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Patient characteristics influencing the variability of distributed parameter-based models in DCE-CT kinetic analysis

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Abstract

Kinetic parameter variability may be sensitive to kinetic model choice, kinetic model implementation or patient-specific effects. The purpose of this study was to assess their impact on the variability of dynamic contrast-enhanced computed tomography (DCE-CT) kinetic parameters. A total of 11 canine patients with sinonasal tumours received high signal-to-noise ratio, test-double retest DCE-CT scans. The variability for three distributed parameter (DP)-based models was assessed by analysis of variance. Mixed-effects modelling evaluated patient-specific effects. Inter-model variability (CV_{inter}) was comparable to or lower than intra-model variability (CV_{intra}) for blood flow (CV_{inter} : [4–28%], CV_{intra} : [28–31%]), fractional vascular volume (CV_{inter} : [3–17%], CV_{intra} : [16–19%]) and permeability-surface area product (CV_{inter} : [5–12%], CV_{intra} : [14–15%]). The kinetic models were significantly ($P < 0.05$) impacted by patient characteristics for patient size, area underneath the curve of the artery and of the tumour. In conclusion, DP-based models demonstrated good agreement with similar differences between models and scans. However, high variability in the kinetic parameters and their sensitivity to patient size may limit certain quantitative applications.

Keywords

canine; DCE-CT; kinetic analysis; perfusion

Introduction

Vasculature status plays a prominent role in oncology. An increase in tumour vascularization may indicate higher tumour potential to metastasize.^{1,2} In addition, vessels noted with poorer perfusion may possess a resistance to therapy.^{3,4} Dynamic contrast-enhanced computed tomography (DCE-CT) serves as a non-invasive imaging technique to measure vasculature status.^{5,6} Studies have investigated dynamic imaging derived vasculature

parameters for differentiation of benign and malignant tumours,⁷ early assessment of treatment for chemotherapy and radiation therapy,^{8,9} predicting outcome³ and for monitoring anti-angiogenesis therapies.¹⁰

For vasculature imaging to increase clinical use in oncology, it is important for vasculature parameters to show a high degree of repeatability in order to make reliable treatment decisions.¹¹ Previous studies have investigated the repeatability of DCE-CT kinetic analysis and shown it to be dependent on the tumour location, such as the colon,¹² lung,¹³ head and neck,^{11,14} or brain.¹⁵ However, even with a consistent tumour location, clinicians may have difficulty comparing kinetic parameters between studies. Kinetic parameters between studies may not be interchangeable owing to factors related to kinetic model choice, kinetic model implementation or patient-specific parameters.^{11,16–20} Therefore, it is of interest to investigate how these factors impact both kinetic parameter variability and interchangeability.

Although distributed parameter (DP)-based models are the most representative of the contrast agent traversing vasculature and tissue,^{5,21} kinetic parameter interchangeability has varied depending on model implementation. Good agreement has been found for kinetic parameters between in-house models from the same authors.⁵ However, poorer agreement has been found when comparing kinetic parameters from in-house models to commercial software or between commercial software versions.^{22,23}

Patient-specific effects may also impact kinetic parameter variability in canines. Canine patients are anaesthetized prior to DCE-CT imaging, where changes in anaesthesia drug concentration, or patient temperature have been shown to influence blood flow values.^{24,25} In addition, alterations in the hemodynamics of canine patients may occur as a result of contrast administration.²⁶

This study investigated the interchangeability and variability of kinetic parameters from three DP-based models, as well as patient-specific effects that may impact kinetic parameters. Two in-house models were implemented, along with a commercial software package to investigate the interchangeability of the kinetic parameters. The intra-model variability was assessed to test kinetic parameter sensitivity to kinetic model selection, kinetic model implementation and patient-specific effects. Test-double retest imaging was performed rather than test-retest imaging to gain a better understanding of the variability through an additional measurement. In addition, this study attempted to limit tumour motion and registration errors by using canine sinonasal tumours, which have been shown to permit submillimetre positioning reproducibility through a bite-block immobilisation system.²⁷

Materials and methods

Models

In DCE-CT kinetic analysis, the uptake of the contrast agent is assumed to be linear with the CT Hounsfield unit. The general equation for DCE-CT kinetic models is given in Equation (1),^{21,22,28,29}

$$C(t) = F[AIF(t) \otimes R(t)] \quad (1)$$

where the tumour time attenuation curve (C) is equal to a scalar blood flow (F), which is multiplied by the convolution ($\otimes$) of the arterial impulse function (AIF) and the impulse response function (R). The DP model is a two-compartmental model containing an intra-vascular and extravascular space.^{29,30} In comparison, the adiabatic approximation to the tissue homogeneity model, ATH, is a two-compartmental model derivation of the DP model. The time-domain representation of the impulse response function is much simpler for the clearance phase and more computationally efficient.^{5,29,32} Both the DP and ATH models were implemented in-house using MATLABTM. The kinetic parameters used in the study were blood flow, fractional vascular volume, transit time and permeability-surface (PS) area product (Table 1).^{22,29,31,33,34}

Subjects and protocol

Our study focused on 11 canine patients with spontaneous tumours. The study was approved by the Institutional Animal Care and Use Committee at the University of Wisconsin-Madison. The patients were imaged as part of a pre-therapy imaging regime prior to receiving radiation therapy. Each patient had treatment naive primary sinonasal tumours of either carcinoma (7) or sarcoma (4) histology. Clinical stages for the 11 dogs were stage 1–3 based on the Adams 2009 staging system.³⁵ None of the dogs had involvement of the cribriform plate (stage 4) as this was an exclusion criterion for the study. Dogs with carcinoma tumour type had CT stage 1 (n = 1), CT stage 2 (n = 3) and CT stage 3 (n = 3). Dogs with sarcoma tumour type had CT stage 1 (n = 1) and CT stage 2 (n = 3).

Each patient received three DCE-CT scans on consecutive days with approximately 24 h between scans. The frames for the DCE-CT images were acquired on an axial, 64-slice CT scanner (GE Discovery VCT). All DCE-CT scans were given prior to therapy for test-double retest imaging. Patients were anaesthetized with propofol before imaging and maintained on inhaled isoflurane (2–4%) during scanning with the isoflurane concentration kept consistent between scans for each patient. In addition, the temperature of the patient was maintained and monitored throughout the scans. Patients were immobilized with a patient-specific bite-block, dental mold and vacuum mattress.²⁷ Patients were injected intra-venously via a power injector (Medrad) with 50 mL of 300mgmL⁻¹ iodine iohexol (Omnipaque 300) given at 5mLs⁻¹ followed by 30mL of saline solution. The scan was initiated 5–10 s after contrast administration. The patients were imaged using shuttle mode acquisition for a total axial field of view (FOV) of 8 cm with a slice thickness of 5 mm. In shuttle mode acquisition, after the scanner table images an axial slice of 4cm, the scanner table moves to image an adjacent axial slice of 4 cm, which doubles the axial FOV for each frame. The scanner table continues to move back and forth, imaging both axial slices per frame for the duration of the scan.³⁶ FOV for the CT scan was 20 cm given over a 512 × 512 imaging matrix. The scanner was set at 80 kV and 500mA with a 0.4 s rotation time. Patients were imaged over 25 frames. The first 17 frames were continuous lasting for a total time of 46.6 s with 2.74 s

between frames. The last 8 frames included a 15 s prep plus a 1.8 s acquisition period for a total of 16.8 s between frames.

Image processing

The analysis of the DCE-CT images was performed with the GE Perfusion 4.0 software, prior to in-house model analysis. Tumours were contoured on the workstation for each scan by a veterinary radiation oncologist (Kubicek, Forrest) with care taken to exclude nearby vessels. Thresholds were applied to contours from -75 to 225HU to exclude air and bone. Voxels with signal-to-noise ratio (SNR) < 3 were excluded as kinetic analysis may be unstable at low SNR values. The SNR for our study was defined as the maximum value of the tissue enhancement curve divided by the noise.^{37,38} The maximum value of the tissue enhancement curve was determined via a gamma variate fit,³⁹ while noise was measured by calculating the standard deviation of three frames prior to the arrival of contrast. The artery along with a vein used for partial volume correction⁴⁰ were segmented to generate parametric maps over the imaged tumour volume. After performing analysis on the GE Perfusion 4.0 software, contours and images were transferred to a personal computer for in-house model analysis.

In order to generate more physiologically representative kinetic parameters, further processing was performed. A t-lag parameter was added to correct for bolus time arrivals between the AIF and the tumour voxels.⁴¹ Prior to parametric map production, a 3×3 median filter was applied, and spatial resolution was decreased by averaging 2×2 voxels before kinetic analysis. In order to take into account haematocrit differences between large and small vessels, the AIF was divided by a factor of 0.88.^{34,42} For the in-house model implementations of the ATH model ($\text{ATH}_{\text{in-house}}$) and of the DP model, the median value of each parameter over the tumour volume was measured for blood flow [$\text{mL (100 g)}^{-1} \text{min}^{-1}$], fractional vascular volume [mL (100 g)^{-1}], transit time (s) and PS area product [$\text{mL (100 g)}^{-1} \text{min}^{-1}$]. The commercial software is an implementation of the ATH model (ATH_{GE})^{9,43} and yielded corresponding kinetic parameters of blood flow [$\text{mL (100 g)}^{-1} \text{min}^{-1}$], blood volume ratio [mL(100 g)^{-1}], mean transit time (s) and PS area product [$\text{mL(100 g)}^{-1} \text{min}^{-1}$]. The mean transit time is the incorporation of both the time to traverse the intra-vascular space (transit time) and the extravascular space.²²

Statistical analysis

Model variability and corresponding kinetic parameter values were compared between $\text{ATH}_{\text{in-house}}$, ATH_{ge} and DP. The intra-model variability for each model and the inter-model variability between the kinetic models were assessed using the test-double retest scans by one-way analysis of variance (ANOVA) for repeated measures.⁴⁴ The variability between models was defined using the coefficient of variation (CV). The variability within a model used the test-double retest scans to determine the within CV (CV_{intra}). In addition, all three models were correlated against one another and compared against one another using a paired t-test.

A mixed effects model was created using the lme4⁴⁵ package in R to ascertain the impact of various fixed patient characteristics that may influence the kinetic parameters. Patient

characteristics treated as fixed effects included patient size (kg), systolic pressure (mmHg), diastolic pressure (mmHg), mean pressure (mmHg), area underneath the curve (AUC) of the AIF (HUs) and AUC of the tumour (HUs). AUC calculations were performed on the first pass of the tracer, where gamma variate fitting was used to correct for recirculation.^{39,46} The mixed effects model produced the expected change of a kinetic parameter as the fixed effect changed by one CV in the population. To quantify the variability of the fixed effects, the CV of fixed effects within a patient (CV_{intra}) were calculated. As CV rises, so does the impact of the patient characteristic on the variability. In addition, the mixed-effects model gave P values for each of the patient characteristics in order to determine significance ($P < 0.05$). All statistical analyses were performed by biostatisticians (Lee and Chappell).

Results

The imaging protocol did not cause adverse affects in the patients nor hinder kinetic analysis. Two of the patients experienced catheter issues for one scan each, and could not complete a third scan. One patient was removed because of the small size (5 kg) hindering kinetic parameter accuracy. Motion and noise were not an issue in the scans as parametric images were generated for all slices with tumour contours. The median voxel SNR (~26) was above 10 for all patients.

A similar intra-model variability (CV_{intra}) was found between the kinetic models (Table 2). Blood flow had the highest CV_{intra} ranging from 28–31%. The variability of the kinetic parameters of fractional vascular volume and transit time were similar ranging from 16–19% and 16–20%, respectively. In comparison, the PS area product had the lowest variability ranging from 14–15% between the models.

For relative inter-model comparisons, good agreement was found between the kinetic models. The three kinetic models displayed high correlations ($r = 0.82$) for blood flow, fractional vascular volume and the PS area product (Table 3 and Fig. 1). Similar relative uptake patterns were illustrated in the parametric maps (Fig. 2). The two in-house models (DP and $ATH_{in-house}$) had the highest correlations ($r = 0.98$) for these parameters with slopes close to 1.

For absolute inter-model comparisons, variability was higher between in-house models and ATH_{ge} than between the two in-house models. The linear fits between in-house models' kinetic parameters (x-axis) and ATH_{GE} model's kinetic parameters (y-axis) produced slopes deviating from 1. The slopes between in-house models and ATH_{GE} for blood flow were around 0.70 indicating a bias in the in-house models towards higher values, which is reflected in high inter-model model variability (27%). The slopes comparing in-house models and ATH_{GE} for fractional vascular volumes were close to 1.20 signifying lower parameter values in the in-house models. The inter-model variability for fractional vascular volumes between in-house models with ATH_{GE} was approximately 17%. The PS area product was fairly consistent between the models demonstrated by a slope close to 1 and inter-model variability between the in-house models and ATH_{GE} of 10%.

The kinetic models lacked absolute agreement for the kinetic parameters. Only fractional vascular volumes between in-house models ($ATH_{in-house}$, DP) and PS area products between ATH models (ATH_{GE} , $ATH_{in-house}$) were not significantly different (Table 3). The kinetic parameter differences for blood flows, fractional vascular volumes and PS area products between the in-house models were approximately 4%, which is much smaller than the intra-model variability of either model. In comparison, these kinetic parameter differed between the in-house models with ATH_{GE} on the order of the variability of test-double retest scans.

In contrast, the transit time had the lowest correlations amongst the models. The two ATH models had a correlation coefficient of only 0.27, in comparison to 0.82 between the in-house models. This is manifested in the uncertainty between the models as the CV between the in-house models was only 11%, while the ATH models were close to 36%. In addition, the slope between the in-house models and ATH_{GE} had the largest difference from 1.0 (1.5+) indicating lower in-house model values.

The application of a mixed effects model allowed the identification and quantification of patient variables affecting the kinetic parameters. The patient variables significantly impacting the kinetic parameters are listed in Table 4. The fixed effects with the largest impact on the kinetic parameter estimation were patient size, AUC of the AIF and AUC of the tumour. For the DP model, the patient size had a high impact on the blood flow and the PS area product. As patient size increased by one CV, the blood flow and the PS area product would decrease by 30 and 27%, respectively. However, patient size was stable within a patient with a low CV_{intra} , 2%. Therefore, it did not have a strong effect on the variability within a patient. The AUC of the AIF, however, had a large CV_{intra} (20%) meaning it had more drastic change within a patient. It affected all four kinetic parameters: blood flow (−30%), fractional vascular volume (−24%), transit time (8%) and PS area product (−22%). The AUC of the tumour affected only the fractional vascular volume with a change of 23%. The mean, diastolic or systolic pressures were not found to have significant impacts on the kinetic models. The effects on the kinetic parameters were similar in both ATH models. However, in the ATH_{GE} , the fixed effects did not appear to influence the blood flow or the transit time kinetic parameter estimations.

Discussion

Our study was able to determine patient-specific characteristics that affect the variability of kinetic parameters. This was accomplished through limiting the effects of noise and motion on the kinetic models. We applied a dose, kVp and an injection rate, in accordance with current recommendations.⁴⁷ Our injection of 50mL of contrast agent increased signal of the contrast agent and improved the SNR at the risk of adverse effects as a result of contrast administration.⁴⁸ No adverse effects were noted in our patients. The benefit of this acquisition protocol was limited noise (~3 HU) in the time attenuation curves and high voxel level SNR (20+) for patients. As accurate kinetic parameters require a SNR of 10,⁴⁹ our models were stable and variations as a result of physiological differences occurring from patient-specific fixed effects were able to be measured. The tumour location in the canine nasal cavity and immobilisation devices applied limited motion as we were able to achieve submillimetre reproducibility for test-double retest scanning.²⁷ For the analysis, we applied

the most physiological representative kinetic models.²¹ Furthermore, the third DCE-CT scan provided another measurement for variability analysis. Moreover, we applied similar isoflurane concentrations during anaesthesia and monitored patient temperatures in order to preserve physiological conditions between DCE-CT scans as changes in both have been shown to influence blood flow values.^{24,25}

The inter-model agreement demonstrated the kinetic parameters from the in-house models had greater interchangeability than with the commercial software. The in-house models displayed high correlations with slopes close to 1 and an inter-model variability much less than intra-model variability. This is in agreement with findings comparing the DP and ATH in-house models for meningiomas.⁵ The differences between the absolute values of ATH_{GE} with in-house models were also in agreement with literature. The largest absolute difference was in blood flow, which compared well to a previous study with measures of $69\text{mL}(100\text{ g})^{-1}\text{ min}^{-1}$ for blood flow (DP) and $54\text{mL}(100\text{ g})^{-1}\text{ min}^{-1}$ (ATH_{GE}).²² Furthermore, similar disagreement was found for the transit time as ATH_{GE} model calculates the mean transit time, which incorporates time needed to traverse vasculature (t_1) and extravascular space.²²

The intra-model variability was not affected by DP model choice or model implementation. The study investigated two different DP-based models (DP,ATH), as well as two different implementations of the same DP-based model ($ATH_{in-house}$, ATH_{GE}). The kinetic models displayed similar intra-model variability for all kinetic parameters, implying kinetic parameter variability indifference to model choice and model implementation. However, kinetic models in general are not interchangeable,¹⁷ and the use of other kinetic models may result in differing degrees of variability for kinetic parameters.

Intra-model variability in DCE-CT imaging has been varied according to patient cohort. Previous studies have focused on DCE-CT variability in a variety of tumours sites, such as colon,¹² lung,⁵² and prostate.⁵⁰ Studies focused on the brain in canines and rabbits have reported variability using one-way ANOVA for repeated measures of 30–35%, 12–15%, for blood flow and fractional vascular volume, respectively.^{15,46} Using ANOVA for repeated measures, our values agree well for variability of blood flow and fractional vascular volume at 30 and 16%, respectively. However, our study had higher kinetic parameter variability than found in a human study of head and neck tumours.¹¹ Differences may arise because of our patients receiving anaesthesia, tumour location, acquisition protocol or model implementation.^{11,18}

The variability of the kinetic parameters from each model was sensitive to patient-specific effects of the AUC of the artery and the tumour. This may be partially attributed to the shuttle mode acquisition used, which doubled the axial resolution at the cost of sparser temporal sampling of the time attenuation curves. This caused an increase in the CV_{intra} of the AUC of the artery and tumour and in turn, the variability of the kinetic parameters.^{36,51,52} While the DP and $ATH_{in-house}$ models were impacted similarly by these patient-specific effects, ATH_{GE} was not. Differences could arise in how the patient characteristics such as TAC of the artery and tumour were implemented in ATH_{GE} compared with the in-house models.²² However, as the models had similar variability, the overall variability was

independent to the different treatments of vessels in the models. The use of other kinetic models may result in different patient-specific effects impacting kinetic parameters.

The patient size was found by the mixed-effects model to influence the kinetic parameters between patients, which may be a result of partial volume effects. The smaller patients have narrower vessels, which are more prone to partial volume effects, leading to an underestimation of the AIF and an overestimation of blood flow.^{5,21} The study used a slice thickness of 5mm to attempt to balance partial volume effects and SNR.⁴⁰ As this study had high SNR, future studies may want to apply thinner slices. Moreover, the impact of patient size on the kinetic parameters, indicates caution should be applied when comparing kinetic parameters across patients and across studies as the kinetic parameters will vary according to patient cohorts.

The variability was not highly impacted by vessel selection. The maxillary artery was segmented for kinetic analysis as the carotids were not in the axial FOV. For patients with more rostral tumours, a lingual arterial vessel was segmented. Sensitivity studies using one-way ANOVA for repeated measures compared two lingual arteries versus the two maxillary arteries and yielded CVs of blood flow values of 5% with a correlation coefficient of 0.99. Similarly, sensitivity testing of four lingual veins yielded a variation in blood flow values of 6%. Hence, vessel selection did not highly impact the kinetic parameter values.

Tumour location in the nasal cavity may have contributed to varying degrees of partial volume effects in patients. Gaussian plots of background-subtracted image profiles⁴⁶ yielded full width at half maximum (FWHM) of 2.12mm for the arteries and 2.82mm for the veins. Patient size also correlated ($r = 0.41$) to the Gaussian FWHM of the four lingual veins used in the aforementioned vessel selection sensitivity study. In addition, there was more FWHM variability between patients ($\sigma_{\text{vein}} = 1.31\text{mm}$ and $\sigma_{\text{artery}} = 0.99\text{ mm}$) than within patients ($\sigma_{\text{intra-vein}} = 0.38\text{mm}$ and $\sigma_{\text{intra-artery}} = 0.33\text{ mm}$) for the vessel size. The larger variation in vessel size between patients than within patients could explain why patient size did not impact the repeatability, but did impact kinetic parameter values between patients.

The blood pressure patient-specific effects were not found to have significant impact on the kinetic parameters. One explanation is that patient blood pressures may not have an effect on the kinetic parameters. Blood flow has shown to be robust over a wide range of blood pressures.^{52,53} Another explanation could be that the blood pressure cuff may not be sufficient to accurately measure the blood pressures. An arterial catheter may be required to measure blood flow, because in 19% of patients there are differences of up to 20mmHg between blood pressure measured by arterial catheters and cuffs.⁵⁴ Further studies may be required with more accurate, but invasive blood pressure measures.

The study has several limitations. With the tumour site being in the nasal cavity, arrival of the contrast agent was measured at 21 s post injection on average in the DCE-CT scan. The DCE-CT scanning acquisition was delayed by 5–10 s to account for the arrival of the contrast agent to the nasal cavity from the injection site (hindlimb or forelimb). Future studies may want to further delay the acquisition protocol for nasal tumours as our protocol yielded 5–8 baseline data points out of a possible 17. However, the first pass in the time

attenuation curves, which is needed to properly measure F , v_1 and t_1 ⁵⁵ was imaged for all input functions using the higher temporal sampling (2.74 s between frames). A single scan of a patient was able to only image a single time point past the peak attenuation of the time attenuation curve, missing recirculation in the higher temporal sampling. This did not impact the overall CV_{intra} , as the patient's CV_{intra} was within 3% of the average patient CV_{intra} for all kinetic parameters. In addition, the study found patient size to be an important patient-specific effect between patients, which may be specific to trials with canine patients of various breeds. One of the breeds had a patient size (5 kg) too small to perform kinetic analysis because of partial volume effects in the vessels. Human trials or canine trials with the same breed may not find similar results as canines of different weights may have higher variance of vessel size. Another study limitation is the inability of the mixed effects model to separate correlated effects as it assumes a linear independence of the fixed effects. Therefore, patient-specific effects such as vessel enhancement, noise and SNR could not be measured as the effects correlated with AUC of the tumour. Another limitation of the mixed-effect model was the large number of scans required. Testing the model with 28 scans was not sufficient for fixed effect quantification. Further investigation may be needed in order to determine the effect of marginally significant ($P < 0.10$) fixed effects because of the low number of patients.

The results of our study have implications for patient care in canine patients. DCE-CT kinetic analysis has shown several potential uses in oncology, including response assessment to chemotherapy and radiation therapy.^{3,7-9} In addition, DCE-CT imaging is easy to implement with CT scanners, adding only 5min to a standard CT scan,^{6,56} and CT scanners are clinically used to assess sinonasal disease in canines.⁵⁷ However, before DCE-CT can be applied to canine patients, it needs to be demonstrated to be highly repeatable. Therefore, future studies may want to use 'cine' mode acquisition in order to more properly sample the curves depicting the contrast agent traversing the vessel and tissue. The drawback of imaging with 'cine' mode acquisition is that the tumour in the nasal cavity may be longer than the axial imaging FOV (2–8 cm) influencing the tumour voxels incorporated for analysis.

The variability in baseline DCE-CT kinetic parameter values may limit specific quantitative applications. For instance, measuring tumour response to treatment may prove to be difficult because of the large uncertainty of measurement, which hinders the ability to depict kinetic parameter changes resulting solely from treatment. Quantitative applications for response assessment may require large changes in kinetic parameter values to overcome the repeatability ($2.77 \times CV_{intra}$) of the measurement.⁵⁸ This has been shown in PET imaging for treatment response, as PET SUV metrics have displayed baseline variability of 15–20% and up to 42%.⁵⁹⁻⁶¹ However, the response of the PET SUV metrics due to treatment can be 30 – 35%, or greater depending on the tumour type.^{59,62}

In conclusion, the three kinetic models were highly correlated, and model differences were on par with differences between patient scans. The mixed effects model demonstrated the patient-specific fixed effects of the AUC's of the AIF and the tumour to impact the variability of the kinetic parameters. The high variability of the kinetic parameters and their

sensitivity to patient size may limit certain quantitative applications in canine sinonasal tumours.

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Figure 1.

Kinetic model correlations. Correlation plots for the average patient value of the four kinetic parameters of blood flow (F), fractional vascular volume (v_1), transit time (t_1) and permeability-surface (PS) area product are shown. The DP kinetic parameters values are represented on the x-axis, while the ATH_{GE} kinetic parameter values are shown on the y-axis. The colour map illustrates the $ATH_{in-house}$ model's vasculature parameters.

Figure 2.

Parametric maps of kinetic parameters. The parametric maps display a transverse slice of a canine sinonasal tumour for blood flow [$\text{mL (100g)}^{-1} \text{min}^{-1}$], fractional vascular volume [mL (100g)^{-1}], transit time (s) and the permeability-surface area product [$\text{mL (100 g)}^{-1} \text{min}^{-1}$]. The DP model is given on the leftmost column, the $ATH_{in-house}$ model in the middle column and the ATH_{GE} model on the rightmost column. The colour bar maximum is set to the median value of the tumour for each kinetic parameter as calculated by the kinetic model. The input function is given by the red arrow pointing to the maxillary artery of the image in the top-left corner.

Table 1.

Summary of vasculature parameters

Parameter	S+	Definition	Calculated ATH'	DP ϵ	Units	Ref.i
Blood flow	F	Volume flow rate	free parameter	free parameter	mL (100g) ⁻¹ min ⁻¹	22,29,33
Fractional vascular volume	v_1	Percent tissue vasculature	$F \times t_1$	$F \times t_1$	mL (100g) ⁻¹	22,29,33
Transit time	t_1	Time to traverse vasculature	free parameter	free parameter	s	22,29,33
Permeability-surface area product	PS	Flux to interstitial space from capillary	$-F \times \ln(1-E)$	$F \times t_1 \times k_{21}$	mL (100g) ⁻¹ min ⁻¹	22,29,34

S+ represents symbol.

ATH' denotes the adiabatic approximation to the tissue homogeneity model.

DP ϵ symbolizes the distributed parameter model.

Ref.i represents references.

Table 2.

Kinetic model comparisons

Characteristic	Model	Blood flow mL(100g) ⁻¹ min ⁻¹	Fractional vascular volume mL(100g) ⁻¹	Transit time s	Permeability-surface area product mL(100g) ⁻¹ min ⁻¹
Absolute value	DP+	72 ± 27	6.2 ± 2.0	5.7 ± 1.1	28 ± 7
	ATH _{in-house} '	69 ± 25	6.2 ± 2.1	6.4 ± 1.1	26 ± 7
	ATH _{GEf}	51 ± 18	7.7 ± 2.1	10.2 ± 1.7	25 ± 6
CV _{intra,i} between scans (%)					
	DP	31	16	20	14
	ATH _{in-house}	30	18	16	14
	ATH _{GE}	28	19	16	15

DP+ represents the distributed parameter model.

ATH_{in-house}' denotes our implementation of the adiabatic approximation to the tissue homogeneity model.

ATH_{GEf} symbolizes a commercial software implementation of the adiabatic approximation to the tissue homogeneity model.

CV_{intra,i} symbolizes the coefficient of variation within a model.

Table 3.

Inter-model comparison

Models	Blood flow	Fractional vascular volume	Transit time	Permeability-surface area product
ATH _{In-house} ⁺ :DP'	<i>r</i>	0.99	0.82	0.98
	slope	0.96	1.10	0.96
	CV ϵ (%)	4.4	11.0	4.6
	<i>p</i>	<0.001	<0.001	<0.001
ATH _{GGE} :DP	<i>r</i>	0.87	0.61	0.82
	slope	0.70	1.75	0.91
	CV(%)	27.5	44.5	12.1
	<i>p</i>	<0.001	<0.001	0.007
ATH _{GGE} :ATH _{In-house}	<i>r</i>	0.85	0.27	0.85
	slope	0.73	1.57	0.95
	CV(%)	26.2	35.9	10.1
	<i>p</i>	<0.001	<0.001	0.17

ATH_{In-house}+denotes our implementation of the adiabatic approximation to the tissue homogeneity model.

DP' represents the distributed parameter model.

CV ϵ symbolizes the coefficient of variation between models.

ATH_{GGE} symbolizes a commercial software implementation of the adiabatic approximation to the tissue homogeneity model.

Table 4.

Covariate effects on kinetic parameters

Patient-effects	CV+ (%)	CV _{intra} (%)	F' (%)	P	v ₁ £ (%)	P	t _{1i} (%)	P	PSr (%)	P
DP _¢										
Patient size	32	02	-22	0.065	-	-	-	-	-27	<0.001
Artery _{AUC} [~]	49	20	-30	0.015	-24	<0.001	8	0.04	-22	<0.001
Tumour _{AUC}	40	17	-	-	23	0.002	-	-	-	-
ATH _{in-houseP}										
Patient size	32	02	-24	0.032	-	-	-	-	-30	<0.001
Artery _{AUC}	49	20	-31	0.006	-25	0.002	-	-	-23	<0.001
Tumour _{AUC}	40	17	-	-	24	0.003	8	0.033	-	-
ATH _{GE}										
Patient size	32	02	-	-	-	-	-	-	-23	0.003
Artery _{AUC}	49	20	-	-	-21	0.009	-	-	-19	0.005
Tumour _{AUC}	40	17	-	-	22	0.009	-	-	-	-

CV+ represents the coefficient of variation across all patients (CV) and within patients (CV_{intra}).

F' symbolizes blood flow.

v₁ £ symbolizes the fractional vascular volume.

t_{1i} symbolizes the transit time.

PSr symbolizes permeability-surface area product.

DP_¢ represents the distributed parameter model.

AUC[~] refers to the patient effect measured by the area underneath the time attenuation curve.

ATHp refers to the adiabatic approximation to the tissue homogeneity model.