4a). Table 2 summarizes the P -values obtained from one-sample Wilcoxon testing of the relative difference between each metrics measured at $T_s^{\max}$ versus each down-sampled value. The trends observed in the clinical data were in good agreement with the simulations for K^{trans} and v_p . For K_{ep} and v_e the T_s -dependence was more distinct in the simulations compared with the clinical results. The estimated number of under-sampled tumor pixels as a function of T_s increased with the value of $k_{ep}^{\max} =$

Figure 1. Distribution of DCE-MRI derived kinetic parameters for all patients. The numbers in brackets on the x-axis indicate number of repeated examinations for each patient and each point represents the median tumor value for each individual examination. The vertical lines inside each graph indicate the division between patients scanned with DCE sequence 1 (patients 1–7) and sequence 2 (8–15).

$1/(2T_s)$, as shown in Figure 5. At $T_s=68$ s, approximately 20% of the tumor voxels were under-sampled whereas $T_s \leq 10$ s resulted in $<1\%$ under-sampled voxels.

Figure 6a shows tumor and AIF CTCs from a sample case (male, 50 years) obtained from the original- and down-sampled DCE images. The corresponding K^{trans} maps obtained in the same patient (Fig. 7a)

reveal very little visual difference in the maps obtained with $T_s=3.4$ s and $T_s=13.6$ s. At higher T_s -values, a gradual loss of high K^{trans} values is observed. This increasing under-sampling of high K^{trans} values with increasing T_s is also evident in the scatter plots (Fig. 7b) and in the narrowing of the corresponding K^{trans} tumor histogram distribution (Fig. 7c).

Figure 2. Results of simulations showing the ratio between nominal- and simulated values of the four kinetic parameter as a function sampling interval (T_s) for different values of K_{ep} (in units of min^{-1}).

Figure 3. Estimated effects of variations in sampling interval (T_s) on median tumor kinetic parameters in patient data. Data obtained with Sequence 1 and Sequence 2 are plotted separately. The y-axes represent fractional change in the respective kinetic parameters relative to reference values obtained at T_s^{min} ($=3.4$ s for Sequence 1 and 2.1 s for Sequence 2). The dotted lines indicate range of $\pm 15\%$ variation from reference values. The error bars represent the 5–95 percentile range.

Effects of Varying Total Sampling Time

Simulations

Reduced total sampling time, T_{acq} , resulted in an increasing over-estimation of K^{trans} and k_{ep} and under-estimation of v_e , and the error in all parameters increased with decreasing values of k_{ep} , as shown in Figure 8. The value of v_p was found to be less sensitive to reduction in T_{acq} compare with the other three kinetic parameters.

Clinical Data

All four kinetic parameters showed a significant dependence on T_{acq} (ANOVA, $P < 0.001$), as shown in Figure 9. Reducing T_{acq} resulted in an increase in K^{trans} and k_{ep} and a reduction in v_e and v_p compared with their values at T_{acq}^{max} . The change in all four parameters was significant at all reduced values of T_{acq} , relative to their values at T_{acq}^{max} . There was no difference in the T_{acq} -dependence between groups scanned with Sequence 1 versus Sequence 2 for any of the four kinetic parameters. The trends observed in clinical

data were in good agreement with the simulations, except for v_p where a much large effect was observed in the clinical data than in the simulations. The relative error in all four kinetic parameters increase with reduced T_{acq} , as shown in Figure 4b.

Figure 6b shows tumor and AIF CTCs from the sample case (same patient as Fig. 6a) obtained from the original and truncated DCE images. The corresponding K^{trans} maps obtained from the same patient show an overall increase in tumor K^{trans} with reducing T_{acq} (Fig. 10a). This effect was also confirmed from the scatter-plot of tumor K^{trans} values obtained at T_{acq}^{max} versus $T_{acq}=3$ min and $T_{acq}=1$ min (Fig. 10b). The resulting tumor histogram distribution in Figure 10c shows a broadening of the tumor K^{trans} distribution with relatively fewer low K^{trans} values and more high K^{trans} values with reducing T_{acq} .

DISCUSSION

The present work systematically investigates the effect of DCE sampling time, and total scan duration on the

Figure 4. Relative error (IQR/median) in kinetic parameters as function of T_s (a) and T_{acq} (b).

Table 2

P Values (One-Sample Wilcoxon) for Testing of Difference in Kinetic Parameters From Down-Sampled Data Relative to Reference Values Obtained at $T_s^{\min}$

Sequence 1 ($T_s^{\min}=3.4$ s)					Sequence 2 ($T_s^{\min}=2.1$ s)				
T_s (s)	K^{trans}	<i>P</i> value K_{ep}	v_e	v_p	T_s (s)	K^{trans}	<i>P</i> value K_{ep}	v_e	v_p
6,8	0,045	0,538	0,059	<.001	4,2	0,46	0,498	0,042	0,002
10,2	<.001	0,195	0,002	<.001	6,3	0,001	0,002	0,331	<.001
13,6	0,193	0,016	<.001	<.001	8,4	<.001	0,039	0,785	<.001
17	0,35	<.001	<.001	<.001	10,5	0,001	0,002	0,743	<.001
20,4	0,19	<.001	<.001	<.001	12,6	0,03	0,577	0,394	<.001
23,8	<.001	0,03	<.001	<.001	14,7	0,887	0,491	0,129	0,11
27,2	<.001	0,1	<.001	<.001	16,8	0,419	0,065	0,027	0,159
30,6	<.001	0,753	0,002	<.001	18,9	0,058	0,844	0,229	0,007
34	<.001	0,56	0,002	<.001	21	0,001	0,031	0,956	<.001
68	<.001	<.001	0,029	<.001	42	<.001	<.001	<.001	<.001

Significance shown in bold typeface.

resulting kinetic parameters obtained in DCE-MRI of HGG patients. This is to our knowledge the first systematic investigation of sampling requirements in DCE-MRI in brain tumor patients. Although a large proportion of clinical glioma DCE-MRI studies reported in the literature have used temporal resolutions in the 2–10 s range and total sampling times in the range of 5–10 min, this choice of sampling parameters does not appear to be particularly evidence based. Given the importance of sampling requirements on image quality and patient compliance, a better founded parameter choice is therefore highly warranted.

Temporal Resolution Requirements

The results, both from clinical data and simulations, suggest that insufficient temporal resolution leads to under-estimation of k_{ep} and K^{trans} and over-estimation of v_p and also a general loss of precision in the parameter estimates, as shown in Figure 4. Comparing Figures 3 and 4a, it appears that the reduction in precision (increase in relative error) is more significant than the reduction in accuracy at T_s -values below approximately 20 s. More specifically, the effect of increasing sampling time was modest (<15%) for $T_s < 20$ s, whereas the relative error increased in an approximately linear manner from $T_s^{\min}$ to approximately $T_s = 20$ s, where the error appeared to reach a plateau. Using $T_s = 20$ s, the highest value of k_{ep} that can be reliably measured is $k_{\text{ep}}^{\text{max}} = 1/(2T_s) = 1.5 \text{ min}^{-1}$; a value higher than the 95 percentile k_{ep} value (0.8 min^{-1}) estimated at $T_s^{\min}$ across all tumor ROIs. From Figure 5 it is evident that using a T_s of 30 s only resulted on average in under-sampling (in terms of pixels with $k_{\text{ep}} 1/(2T_s)$) of <5% of tumor pixels across all 101 DCE-MRI acquisitions. Despite a small effect on median tumor values, under-sampling resulted in decreased precision (as reflected in increased relative error) and may result in a bias in the estimated values in heterogeneous tumors by under-estimation of a (small) fraction of highly leaky voxels. This is clearly evident from Figure 7B, showing how the under-esti-

mation of K^{trans} increases with the actual tumor K^{trans} as measured with the highest temporal resolution. The same conclusion can be drawn from the simulations (Fig. 2), showing the dramatic increase in the under-estimation of K^{trans} with increasing k_{ep} . This is important because HGGs are known to be heterogeneous tumors characterized by disordered neo-angiogenic microvessel structures (28,29) and small “hot-spots” of very high K^{trans} values may, therefore, be missed if T_s is too long. The same effect should be expected in other tumor types exhibiting regions of high capillary permeability. The effect of under-sampling is visually evident from the sample patient shown in Figure 7a. Compared with the K^{trans} map obtained with $T_s=3.4$ s the corresponding map generated with $T_s=34$ s is more homogeneous with poorer visualization of “hot-spots”. There is, however, very little visual difference in the K^{trans} maps generated with $T_s = 3.4$ versus $T_s = 13.6$.

Total Acquisition Time Requirements

Shortening the total sampling time resulted in over-estimation of K^{trans} and k_{ep} and under-estimation of v_e and v_p . This effect was seen both in simulations and in clinical data, although the increasing error in

Figure 5. Estimated average (SD) percent of tumor pixels under-sampled as function of T_s based on actual tumor K_{ep} values in 101 examinations.

Figure 6. Concentration-time-curves (CTCs) obtained from tumor and arterial input function (AIF) in a sample patient, showing effects of down-sampling (increasing T_s) (a) and data truncation (reducing T_{acq}) (b) of the original CTCs.

Figure 7. K^{trans} maps obtained from sample patient showing the effect of down-sampling (a). The scatter plot (b) shows the resulting pixel-wise correlation between the K^{trans} values obtained at reference $T_s = 3.4$ s and three down-sampled T_s -values. The corresponding histograms (c) shows the distribution of K^{trans} values in tumor as function of T_s .

Figure 8. Results of simulations showing the ratio between nominal- and simulated values of the four kinetic parameters as a function of total measurement time (T_{acq}) for different values of K_{ep} (in units of min^{-1}).

v_p with reducing T_{acq} was more evident in the clinical data than in the simulations. The simulations showed that the error in the four metrics increases with reducing k_{ep} , in agreement with the sampling theory. Reduced total sampling time therefore has the opposite effect to reduced temporal resolution in that the resulting measurement error is biased toward regions with low permeability. This bias results in a broadening of the tumor histogram distribution by increasing

the relative weighting toward higher K^{trans} values, as shown in the sample case (Fig. 10c). The total sampling time in the present work was in excess of 5 min, and results from simulations suggest that this is borderline too short for correct kinetic estimation in this patient group. Increasing T_{acq} significantly beyond 5 min will, however, increase the probability of severe patient motion which could negate the gain from more robust kinetic analysis.

Figure 9. Estimated effects of variations in total sampling time (T_{acq}) on median tumor kinetic parameters in patient data. Data obtained with Sequence 1 and Sequence 2 are plotted separately. The y-axes represent fractional change in the respective kinetic parameters relative to reference values obtained at $T_{acq} = 5.2$ minutes. The dotted lines indicate range of $\pm 15\%$ variation from reference values. The error bars represent the 5-95 percentile range.

Figure 10. K^{trans} maps obtained from sample patient showing the effect of data truncation (reducing T_{acq}) (a). The scatter plot (b) shows the resulting pixel-wise correlation between the K^{trans} values obtained at reference $T_{acq} = 5.2 \text{ min}$ and two truncated T_{acq} -values. The corresponding histograms (c) shows the distribution of K^{trans} values in tumor as function of T_{acq} .

The effect of dynamic sampling rate- and duration on kinetic parameter estimations in dynamic imaging has previously been studied by others. Goh et al compared three different total dynamic acquisition times in CT based perfusion of colon cancer and found that estimated mean tumor permeability decreased with decreasing total acquisition time (30). This is contrary to our results. However, their results in based on only 10 subjects and they tested a much shorter range of acquisition times (45, 65, and 130 s). Also, no information about the kinetic model used to analyze the data was provided, making a direct comparison difficult. Michaely et al investigated the effect of both total sampling time and temporal resolution in MR based kidney perfusion using a downsampling scheme similar to ours, except that no image averaging was applied during down-sampling (31). They applied a kidney-specific two-compartment model to assess different functional kidney parameters. Given that their results are based on a different kinetic model which probably exhibits a different frequency response compared with the extended Tofts model their results cannot be directly compared with ours. They did, however observed a general increase in the parameter estimation errors with increasing T_s and reduced T_{acq} , in line with our results.

Study Limitations

The study has limitations. First, fixed baseline T1 values in blood and tissue was assumed when converting

SI to CTCs. Although it has been recommended to estimate pixel-wise baseline T1 values in DCE analysis (32), it has also been claimed that fixing baseline T1 has little influence on the resulting dose-response curve, and that attempts to quantify baseline T1 may in fact introduce more error (33). Because variations in tumor baseline T1 would result in subtle changes in the shape of the CTC, using a fixed baseline values could theoretically result in incorrect k_{ep} estimates. From Eq. [4], it can readily be appreciated that, e.g., a 20% error in the baseline T1 value used results in less than 1% error in the estimation of peak $\Delta R1$ (assuming peak T1 = 300 ms). The effect of incorrect baseline T1 on estimated k_{ep} is therefore expected to be small compared with the large variation in k_{ep} as a function of sampling rate- and duration. It is of importance to observe that the sampling requirement in DCE-MRI is completely determined by the value of $k_{ep} = K^{trans}/v_e$ (Eq. [1]). Correct estimation of k_{ep} is, therefore, only dependent on correctly measuring the shape of the AIF and CTC, and not on correct estimation of their magnitude, because any magnitude error will act as a scaling factor with equal effect on both K^{trans} and v_e . Potential imperfections in the applied PV correction method, and resulting errors in the amplitude of the AIF would therefore not affect the estimates of k_{ep} . Second, the sequence parameters for the DCE-MRI sequence was slightly modified half-way through the study resulting in a SR sequence with shorter TD- and T_s^{min} for the last eight patients. There was a borderline significant ($P = 0.03$) group

difference in K^{trans} between the patients scanned with Sequence 1 versus Sequence 2, but not in the other three parameters. This difference could be due to a true incidental difference between the two patient groups. The relative error in v_e and v_p as a function of T_s was generally large in the Sequence 1 group compared with Sequence 2. This can be explained by the fact that T_s^{min} was 40% shorter in Sequence 2, resulting in more image averages and hence a higher SNR for a given down-sampled T_s . This suggests that the exact error response to changes in T_s depends on T_s^{min} . Despite the sequence specific difference in SNR as a function of T_s , the median response to variations in T_s was similar and the response to changes in T_{acq} almost identical for the two sequence groups, suggesting that the overall conclusions are not sequence dependent for the range of parameters investigated here.

The effect of down-sampling was simulated by averaging multiple images from the dynamic DCE series. This was done to account for the effect of the higher achievable SNR with increasing T_s at constant spatial resolution. This would be the correct assumption to use if an increase in T_s would, e.g., be used to increase brain coverage in a 3D sequence. If, on the other hand the increased acquisition time available as T_s increases were to be used to increase the spatial resolution of the DCE acquisition, then the actual gain in SNR with increasing T_s could be much reduced or even negative. Although the effect of different SNR scenarios was not systematically investigated in the present work, it is clear that keeping SNR constant for increasing T_s would lead to a more dramatic increase in measurement uncertainty with increasing T_s . The shape and duration of the AIF may be an additional factor influencing sampling requirements. For narrow AIFs compared with T_s , down-sampling can have an arbitrary effect on the peak amplitude of the resulting down-sampled AIF, resulting in an increase in random effects error. The AIF frequency distribution may be expected to have a particular impact on V_p because the plasma fraction acts as a frequency independent input-output attenuation factor [Eq. [2]]. Hence, the sampling frequency requirement for correct estimation of V_p is determined by the bandwidth of the AIF, and it would, therefore, be expected that a sharper AIF would require a higher sampling rate. The effect of varying AIF shape was not specifically tested here and warrants further investigation.

It should finally be mentioned that the presented methods and conclusions are based on the analysis of CA kinetics using a model which is only strictly correct when the tracer mean transit time (MTT) in tissue is negligible so that in the absence of leakage the tissue response is simply a scaled version of the AIF (13,34,35). This assumption is increasingly violated with increasing MTT values and also with reducing T_s because higher sampling rates increases sensitivity to MTT effects. MTT in HGG has been shown to be >5 s (36), which is not negligibly short relative to the T_s^{min} values used in the present study. Figure 11 shows a sample curve obtained from tumor and AIF obtained from DCE images acquired at $T_s=2.1$ s. The resulting curve fit suggests that the extended Tofts model fits

Figure 11. Sample curves from AIF and tumor obtained in patient scanned with Sequence 2 ($T_s = 2.1$ s), and the corresponding curve fit obtained with the extended Tofts kinetic model.

the data well in this case. However, the goodness-of-fit of the data to the model was not systematically tested and it is expected that the model error would depend on the value of K^{trans} , because absence of significant leakage would “force” the model to interpret non-zero MTT as elevated K^{trans} . The application of more complex kinetic models also enables combined measurements of both perfusion and permeability in a single DCE-MRI experiment (11,37), and for such combined analysis a higher temporal resolution is clearly required.

In conclusion, both accuracy and precision is reduced with increasing sampling time based on systematic simulations and investigation in 101 DCE-acquisitions obtained from HGG patients undergoing combined RT and chemotherapy. Whereas the accuracy of the kinetic parameter estimates is only marginally affected by increasing the sampling time from 2–3 s to approximately 20 s, the precision in the estimates is more rapidly reduced with increasing T_s . It is thus recommended to use a temporal resolution lower than 20 s to minimize uncertainties due to sampling errors and to ensure that tumor “hot-spots” with rapid CA extravasation are not missed. Total DCE sampling time should be at least 5 min for this patient group.

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Original Research

T₁ in High-Grade Glioma and the Influence of Different Measurement Strategies on Parameter Estimations in DCE-MRI

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Background: To investigate the evolution of T₁ in tumor and the necessity of baseline T₁ (T₁(0)) mapping for the accurate estimation of kinetic parameters during standard therapy using dynamic contrast enhanced (DCE) MRI in patients with high-grade glioma (HGG).

Methods: Longitudinal DCE-MRI was performed in 23 patients (196 scans) with confirmed HGG. Kinetic parameters were derived from the extended Tofts model and analyzed both using fixed and pixel-wise T₁(0) values estimated from a Look-Locker sequence. Median tumor T₁ value from all scans was used for fixed T₁(0) analysis. Dependence of accurate T₁(0) mapping for the estimation of the kinetic parameters was further investigated through computer simulations and histogram analysis.

Results: T₁ in tumor increased significantly during and after treatment ($P < 0.001$). There was a linear correlation between the error in 1/T₁(0) and the resulting error in estimated parameters in both simulations and clinical data ($r^2 > 0.98$ for all parameters). A strong correlation between the estimated longitudinal change in all kinetic parameters obtained using pixel-wise and fixed T₁(0) was observed ($r^2 > 0.84$ for all parameters). Histogram analysis revealed a linear change ($r^2 > 0.62$) in K^{trans} normalized histogram peak height ratio as function of percentage deviation from the nominal T₁(0) value. No effect of T₁(0) histogram distribution on K^{trans} was observed ($P = 0.52$).

Conclusion: Temporal changes in the median kinetic parameters in tumor were equally well described using pixel-wise and fixed T₁(0) despite an increase in T₁(0) over time, suggesting that T₁ mapping is not generally required in DCE-MRI based monitoring of glioma patients.

Key Words: DCE-MRI; glioma; T₁; relaxometry; Tofts model; brain tumor

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DYNAMIC CONTRAST-ENHANCED (DCE) MRI is an established method to assess and quantify blood–brain barrier (BBB) integrity and brain hemodynamics. Several studies have shown its usefulness in diagnosis and assessment of treatment response in patients with primary brain tumors (1,2). Kinetic modeling applied to signal changes induced by contrast agent (CA) enables estimation of metrics reflecting capillary permeability and relative tissue volume fractions (3). Quantification of these parameters requires measurement of the CA-induced changes in T₁ relaxation rates in blood and tissue and thereby knowledge of pixel-wise T₁ values before CA arrival (T₁(0)) (4,5). Several methods are available for rapid T₁ measurements (6), but the need for T₁(0) estimations inevitably increases total scan-time, and introduces challenges related to image co-registration and additional image processing steps. The accuracy of T₁(0) measurements is in itself a potential source of error in the estimation of kinetic parameters and has been rigorously investigated (7).

To circumvent the need for T₁(0) measurements, analysis of a normalized ratio of estimated median metrics between scan sessions has been proposed (8,9). However, this approach assumes stable T₁(0) in tumor over time which might not be the case in progressive disease. Furthermore, the use of a ratio based on stable T₁(0) values might not be sensitive to time-dependent variations in the parameter distributions due to heterogeneous and time-dependent T₁ distributions in tumor.

To this end, the purpose of this study was to measure the temporal evolution of T₁(0) and assess the necessity for T₁(0) measurements in longitudinal analysis of HGG.

THEORY

In DCE-MRI, the signal intensity (SI) response following a bolus CA injection is measured dynamically

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using a heavily T_1 weighted sequences typically obtained using a short repetition time/echo time (TR/TE) spoiled gradient-echo (GRE) (SPGR) sequence (10), or a saturation recovery (SR) sequence. Using an SR sequence, the SI response may be approximated as (4):

$$SI(C) \propto M_0[1 - \exp(-TD \cdot R_1(C))], \quad [1]$$

where M_0 is the equilibrium magnetization, $R_1=1/T_1$ is the longitudinal relaxation rate and TD is the delay time between the saturation RF pulse and the center of k -space during signal readout. The CA induced change in R_1 is then found from:

$$\Delta R_1(t) = -\frac{1}{TD} \ln \left[1 - E_0 \frac{SI(t)}{SI(0)} \right] - R_1(0), \quad [2]$$

where $E_0 = 1 - \exp(-TD \cdot R_1(0))$ and $R_1(0) = 1/T_1(0)$.

CA concentration, assumed to be proportional to $\Delta R_1(t)$, therefore requires knowledge of $R_1(0)$. For $TD \ll T_1$, $\Delta R_1(t)$ scales approximately linearly with measured change in SI according to:

$$\Delta R_1(t) = R_1(0) \left[\frac{SI(t)}{SI(0)} - 1 \right]. \quad [3]$$

A similar linear $R_1(0)$ dependence can be approximated for SPGR-type sequences (8).

Assuming, as a first approximation, a linear dose-response according to Eq. (3), a fractional error in $R_1(0)$ then results in a corresponding linear error in the estimation of the kinetic parameters. Using the extended Tofts model for bi-directional kinetic modeling the effect of errors in $R_1(0)$ can be expressed as Eq. (3):

$$\begin{aligned} \Delta R_1(t, \varepsilon) &= (1 + \varepsilon) \Delta R_1(t) \\ &= (1 + \varepsilon) K^{\text{trans}} \int_0^t \Delta R_{1a}(\tau) \exp\left(-\frac{K^{\text{trans}}(t - \tau)}{v_e}\right) d\tau \\ &\quad + (1 + \varepsilon) v_p \Delta R_{1a}(t) \end{aligned} \quad [4]$$

where $\Delta R_{1a}(t)$ is the relaxation rate in blood (measured by the arterial input function (AIF) and neglecting hematocrit factors) and $\Delta R_1(t, \varepsilon)$ is the apparent change in relaxation rate due to incorrect $R_1(0)$ with fractional error ε . It, therefore, follows that the apparent values of K^{trans} , v_e , and v_p will all be scaled by the same relative error $1/(1+\varepsilon)$.

Because the exponent in the convolution integral of Eq. (4) is not affected by the scaling due to ε , K^{trans} , and v_e must be equally affected so that $k_{ep} = K^{\text{trans}}/v_e$ (3) is not sensitive to errors in $R_1(0)$ under the linear dose-response assumption.

Quantification of $T_1(0)$ can be obtained using sequences acquired either with two or more flip angles (FA) (11,12) or using a saturation- or inversion preparation pulse followed by multiple low FA readouts during magnetization recovery. The latter method using inversion recovery; the Look-Locker method (13), is established as a fast and robust method of T_1 mapping for both two-dimensional (2D) and 3D acquisitions (14,15).

SUBJECTS AND METHODS

Patients

A total of 196 examinations from 23 patients with confirmed HGG WHO grade III and IV were included in the study. All patients were imaged at multiple time points before, during and after radiochemotherapy (RCT) according to the standard treatment proposed by Stupp et al (16), as part of an ongoing treatment monitoring study. Each patient was imaged at RCT start and every 2 weeks for 8 weeks (five scans) and subsequently every third month for a maximum of 3 years (11 additional scans). Study approval was obtained from the Regional Medical Ethics Committee and patients were included only if informed consent was signed.

MRI

The study was conducted on a 3 Tesla (T) Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an eight-channel head coil (InVivo, Gainesville, FL, USA). $T_1(0)$ maps were generated from a 3D Look-Locker sequence using 38 dynamic measurements with initial inversion time (TI); 38 ms; spacing between measurements (ΔTI); 69 ms; TE 1.4 ms; TR; 2.6 ms and FA; 4° . DCE images were acquired using a 3D SR based GRE sequence. Eleven slices maximally covering the tumor volume were acquired with the following sequence parameters: acquisition matrix 120×120 , voxel size $1.875 \times 1.875 \times 4 \text{ mm}^3$, pixel bandwidth 434 Hz, TR/TE/FA = 8.2 ms/2.5 ms/ 26° . Additional parameters are previously described (17). After five time-points 0.1 mmol/kg of gadobutrol (Gadovist[®], Bayer Schering Pharma AG, Berlin, Germany) was injected using a power injector at a rate of 3 mL/s, immediately flushed by a 20 mL bolus of saline. The imaging protocol included the following structural image series: isotropic 1 mm^3 3D sagittal fluid-attenuated inversion recovery (FLAIR), $0.45 \times 0.45 \times 3.5 \text{ mm}^3$ 2D axial T_2 weighted images and isotropic 1 mm^3 3D sagittal T_1 weighted images acquired before- and after CA administration. The CA-enhanced T_1 weighted images were acquired directly after the DCE series.

$T_1(0)$ Sensitivity Analysis

Identification of partial volume corrected AIFs and kinetic modeling were performed on the patient data as previously described (17) according to the extended Tofts model (3,18). $T_1(0)$ maps were generated using the Look-Locker method (13), which is established as a fast and robust method of T_1 mapping for both 2D and 3D acquisitions (14,15). $T_1(0)$ in blood was assumed constant at 1664 ms in both clinical data and simulations (19). To investigate the sensitivity of the resulting kinetic parameter values to the underlying $T_1(0)$ assumptions, parameter estimation was performed under the following conditions: Using voxel-wise $T_1(0)$ values estimated at each exam (method 1) and using a fixed value for tumor $T_1(0)$ ($T_1(0)^{\text{fixed}}$) (method 2).

Figure 1. Boxplot of median $T_1(0)$ in tumor from all patients at each time point. The number of patients at each time point is indicated. Significant change in $T_1(0)$ from the previous exam is shown with an asterisk. Significant change from the first exam is shown with a hashtag. Outliers not included in the boxplot are shown by crosses. The grey stapled line shows the median $T_1(0)$ for all patients (1490 ms) and the black stapled line shows the median $T_1(0)$ at each time point. Radiochemotherapy (RCT) is given the first 6 weeks.

Errors due to incorrect $T_1(0)$ estimations was not investigated in the current work. The Look-Locker sequence was run with identical geometry and orientation as the DCE data to minimize mis-registration errors, and the resulting $T_1(0)$ maps were co-registered to the DCE before kinetic analysis. Image co-registration was performed in Statistical Parametric Mapping (SPM 8, <http://www.fil.ion.ucl.ac.uk/spm/>) and kinetic analysis of clinical data was performed using in-house developed tools implemented in Matlab (MatlabR2013B, The Mathworks Inc, Natick, MA)

Simulations

Using Eqs. (1–3) above, the effect of varying $T_1(0)$ values on the resulting estimates of kinetic parameters was simulated by assessing the errors resulting from deviations from the true value of $T_1(0)$ used in calculations. To facilitate this, an arterial concentration time-curve ($C_a(t)$) was generated using the software JSim (<http://www.physio.me.org/>). Corresponding tissue concentration time curves ($C_t(t)$) were generated based on kinetic parameters chosen at random within the following ranges: $0.01 \text{ min}^{-1} \leq K^{\text{trans}} \leq 0.9 \text{ min}^{-1}$, $0\% \leq v_e \leq 40\%$ and $1\% \leq v_p \leq 4\%$. The resulting $R_1(t)$ in tissue was then calculated using a randomly chosen $T_1(0)$ value between 600 and 2200 ms, a range covering all tumor $T_1(0)$ values observed in the clinical

data included in the study. Next, the corresponding tissue signal curve was generated from Eq. (3) and Gaussian noise was added to give a raw data signal-to-noise ratio (SNR) of 40, defined as average signal difference between maximum and baseline signal divided by the standard deviation of the baseline signal. The value was selected based on actual SNR measurement in the raw clinical data. Using the predefined range of kinetic parameter values, corresponding raw signal intensity curves were generated and converted to $\Delta R_1(t)$ curves using the range of $T_1(0)$ values, and compared with the values obtained using $T_1(0)^{\text{fixed}}$. The resulting $\Delta R_1(t)$ curves were then used to estimate the kinetic parameters using the extended Tofts model. This operation was repeated $3 \cdot 10^4$ times with random combinations of kinetic parameter values and $T_1(0)$ values, resulting a large dataset of kinetic parameters with known errors. Based on the same simulation model, plots of the error in K^{trans} as function of deviation from ground truth $T_1(0)$ was further estimated. The simulations were implemented in Matlab.

Tumor Region of Interest

In the patient data, tumor regions-of-interest (ROIs) were generated semi-automatically from FLAIR and T_1 postcontrast images, as previously described (17). The

Table 1
Wilcoxon Analysis of Evolution in Median $T_1(0)$ From First and Previous Exam*

From first exam				From previous exam			
Weeks	N (exams)	P-value	Estimated median change (ms)	Weeks	N (exams)	p-value	Estimated median change (ms)
2	15	0.410	25.34	2	14	0.209	36.12
4	14	0.802	-16.16	4	18	0.760	6.939
6	15	0.244	56.24	6	16	0.394	24.31
8	15	0.038	97.47	8	16	0.028	61.81
20	13	0.012	215.2	20	15	0.018	95.21
32	11	0.023	202.1	32	14	0.268	32.89
44	9	0.097	149.3	44	12	0.666	-6.57
56	9	0.097	29.47	56	10	1.000	3.04
68	7	0.800	99.96	68	8	0.107	-48.40

*One-sample Wilcoxon of evolution in median $T_1(0)$ compared to the first and previous exam. Weeks since start of radiochemotherapy, number of exams, P -value and the estimated change in ms is shown. Significant Holm-Bonferroni corrected values shown in bold.

Figure 2. Error in K^{trans} (left), v_e (middle) and v_p (right) from simulations (a) and clinical data (b), comparing estimations made from $R_1(0)$ differing from -60% to $+40\%$ to estimations based on a $T_1(0)^{\text{fixed}}$ of 1490 ms, the median $T_1(0)$ in our high grade glioma material. Parameter magnitude for K^{trans} (min^{-1}) and v_e and v_p (percent) is indicated by the color scales.

ROIs were reviewed by a radiologist (4 years experience) and manually edited when needed. Only tumor ROIs larger than 1 mL were included in the DCE-analysis (151 exams).

Statistical Analysis

$T_1(0)^{\text{fixed}}$ was calculated as the median of all tumor voxels from all exams in all patients. Differences in tumor $T_1(0)$ between successive scan sessions or dif-

ference from first exam were tested using 1-sample Wilcoxon test with Holm-Bonferroni correction for multiple comparison. Error in kinetic parameter estimations was plotted against the error in $R_1(0)$ and their dependence was assessed using multiple linear regression with kinetic parameter magnitude as the second regressor. Change in estimated kinetic parameter values between successive exams was compared using method 1 versus method 2 and tested for linear correlation. Systematic error between the two methods was assessed by Bland-Altman plots. The influence of $T_1(0)$ on the distribution of kinetic parameters in the tumor volume was investigated by histogram analysis. By unity normalizing the area under the resulting histogram curve, the histogram peak height is inversely proportional to distribution width thereby providing a measure of parameter heterogeneity. To investigate the effect of histogram distribution on choice of $T_1(0)$ method, the ratio of the histogram peaks obtained with method 1 versus method 2 (PHR) was used as the dependent variable. The effect of deviation in median tumor $T_1(0)$ from $T_1(0)^{\text{fixed}}$ and $T_1(0)$ histogram width on PHR were then investigated using multiple linear regression analysis. The percentage change in median tumor $T_1(0)$ was then clustered in bins of 10% and 1-sample Wilcoxon test was performed to assess significant change in PHR. All correlation was tested by Pearson correlation. Probability values of $P < 0.05$ were chosen as level of significance. Statistical analysis was performed in Matlab, Minitab 17 (Minitab Inc, PA, USA) and Stata 13 (Statacorp LP, College Station, TX).

Figure 3. Simulation of T_1 deviation from ground truth for a given error in K^{trans} . A positive value represents a fixed value higher than the ground truth (overestimation) and a negative value represents a fixed value lower than the ground truth value (underestimation). Ground truth T_1 value printed on the curves. Larger T_1 deviations are accepted for high ground truth values compared with low and overestimation of the fixed T_1 value is better than underestimation.

RESULTS

Figure 1 shows a boxplot of the time-evolution of median $T_1(0)$ tumor values in all patients. Results

Figure 4. Scatterplot and corresponding Pearson linear correlation values comparing estimated percent change in median kinetic parameters (K^{trans} , v_e , and v_p) between successive time-points using method 1 ($T_1(0)$) versus method 2 ($T_1(0)^{\text{fixed}}$).

from the temporal evolution in $T_1(0)$ is shown in Table 1. A significant increase is seen at 8 weeks and 20 weeks compared with both previous and first exams. Additionally, a significant increase is seen at 32 weeks compared with the first time point. Median tumor $T_1(0)$ in all patients across all time points was 1490 ms and 61.2% of all pixels from all tumors in all patients were within a range of ± 200 ms of the median.

Figure 2a shows the simulated error in K^{trans} , v_e , and v_p relative to their true values as a function of the deviation in $R_1(0)$ from the true value. In accordance with theory the error in K^{trans} , v_e , and v_p scaled linearly with the error in $R_1(0)$ with a slope close to unity (1.046, 1.085, 1.020, $r^2 = 0.997$, 0.994, 0.982 for K^{trans} , v_e , and v_p , respectively). Consequently, all three parameters are over/underestimated when $T_1(0)$ is under/overestimated. For v_p , a somewhat broader distribution of errors was observed even for $R_1(0)$ value at the ground truth value. k_{ep} was not affected by errors in $R_1(0)$. The relative error in K^{trans} was found to be relatively insensitive to actual K^{trans} values for a given error in $T_1(0)$ by multiple regression analysis (standardized coefficient: 0.9981 for R_1 error and 0.0028 for K^{trans} value). Figure 2b shows the results from the clinical data where the relative error in K^{trans} , v_e , and v_p using $T_1(0)^{\text{fixed}}$ is plotted as a

function of the deviation in $T_1(0)$ from $T_1(0)^{\text{fixed}}$ (method 1 versus method 2). The resulting error trends from the clinical data are seen to be similar to the simulations.

Figure 3 shows the error in K^{trans} as function of absolute deviation in $T_1(0)$ from its ground truth value. The y-axis value signifies the acceptable deviation in $T_1(0)$ from ground truth for a given maximum error in K^{trans} (the x-axis). The simulations indicate that K^{trans} is less sensitive to overestimation in $T_1(0)^{\text{fixed}}$ compared with underestimation.

Figure 4 shows the correlation between method 1 and method 2 when estimating the temporal change in K^{trans} , v_e and v_p between successive DCE examinations. A significant ($P < 0.001$ for all parameters) linear correlation was observed for all three parameters ($r^2 = 0.93$, 0.84 and 0.97 for K^{trans} , v_e , and v_p , respectively). No clear bias was observed in Bland Altman plots (results not shown) using $T_1(0)^{\text{fixed}}$ compared with the estimated change in kinetic parameter values obtained with pixel-wise $T_1(0)$ determination.

The time-evolution of median tumor K^{trans} values obtained using the two $T_1(0)$ estimation approaches is shown for a sample patient in Figure 5. Median $T_1(0)$ in tumor increased after RCT reaching a peak value of approximately 1630 ms. At the last time point, a dip in $T_1(0)$ is seen. As expected, a slight underestimation in K^{trans} was observed using method 2 for the early time-points when actual $T_1(0)$ values are lower than the assumed value of 1490 ms. Similarly, a slight overestimation in K^{trans} was observed in the later time-points when actual $T_1(0)$ is higher than the assumed value. Figure 6 shows tumor K^{trans} maps obtained using method 1 and method 2 overlaid on structural scans in two sample patients. The corresponding $T_1(0)$ error map is also shown as the difference between $T_1(0)$ and $T_1(0)^{\text{fixed}}$. For the sample patient shown in the top row, the tumor exhibits regions of both over- and underestimation of $T_1(0)$ when using $T_1(0)^{\text{fixed}}$. Despite this, only minor visual difference is observed between the K^{trans} maps obtained with the two methods. A slight but subtle underestimation of K^{trans} , due to a too high $T_1(0)^{\text{fixed}}$ is noted in the anterior part of the K^{trans} map obtained from method 2 (arrow). For the sample patient in the bottom row, the whole tumor has $T_1(0)$ values higher than the $T_1(0)^{\text{fixed}}$ leading to an overestimation of

Figure 5. Estimated absolute median tumor K^{trans} (left axis) over time for method 1 and 2 in a sample patient. Temporal change in actual median $T_1(0)$ (right axis) is shown as a dotted line and the horizontal line indicates the assumed $T_1(0)^{\text{fixed}}$ of 1490 ms.

Figure 6. Estimated K^{trans} maps obtained from two sample patients comparing method 1 (pixel-wise $T_1(0)$, left column) and method 2 ($T_1(0)^{\text{fixed}}$, middle column). The right column shows $T_1(0)$ error maps representing the pixel-wise difference between assumed $T_1(0)^{\text{fixed}}$ (1490 ms) and $T_1(0)$ where red colors indicate actual $T_1(0)$ value higher than the assumed value and blue color values lower than the assumed value.

K^{trans} in the whole tumor when using method 2. This is also seen to create a false hot-spot in the part of the tumor where the difference between actual and assumed $T_1(0)$ is largest (circle).

Figure 7 shows K^{trans} PHR versus the percentage deviation in median $T_1(0)$ from $T_1(0)^{\text{fixed}}$. Using a $T_1(0)^{\text{fixed}}$ lower than median tumor $T_1(0)$ leads to narrower distribution in K^{trans} ($\text{PHR} > 1$), as indicated by points at positive x-axis values. For negative x-values $T_1(0)^{\text{fixed}}$ is higher than the median tumor $T_1(0)$, resulting in a broader K^{trans} distribution ($\text{PHR} < 1$). The two scenarios are exemplified by inserted histogram distributions from two sample cases. Multiple linear regression revealed a significant ($r^2 = 0.62$; $P <$

0.001) linear relationship between percent median $T_1(0)$ deviation from $T_1(0)^{\text{fixed}}$ and K^{trans} PHR. $T_1(0)$ histogram width did not correlate with K^{trans} PHR ($P = 0.52$). Table 2 shows significant change in PHR from Wilcoxon analysis of the clinical data from Figure 7. The data is clustered in steps of 10% deviations in $T_1(0)$ from $T_1(0)^{\text{fixed}}$ and the estimated median PHR for each cluster is shown.

DISCUSSION

In the present work we address the influence of tumor $T_1(0)$ on the estimated kinetic hemodynamic and BBB integrity parameter values derived from DCE analysis

Figure 7. Linear regression of normalized tumor histogram K^{trans} peak height values obtained from method 1 versus method 2 (y-axis) and percentage change in median $T_1(0)$ from the $T_1(0)^{\text{fixed}}$ of 1490 ms (x-axis). Change in distribution is shown in two sample patients and the arrows shows the corresponding dot. In the top left example median $T_1(0)$ (1625 ms) in tumor is larger than 1490 ms resulting in a decreased peak height and increased distribution in the histogram. Conversely, the bottom right example shows a median $T_1(0)$ (1190 ms) in tumor lower than 1490 resulting in an increased peak height and a narrower distribution.

Table 2
Wilcoxon Analysis of Change in K^{trans} PHR Compared to Clustered Percent Change in Median $T_1(0)$ from $T_1(0)^{\text{fixed}}$ *

Range of deviations from $T_1(0)^{\text{fixed}}$	N (exams)	P-value	Estimated PHR
-45% - -36%	2	0.371	0.699
-35% - -26%	10	0.006	0.706
-25% - -16%	14	0.001	0.811
-15% - -6%	30	0.002	0.920
-5% - -4%	42	0.312	1.01
5%-14%	42	<0.001	1.12
15%-24%	5	0.059	1.21

*One-sample Wilcoxon analysis of change in the ratio of the histogram peaks obtained with method 1 versus method 2 (PHR) compared to clustered percent change in median $T_1(0)$ from $T_1(0)^{\text{fixed}}$. Number of exams, P-value and estimated median PHR is shown for each cluster. Significant clusters are shown in bold.

in a population of HGG patients undergoing RCT. There are three main findings from this study:

First, median $T_1(0)$ in tumor increases during the course of treatment in HGG. Despite the large variation in $T_1(0)$ in tumor at treatment start, an increase of $T_1(0)$ is seen consistently during and after RCT treatment. A general increase in $T_1(0)$ is seen after 8 weeks with an estimated average increase of 97 ms from the first exam. Three and 6 months after RCT (week 20 and 32) the estimated median increase in $T_1(0)$ was 200 ms compared with the first exam.

Second, a linear relationship between error in $R_1(0)$ and the error in kinetic parameters was observed both in simulations and clinical data. This is in line with the theory that for a linear dose-response approximation, $R_1(0)$ becomes a scaling factor in the estimated kinetic parameters. These results are in agreement with previous studies (8,9). One exception was the simulation of errors in v_p due to incorrect $R_1(0)$. Here, errors in v_p were seen even for zero error in $R_1(0)$. This is thought to be due to limitations in the extended Tofts model for certain combinations of parameter values, resulting in an overestimation for very low v_p when combined with high K^{trans} values (18). Simulations revealed that v_p estimates were more sensitive to such model instabilities than the other kinetic parameters. The ability to detect changes in the kinetic parameters during the course of disease progression was not affected by the assumption of a fixed $T_1(0)$. The bias in parameter estimations introduced by using incorrect $T_1(0)$ values was shown to be small relative to the overall temporal trend in K^{trans} . A similar conclusion was previously reached for the dependence of K^{trans}/v_e on $T_1(0)$ but using much slower SE based acquisition methods (20).

Third, using a $T_1(0)^{\text{fixed}}$ results in an artificial change in the distribution of tumor kinetic parameter values. HGGs tend to have a rather heterogeneous distribution of $T_1(0)$ values, which is not accounted for when a $T_1(0)^{\text{fixed}}$ is assumed. Despite this heterogeneity, no effect on K^{trans} histograms was found due to the distribution width of $T_1(0)$ in tumor, suggesting that pixel-wise analysis may be unnecessary. The value of K^{trans} PHR was, however, seen to depend on the actual median tumor $T_1(0)$ compared with the

assumed $T_1(0)^{\text{fixed}}$. Therefore, obtaining an accurate estimation of $T_1(0)^{\text{fixed}}$, which is as close as possible to the actual median tumor $T_1(0)$, is concluded to be the most important criterion for correct representation of parameter distributions in the tumor volume. This single value may be more readily obtained and does not require co-registration or other time-consuming processing steps.

The study has limitations. $T_1(0)$ maps were generated using a standard 3D implementation of a Look-Locker sequence, and the error in the $T_1(0)$ measurements was not assessed. This sequence has been thoroughly tested and validated by others (7), and shown to provide reasonable estimates over a large range of T_1 values. Any T_1 estimation obtained in a clinical setting will, however, be subject to error due to limited SNR and methodological approximations in the analysis. The inevitable errors in the T_1 estimations is in itself an argument for using $T_1(0)^{\text{fixed}}$ rather than pixel-wise estimations, as previously argued (8). We used a SR DCE sequence in the current work, as this sequence has been shown to be relatively insensitive to water exchange effects and to provide good SNR (4). The dose-response dependency on $T_1(0)$ may be different if a different type of DCE sequence is used. However, all heavily T_1 weighted DCE approaches are expected to have an approximately linear dose-response and are expected to have similar error characteristics to the one used here. We did not consider errors in the analysis due to errors in $T_1(0)$ in blood, potentially affecting the accuracy of the AIF determination. Although T_1 in blood is known to depend on hematocrit, it is still reasonable to assume that this variation is small relative to the observed variations in tumor.

In conclusion, in HGG patients undergoing RCT, an increase in tumor $T_1(0)$ values should be expected during the course of the treatment as well as in the posttreatment period. Despite the increase in $T_1(0)$, longitudinal changes in K^{trans} and other DCE derived parameters can be estimated with good accuracy assuming a fixed $T_1(0)$. The $T_1(0)^{\text{fixed}}$ used should however, be selected with care, reflecting median $T_1(0)$ in a given tumor to ensure that the error introduced by the fixed $T_1(0)$ assumption is small relative to the expected temporal change in the estimated kinetic parameters; a condition met in the current work. When a fixed $T_1(0)$ is used, the resulting distribution of tumor K^{trans} values is affected by the choice of $T_1(0)$ and $T_1(0)$ need to reflect median tumor value for correct distribution estimates.

The use of a fixed $T_1(0)$ may be recommended when monitoring changes in DCE-MRI derived parameters in HGG patients, thereby simplifying the implementation and analysis of DCE-MRI in a clinical setting.

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Operator dependency of arterial input function in dynamic contrast-enhanced MRI

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Abstract

Objective To investigate the effect of inter-operator variability in arterial input function (AIF) definition on kinetic parameter estimates (KPEs) from dynamic contrast-enhanced (DCE) MRI in patients with high-grade gliomas.

Methods The study included 118 DCE series from 23 patients. AIFs were measured by three domain experts (DEs), and a population AIF (pop-AIF) was constructed from the measured AIFs. The DE-AIFs, pop-AIF and AUC-normalized DE-AIFs were used for pharmacokinetic analysis with the extended Tofts model. AIF-dependence of KPEs was assessed by intraclass correlation coefficient (ICC) analysis, and the impact on relative longitudinal change in K^{trans} was assessed by Fleiss' kappa (κ).

Results There was a moderate to substantial agreement (ICC 0.51–0.76) between KPEs when using DE-AIFs, while AUC-normalized AIFs yielded ICC 0.77–0.95 for K^{trans} , k_{ep} and v_e and ICC 0.70 for v_p . Inclusion of the pop-AIF did not reduce agreement. Agreement in relative longitudinal change in K^{trans} was moderate ($\kappa = 0.591$) using DE-AIFs, while AUC-normalized AIFs gave substantial ($\kappa = 0.809$) agreement.

Discussion AUC-normalized AIFs can reduce the variation in kinetic parameter results originating from operator input. The pop-AIF presented in this work may be applied in absence of a satisfactory measurement.

Keywords Dynamic contrast-enhanced MRI · DCE-MRI · Glioblastoma · AIF · Arterial input function · Observer dependency

Abbreviations

AIF Arterial input function
AUC Area under the curve
CA Contrast agent
DCE Dynamic contrast-enhanced
DE Domain expert

FLAIR Fluid-attenuated inversion recovery
HGG High-grade glioma
IVS Intravascular space
KPE Kinetic parameter estimate
MRI Magnetic resonance imaging
PK Pharmacokinetic

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Pop-AIF	Population-averaged AIF
ROI	Region-of-interest
TD	Saturation recovery delay
TE	Echo time
TR	Repetition time

Introduction

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is increasingly being used to assess microvascular properties of tissue in oncology and has proven well suited to quantify brain tumor hemodynamics and damage to the blood–brain barrier. DCE-MRI is a technique in which a series of T_1 -weighted images is rapidly acquired before, during and after the administration of a paramagnetic contrast agent (CA) [1]. Using pharmacokinetic (PK) modelling, these dynamic images allow for the quantification of kinetic biomarkers that are of use in the evaluation of tumors. The most commonly used PK model in high-grade glioma (HGG) diagnostics is the extended Tofts model [2], which describes the tissue by the rate constants K^{trans} and k_{ep} as well as the volume fractions v_e and v_p .

Quantitative descriptors of tumor vasculature that—in theory—can be obtained independently of equipment and technique, would be a very powerful tool in disease management and monitoring. However, DCE-MRI suffers from a lack of reproducibility across different imaging sites. This is due to several potential sources of error, including inadequate temporal resolution, insufficient acquisition time frame [3], pre-contrast T_1 measurement uncertainty [4, 5] and difficulty in determining the dynamic CA concentration in plasma (C_p)—the arterial input function (AIF) [6, 7].

Different approaches exist for determining the AIF, including fully automatic algorithms [8], semi-automatic methods [9], manual selection and the use of standard models [10]. It is generally accepted that the AIF is dependent on cardiac output, blood pressure and vascular auto-regulation in the region-of-interest []. The gold standard for DCE-MRI imaging is thus an individual AIF from each time-point in each patient measured in a feeding artery of the pathology/region-of-interest (ROI). The accuracy of this AIF varies by the temporal resolution, potential partial volume effects from low spatial resolution [11] and inter-observer variability from manual selection.

The aim of this study was to investigate the inter-observer variability, among domain experts (DEs), in AIF determination and corresponding variability in kinetic parameters obtained using the extended Tofts model in HGG patients. Further, we define a parametric form of a population-averaged AIF from brain data according to the framework previously published [10].

Methods

Patients

Study approval was obtained from the regional medical ethics committee and patients were included only if written informed consent was signed. A total of 118 DCE-MRI examinations from 23 patients (17 males, mean age 53.7 years, range 32–66 years) with histologically confirmed HGG (one grade III and 22 grade IV) were included in a prospective study of early detection of perfusion changes during radiochemotherapy [12]. Patients were imaged once before, thrice during, and up to five times for a maximum of 15 months after initiation of standard treatment regime [13]. In the present work, the initial six imaging time-points in each patient, encompassing two post-radiochemotherapy follow-ups at two and 14 weeks, were considered for inclusion. Examinations were excluded if there were no contrast-enhancing voxels ($N=2$) or if DCE-MRI was not successful ($N=18$), resulting in a total of 118 included examinations. A surgical debulking procedure was performed in 22 patients prior to baseline imaging, whilst the remainder received biopsy.

MRI

All imaging was performed at 3.0 T (Philips Achieva, Philips Medical Systems, Best, The Netherlands), using an eight-channel head coil. DCE images were acquired from a 3D- saturation recovery-based gradient echo sequence. The sequence was designed to minimize water exchange effects by employing a short saturation recovery delay (TD) [14]. Eleven slices covering the tumor volume were acquired with the following key sequence parameters: field of view (FoV): $240 \times 240 \text{ mm}^2$; acquisition matrix: 120×120 ; partial Fourier: 5/8; voxel size: $1.9 \times 1.9 \times 4 \text{ mm}^3$; pixel bandwidth: 434 Hz; echo time (TE)/flip angle: 2.5 ms/26°; sensitivity encoding (SENSE) factor: 2.3 in the anterior–posterior phase-encoding direction. Two variants of the DCE sequence were used: one using repetition time (TR)/TD/temporal resolution: 8.2 ms/80 ms/3.4 s, 100 dynamic scans and scan time: 5:40 (variant 1) in seven patients for a total of 38 examinations, and one using TR/TD/temporal resolution: 5.1 ms/50 ms/2.1 s, 150 dynamic scans and scan time: 5:10 (variant 2) in 16 patients for a total of 80 examinations. 0.1 mmol/kg gadobutrol (Gadovist®, Bayer Schering Pharma AG, Berlin, Germany) was administered after a pre-contrast baseline duration of five timepoints using a power injector at a rate of 3 ml/s, immediately followed by a 20 ml saline flush at the same rate. The full imaging protocol included

the following structural image series: sagittal 3D fluid-attenuated inversion recovery (FLAIR) images, axial 2D T_2 -weighted images and sagittal 3D T_1 -weighted gradient echo images acquired before and after CA administration. All image series were acquired before the DCE series except the CA-enhanced T_1 -weighted images which were acquired directly afterwards. Tumor region-of-interest (ROI) containing contrast-enhancing tissue was defined in all examinations by a radiologist (4 years of experience) using a previously described method [12, 15].

AIF extraction

AIFs were determined independently in each DCE series by three DEs (two radiologists with 1 (J. V.) and 5 (M. Kim.) years of experience and one clinician with 10 years of experience in DCE-MRI (C. L.)) using a semi-automatic algorithm based on automated identification of most likely AIF voxels using K-means clustering from a user-defined search region, implemented in the software tool nordicICE (NordicNeuroLab, Bergen, Norway) [8]. The AIF search region was selected independently by each DE to include the large intracerebral arteries according to the tumor location and hence the available volume covered by the DCE acquisition. Since the K-means method is iterative with a random seed starting point, repeated AIF searches may not result in identical results. Hence, multiple AIF searches were performed for a selected search region and the AIF with the highest first-pass arterial signal peak and the highest signal tail during the wash-out phase was chosen. This process was repeated until the AIF was considered satisfactory by the DE. An overview of the process is given in Fig. 1. In addition, a venous output function from the large sinuses

was obtained in each examination for AIF partial volume correction [3].

The AIFs were supplied as single-column text files containing change in longitudinal relaxation rate $\Delta R_1 = R_1(t) - R_1(0)$ from baseline for each timepoint t , which was converted to CA concentration by:

$$C_p(t) = \frac{R_1(t) - R_1(0)}{r_1(1 - \text{Hct})}, \quad (1)$$

where $r_1 = 4.4 \text{ mM}^{-1} \text{ s}^{-1}$ is the relaxivity of gadobutrol at 3.0 T [16] and Hct is the hematocrit, set to 0.45. $R_1(0)$ of arterial blood at 3.0 T was assumed to be 0.60 s^{-1} [16].

This procedure resulted in a total of 354 DE-defined AIFs from 23 patients, of which 114 AIFs from seven patients were from DCE sequence variant 1 and the remaining 240 AIFs in 16 patients were from DCE sequence variant 2.

Population-averaged AIF

A population-averaged AIF (pop-AIF) was created by fitting the mean of all measured AIFs with DCE sequence variant 2 ($N = 240$ AIFs) to the sum of two Gaussians and an exponential modulated by a sigmoid function, as described by Parker et al. [10]:

$$C_b(t) = \sum_{n=1}^2 \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp\left(-\frac{(t - T_n)^2}{2\sigma_n^2}\right) + \frac{\alpha \exp(-\beta t)}{1 + \exp(-s(t - \tau))}. \quad (2)$$

Here, A_n are scaling factors, T_n are centers and σ_n are widths of the n th Gaussian; α and β describe the amplitude and slope of the exponential function, respectively, and s and τ are the width and center of the sigmoid. Prior to calculating

Fig. 1 Outline of the arterial input function (AIF) extraction process. Top right: the search area (yellow rectangle) is placed in an area likely to contain arterial signal, and the algorithm selects the best pixels (red squares). The AIF is the mean signal of the selected pixels and is plotted in red. The venous output function is detected similarly and is plotted in blue along with mean tumor

the mean AIF, each individual AIF was time-shifted so that the peak occurred at the same timepoint.

Pharmacokinetic modeling

The DCE time series were analyzed using the extended Tofts model according to:

$$C_t(t) = K^{\text{trans}} \int_0^t C_p(\tau) \exp\left(-\frac{K^{\text{trans}}(t-\tau)}{v_e}\right) d\tau + v_p C_p(t), \quad (3)$$

where $C_t(t)$ is the time-dependent CA concentration in tissue, $C_p(t)$ is the time-dependent CA concentration in blood plasma (the AIF), K^{trans} is the flux of contrast agent from the intravascular space (IVS) to interstitium, k_{ep} is the flux of contrast agent back to the IVS, v_e is the ratio of K^{trans} and k_{ep} , denoting the fraction of extracellular, extravascular volume and v_p is the fractional plasma volume.

From Eq. 3, it is evident that errors in the amplitude of $C_p(t)$ will directly scale to corresponding errors in K^{trans} and v_p . Therefore, to assess the contribution of differences in AIF peak values, the analysis was repeated using AIFs normalized to an area under the curve (AUC) equal to the mean of all measured AIFs (600 mM s). Because each patient received the same CA dose at each imaging session, the AIF AUC is expected to remain constant, and normalization should therefore reduce variability in parameter estimates due to errors in measured peak AIF amplitudes, but at the cost of loss of absolute quantitative parameter estimates. Consequently, kinetic analysis was performed with seven different AIFs in each examination: three DE-supplied, the same three AUC-normalized and the pop-AIF obtained by fitting the mean AIF across all examinations to Eq. 2. From each analysis, the median parameter values from each tumor ROI were extracted and used for comparison. Voxels in which parameters v_e or v_p took an unphysiological value outside the range 0–100% was excluded from median calculation for all AIFs in that examination. The PK modeling and AIF analysis were performed in MATLAB 2020a (MathWorks, Natick, MA, United States).

Statistical analysis

AIF peak and AUC, as well as estimates of parameters K^{trans} , k_{ep} , v_e and v_p , were used for statistical analysis. The median value of each parameter in each tumor ROI was used for analysis. AIF characteristics were assessed using Wilcoxon signed-rank test on the AIF peak and AUC of each DE-supplied AIF against each other (e.g. DE 1 vs DE 2; four combinations). Intraclass correlation coefficient (ICC) estimates with 95% confidence intervals (CI) were calculated based on an absolute-agreement, two-way random-effects model [17]. The ICC estimate evaluates the degree of inter-operator agreement in the KPE estimates

within each examination, such that identical results from all AIFs in every examination would give ICC = 1. ICCs were estimated both using the complete dataset, and including only the examinations with DCE sequence variant 1 ($N=38$) to assess the performance of the pop-AIF. To investigate the effect of different AIFs on predicting clinical outcome, the change in median K^{trans} for each patient from the first to the sixth imaging time-point was compared using the measured DE-AIFs and the normalized variants. An increase or decrease of more than 10% was labeled as, respectively, progression or remission, and the scores were assessed with Fleiss' kappa using linear weights. The kappa statistic was interpreted according to the Landis and Koch benchmarking scale [18]. ICC and Fleiss' kappa statistics were performed using Stata SE 16.1 (StataCorp LLC, College Station, TX, United States) with the kappa, etc., command [19].

Results

Population-averaged AIF

Figure 2 shows the fitted population AIF together with the mean $C_b(t)$. The fitted value for each AIF parameter (Eq. 2) is given in Table 1. The fitted AIF is seen to closely follow the mean AIF, with a first-pass peak followed by a smaller second-pass peak and subsequent washout. The standard deviation of the mean AIF demonstrates a higher variation in measured AIFs during the early phase than during washout. A comparison of the pop-AIF and DE-AIFs with resulting K^{trans} maps is shown in Fig. 3.

Fig. 2 Mean arterial input function (AIF) across all domain expert-measured AIFs in individual subjects at all timepoints represented with crosses, and error bars showing ± 1 standard deviation. The fitted population AIF is shown in red

Statistical analysis

The AIF peaks were found to be significantly different between all domain experts ($p=0.03$), while AUC was found to be different between DE 2 and 3 ($p < 10^{-8}$), but not between 1 and 2 ($p > 0.80$) or 1 and 3 ($p > 0.14$).

Table 1 Parameter values and their standard deviation (SD) for the fitted population AIF (Eq. 2)

Parameter	A_1	A_2	T_1	T_2	σ_1	σ_2	α	β	s	τ
Value	2.092	0.118	0.696	1.051	0.059	0.067	3.161	0.200	818.4	0.667
SD	0.028	0.032	0.001	0.016	0.0008	0.0178	0.0982	0.011	0.000	0.001
Units	mmol min	min	min	min	min	min	mmol	min ⁻¹	min ⁻¹	min

Table 2 shows ICC for median kinetic parameter values from the 118 examinations. There is a moderate to substantial agreement for all kinetic parameters when using the measured AIFs [18]. Inclusion of the pop-AIF yields a lower agreement estimate for k_{ep} , while the other parameters are negligibly affected. The normalized AIFs give an

Fig. 3 Top: measured (left) and normalized (right) AIFs from each domain expert (DE) in a sample examination, with the time-aligned population AIF (pop-AIF) (11). Bottom: resulting tumor K^{trans} maps overlaid on structural post-contrast T1 images. The K^{trans} color scale ranges from 0.0 to 0.4 min⁻¹. Median K^{trans} of the whole tumor for DE 1, 2 and 3 and pop-AIF was, respectively: 0.049 min⁻¹, 0.053 min⁻¹, 0.044 min⁻¹, 0.101 min⁻¹ (measured AIFs) and 0.071 min⁻¹, 0.067 min⁻¹, 0.071 min⁻¹ and 0.080 min⁻¹ (normalized AIFs)

Table 2 Intraclass correlation coefficient (95% confidence interval) of median parameter values estimated using measured and normalized arterial input functions (AIF) from domain experts (DE) 1–3 and

population AIF (pop-AIF), including all imaging time-points in all patients ($N=118$)

AIFs used	K^{trans}	k_{ep}	v_e	v_p
DE 1–3	0.670 (0.543–0.766)	0.762 (0.694–0.820)	0.702 (0.588–0.787)	0.510 (0.395–0.617)
DE 1–3 and pop-AIF	0.671 (0.572–0.754)	0.692 (0.619–0.760)	0.678 (0.581–0.758)	0.497 (0.399–0.594)
AUC-normalized DE 1–3	0.951 (0.934–0.964)	0.765 (0.698–0.823)	0.891 (0.857–0.921)	0.698 (0.616–0.769)
AUC-normalized DE 1–3 and pop-AIF	0.940 (0.921–0.956)	0.694 (0.622–0.761)	0.858 (0.817–0.892)	0.693 (0.620–0.760)

Table 3 Intraclass correlation coefficient (95% confidence interval) of median parameter values estimated using measured and normalized arterial input functions (AIF) from domain experts (DE) 1–3 andpopulation AIF (pop-AIF), including only examinations with DCE sequence variant 1 ($N=38$)

AIFs used	K^{trans}	k_{ep}	v_e	v_p
DE 1–3	0.559 (0.364–0.725)	0.746 (0.611–0.850)	0.697 (0.507–0.823)	0.446 (0.250–0.635)
DE 1–3 and pop-AIF	0.552 (0.379–0.710)	0.761 (0.645–0.853)	0.668 (0.476–0.805)	0.439 (0.275–0.614)
AUC-normalized DE 1–3	0.967 (0.950–0.984)	0.758 (0.623–0.855)	0.928 (0.879–0.953)	0.792 (0.675–0.879)
AUC-normalized DE 1–3 and pop-AIF	0.965 (0.944–0.980)	0.765 (0.650–0.856)	0.923 (0.876–0.955)	0.803 (0.703–0.882)

almost perfect (0.8–1.00) agreement for parameters K^{trans} and v_e , while v_p 's agreement is substantial (0.61–0.80). As expected, k_{ep} is the least affected by normalization of the AIF, as it is not sensitive to the AIF amplitude [20]. Table 3 shows the same ICC estimates calculated from only the examinations using DCE sequence variant 1 and demonstrates a similar relationship between ICC estimates with and without inclusion of the pop-AIF.

Figure 4 shows the relative K^{trans} change from baseline to the sixth exam for two sample patients that demonstrate different degrees of observer dependence. Panel B represents a worst-case scenario, where different DE-AIFs produce opposing estimates of disease progression.

When change in median K^{trans} is segmented into remission ($< 10\%$), *status quo* ($-10\% \leq$ and $\leq +10\%$) and progression ($> +10\%$), Fleiss' kappa (3 raters, 23 subjects) is calculated as 0.595 with a 95% CI of (0.363, 0.827) for the measured AIFs, suggesting a fair to moderate agreement, while the normalized counterparts yield a kappa of 0.809 with CI (0.661, 0.958), suggesting a substantial to almost perfect agreement.

Discussion

The aim of the present work was to investigate the effect of differences in user-defined AIFs on kinetic parameters estimated from DCE using the extended Tofts model on data from HGG patients. Three experienced DEs individually produced AIFs for 118 examinations of 23 patients with HGG, following a common guideline that included the use of a semi-automatic detection algorithm. Additionally, a population-averaged AIF was fitted to a subset of the measured AIFs. A fixed $T_1(0)$ both in tissue and blood was assumed in all patients, and all analyses were performed at the same facility without input from the DEs other than their supplied AIFs. Therefore, the results of the kinetic analyses in this study should not be influenced significantly by factors other than the difference in AIFs.

The results in this study show moderate to substantial agreement in kinetic parameters estimated with AIFs from different DEs (Table 2). Agreement in estimated parameters

is not substantially affected when the pop-AIF is included. This suggests that the pop-AIF represents an appropriate alternative to manually measured AIFs on a per-examination basis. The AUC-normalized DE-AIFs is seen to yield higher agreement in parameter estimates for K^{trans} , v_e and v_p , as expected from the known sensitivity of these parameters to the AIF peak amplitude. The parameter k_{ep} depends more on the shape of the AIF [20] and is therefore virtually unaffected by the AIF normalization. This is in agreement with previous work investigating the effects of measuring the AIF for brain DCE in different vessels [21], which found a strong correlation between lower AIF peak and overestimation of all parameters except k_{ep} .

Comparing the relative change in parameter estimates over time as an indicator for disease progression shows that the use of AUC-normalized AIFs increases the agreement between DEs. The case presented in Fig. 4b represents a worst-case scenario where longitudinal change in K^{trans} is labeled differently (progression, stable, remission) by each of the DE-AIFs, while all AUC-normalized DE-AIFs and the pop-AIF indicate progression. This demonstrates that a single DCE series can contain several clusters of voxels that produce subjectively acceptable, yet consequentially different AIFs. This operator-dependency is reduced with the AUC-normalized DE-AIFs and completely removed with the pop-AIF, at the cost of potential loss of relevant information.

The AIFs in this study were not accompanied by per-examination measurement of hematocrit, which is known to fluctuate significantly during chemotherapy treatment [22]. Hematocrit variations would lead to a true variation in AIF peak amplitude, which would not be reflected in the AUC-normalized AIF or the pop-AIF. However, if hematocrit values were available, this could be incorporated as an additional per-patient and per-examination scaling factor in the resulting AUC-normalized or population-based AIFs [23].

This study included data acquired with two slightly different DCE-MRI sequences, differing in TR, TE, TD and number of dynamic scans. The pop-AIF was derived using only data from the sequence variant with the largest number (variant 2, $N=220$) of scans. To confirm that this pop-AIF was valid for both sequence variants, the ICC was compared including either all data from

Fig. 4 Relative change in K^{trans} in two sample patients from the first to the sixth exam estimated using AIFs from each domain expert (DE) and population AIF (pop-AIF) (11). **a** Patient with similar development in K^{trans} with all DE-measured and population AIF. The largest absolute change with measured AIFs was -0.016 min^{-1} (DE 2), and 0.0091 min^{-1} (DE 1) with normalized AIFs. **b** A patient where measured AIFs from the three DEs give diverging progression, while the normalized AIFs give a unidirectional progression. With measured AIFs from DE 1 the change is $+0.022 \text{ min}^{-1}$, while normalized AIFs from DE 2 gives a change of -0.014 min^{-1}

both sequences and only data from sequence variant 1. The results (Tables 2, 3) show that agreement is equally affected when including the pop-AIF in both datasets, indicating that the pop-AIF can be used on data acquired with sequence parameters deviating from the ones used when defining the pop-AIF.

One major challenge with the DCE-MRI field is lack of standardization between sites and studies. Although white papers suggesting standards for MRI protocol and analysis exist [2], there is still a substantial variation in both acquisition and analysis methods in the published data, making comparison of quantitative parameter estimates challenging. In treatment response studies, like the one presented here, the absolute values of the kinetic parameters may be of less importance and the emphasis should be on the ability of a given method to accurately detect parameter changes during the course of disease progression and treatment response. This is in line with previous findings in a large multicenter study concerning prostate cancer [7]. Our results suggest that this can readily be achieved through a combination of standardized and fixed protocols for AIF determination and a fixed imaging protocol over time. Further, and more importantly, our results suggest that the derivation of a population-wide AIF derived from the mean of many DCE-MRI examinations acquired on the same system provides a good alternative to the need for time-consuming identifications of individual AIFs by domain experts. It is, however, important to stress that such population AIF may need to be adjusted according to site-specific variations in MRI protocol and scanner type. Still, the population AIF obtained

here, based on the same functional form as previously suggested by Parker for abdominal use [10], may form the basis for a similar pop-AIF for use in brain DCE-MRI applications.

In conclusion, normalizing the measured AIFs to a reasonable AUC can serve to reduce the variation in kinetic parameter results that stem from operator input. Further, using a parametric population AIF for the brain as presented in this study may be applied in absence of a satisfactory measurement in kinetic parameter estimation from DCE-MRI data in HGG patients.

Author contributions AB: study conception and design, analysis and interpretation of data, critical revision. IRG: study conception and design, drafting of manuscript, critical revision. MK: acquisition of data, critical revision. MK: study conception and design, analysis and interpretation of data, drafting of manuscript, critical revision. CL: study conception and design, analysis and interpretation of data, drafting of manuscript, critical revision. JV: acquisition of data, critical revision.

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Declarations

Conflict of interest Author Atle Bjørnerud is a paid consultant of NordicNeuroLab AS. No other conflict of interest was reported from any of the authors. No funding was received for the writing of this study.

Ethical standards Informed consent from all participants was acquired before imaging according to the ethical regional committee and the Helsinki declaration from 1964.

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