Intravoxel Incoherent Motion (IVIM) MR Imaging for Prostate Cancer: An Evaluation of Diffusion Coefficient and Perfusion Fraction Derived from Different b-Value Combinations

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**Purpose:** To evaluate the effect of different b-values on intravoxel incoherent motion (IVIM) and diffusion parameters for prostate cancer detection.

**Materials and methods:** Thirty three patients (mean age of 61.6 years, mean serum PSA of 10 ng/dl) undergoing endorectal coil MRI of the prostate underwent multiparametric imaging including diffusion weighted (DW) imaging with five b-values (0, 188, 375, 563 and 750 s/mm²), T2 weighting and dynamic contrast enhanced MRI. Diffusion coefficients were obtained from a simple mono-exponential fit using different non-zero b-values. A simplified IVIM model was used to generate perfusion fractions, by combining both the measured and the extrapolated diffusion data at a b-value of zero. Correlations were made with the results of DCE-MRI using an extended Tofts pharmacokinetic model. Pathologic correlation was obtained by precisely targeting the needle via a fused MRI-Transrectal Ultrasound (MR-TRUS) image-guided biopsy system.

**Results:** Diffusion coefficients differentiated tumors from normal tissues in the prostate using all possible combinations of non-zero b-values; however, perfusion fractions demonstrated large variations depending on the choice of b-values. Exclusion of the highest b-value of 750 (s/mm²) led to better correlations of perfusion fraction with DCE-MRI and predicted the presence of cancer independent of diffusion.
Conclusions: Estimates of perfusion fraction using IVIM obtained on DW-MRI correlate with DCE-MRI parameters and are predictive for cancer in MRI of the prostate. Perfusion fraction therefore represents another independent parameter to help differentiate prostate cancers from surrounding benign tissue using multiparametric MRI.

Key Words: IVIM MR imaging; prostate cancer; perfusion fraction and diffusion coefficient; DCE-MRI
INTRODUCTION

Prostate cancer is the second most common cancer in American men; approximately one in six men will be diagnosed with prostate cancer during his lifetime (1). Currently, the definitive diagnosis of prostate cancer depends on histologic confirmation by prostate biopsy or surgery. However, recently, multiparametric prostate MRI, including T2 weighting, diffusion weighting (DW), dynamic contrast enhanced (DCE) imaging and MR spectroscopy, has been used to localize prostate cancer to permit image guided biopsy of suspicious lesions with increased accuracy and yield compared with random biopsies (2-3). Multi-parametric MR imaging (MP-MRI) has thus garnered interest because of its ability to guide biopsy and monitor patients (4-6).

Diffusion weighted imaging is an important part of this resurgence in interest of MP-MRI. Apparent diffusion coefficient (ADC), a measure of water diffusion within tissues, is usually based on applying a mono-exponential fit to signal intensity data from images obtained with at least two different diffusion sensitizing gradients (b-values) (7). The ADC is distinctly reduced in tumors, correlating with Gleason grade and thus, has proven useful in localizing and grading tumors (8-10). Nonetheless, there is another component of DW-MRI that is largely ignored, i.e. intravoxel incoherent motion (IVIM) (11). It was recognized early in the development of DW-MRI by LeBihan et al. who observed that at very low b values, bulk motion due to perfusion, rather than diffusion alone, modulates the DW-MRI signal. Moreover, it is known from DCE-MRI studies that tumors tend to have increased perfusion and permeability (12-13), and thus, IVIM could provide an
independent measure of tissue perfusion. Measurement of perfusion fraction based on IVIM is appealing because it is obtained simultaneously with ADC measurements thus providing an additional parameter without increasing scan time. In recent years, there has been renewed interest in IVIM thanks to improved MR hardware performance (14-23). In particular, diffusion signals in prostate were shown to be significantly better characterized by bi-exponential versus mono-exponential decay functions based on 1.5T DW-MRI images with 11 b-values (0, 1, 2, 4, 10, 20, 50, 100, 200, 400 and 800 s/mm²), and the diffusion coefficients and perfusion fractions in cancerous tissues were reportedly lower compared to benign tissues (20). These findings were echoed by another IVIM study of the prostate at 3T, where 4 b-values (0, 50, 500 and 800 s/mm²) were used in 13 subjects (18). Interestingly, bi-exponential (fast and slow) ADCs in prostate were documented using an extended range of b-values from 200 to 3000 s/mm², where the b-value of zero was specifically excluded from the analysis (24-25). Increasingly, it is recognized that there are probably three components to the signal response at different b-values during DW-MRI: perfusion, fast diffusion and slow diffusion all contributing to signal intensity, with the perfusion playing a significant role only at very low b-values and slow diffusion becoming apparent at very high b-values. Because of its dependence on low b-values, it is unclear what maximal b-values should be used to generate IVIM-based perfusion fractions, and it might be invalid to apply IVIM directly on a multi b-value DW-MRI with the maximum b-value beyond a certain limit. Thus, we investigated the applicability of IVIM-based diffusion coefficients and perfusion fractions based on different combinations of 5 b-values (0,188, 375, 563 and 750 s/mm²) DWI in identifying prostate cancers on MP-MRI.
MATERIAL AND METHODS

Patients

This study was approved by the local institutional review board (IRB) and was compliant with the Health Insurance Portability and Accountability Act (HIPAA); informed consent was obtained from each patient. The study population consisted of 33 patients (mean age of 61.6 years ranging between 53 and 81 years; mean PSA of 10 ng/dl ranging between 1.32 and 45 ng/dl) who underwent dual coil MRI of the prostate and subsequently had MR-TRUS fusion biopsies of each lesion. Each lesion was characterized by its Gleason Score (GS), and its malignancy was defined as either high grade (GS > 4+3, N=16) or low grade (GS < 3+4, N=17).

Phantom

An ice-water phantom was created by immersing a vial of water into a larger container filled with ice (7,26). Diffusion was measured using 16 b-values during acquisition. Since the water phantom consists of only one compartment, any deviations from mono-exponential decay indicated poor performance of the gradient hardware. The phantom study result showed that the ice-water diffusion signal was indeed a mono-exponential decay with a diffusion coefficient of $1.124 \pm 0.002 \ (10^{-3} \text{ mm}^2/\text{s})$.

IVIM Simulation

According to IVIM, the measured diffusion signal $S(b)$, under the influence of a diffusion sensitizing gradient (b), is attenuated by two different physical processes, i.e. thermal-
energy driven molecular diffusion (D) and perfusion (D*) induced by active bulk motion due to blood flow in micro-vascular networks. The fraction of signal attenuation due to perfusion is indicated by \( f \), the perfusion fraction.

\[
S(b) = S_0 \left\{ \left( 1 - f \right) e^{-bD} + fe^{-bD^*} \right\}
\]  

[1]

According to the literature(11,27), D* is one or two magnitudes larger than D, but it only becomes significant at low b-values (28). If a b-value is above a threshold such that the perfusion contribution is negligible, then Eq. [1] would simply become a mono-exponential model. Given the minimal non-zero b-value of 188 (s/mm²) in the current study and assuming D of \( 1.0 \times 10^{-3} \) mm²/s, D* of \( 20.0 \times 10^{-3} \) mm²/s and \( f \) of 20%, the perfusion contribution to S(b) would be less than 1.0%. On a semi-log plot of normalized pixel signal intensities vs. b-values (Figure1), the slope of the curve is D and the y-intercept is f under the assumption that it is small (see Eq. [2]).

\[
\log \left( \frac{S(b)}{S_0} \right) = -f - bD
\]  

[2]

**MR Imaging Protocol**

All measurements on patients and the phantom were performed on a 3T MR scanner (Achieva 3.0T, Quasar Dual, Philips Healthcare, Best, The Netherlands) using a
combination of 16-channel SENSE Cardiac Coil with an Endorectal Coil (Medrad, Indianola, PA). After three orthogonal (axial/coronal/sagital) high-resolution T2-weighted turbo spin-echo (TSE) scans, an axial DW-MRI was performed using a single-shot spin-echo (SE) echo-planar imaging (EPI) sequence with the parameters: repetition time (TR) / echo time (TE) of 4584 / 59 ms, field of view (AP/RL/FH) of 160 / 180 / 60 mm, number of slices of 20, acquired/reconstructed voxel size of 1.25*1.25*3.00 / 0.55*0.55*3.00 mm^3, the diffusion sensitizing gradient applied in three orthogonal directions, b-values of 0, 188, 375, 563,750 s/mm^2, the number of signal averages (NSA) of 4 (for b-values of 0, 188, 375 s/mm^2) and 8 (for b-values of 563,750 s/mm^2), parallel imaging (SENSitivity Encoding [SENSE]) factor of 2 (along the phase encoding [RL] direction) and an over-sampling factor of 2 to avoid fold-over artifacts, half scan factor of 0.73, EPI factor of 73, spectrally (adiabatic) selective attenuated inversion recovery (SPAIR) for fat suppression, and total scan time of 5.9 min. For T1-weighted (T1W) dynamic contrast enhanced (DCE) MRI, two separate axial scans were acquired - a pre-contrast dry run with a low flip-angle (5º) and a dynamic one with a higher flip-angle (15º) after a single-dose injection of gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ) at a dose of 0.1 mmol/kg through a peripheral vein at a rate of 3 mL/sec via a mechanical injector (Spectris MR Injection System; Medrad). The temporal resolution of the dynamic scans was either 3 or 5.6 seconds, and final total scan time was kept within 5 minutes. FOV (AP/RL/FH) was 262 / 262 / 60 mm, the voxel size was 1.02*1.02*6 mm^3, TR and TE were the shortest possible, and the number of scan averages (NSA) was 10 and 2 for pre-contrast and dynamic scans respectively.
**MR Image Analysis**

Based on T2W images, one of the authors (B.T) drew two regions of interest (ROIs) on each patient’s DW-MRI images (acquired with high b-values): one covering tumors in the peripheral zone (PZ) and the other representing contra-lateral normal regions in the PZ. For all 33 patients, the average number of pixels contained in two ROIs was 46 ± 33 and 34 ± 23 in the normal and tumor regions, respectively. Volume of interest measurements (VOIs) in the normal and tumor regions were also calculated based on the reconstructed pixel size. Subsequent analyses were performed on the average of all pixel values within predefined ROIs (for enhanced signal to noise ratio [SNR]) instead of individual pixels.

Diffusion coefficients (D) were generated from nine (tabulated in Table 1) different combination of b-values (excluding zero) based on Eq. [2]; perfusion fractions (f) were then calculated using the measured (S0) and extrapolated (S0*(1-f)) from Eq. [2] pixel values at b-value of zero (28). With three and four b-values (Group 1-3), D was derived from the linear least-squares curve fitting, and with two b-values (Group 4-9), it was obtained simply by solving two independent linear equations.

For DCE-MRI data analysis, a pre-contrast T1 map was generated using the dual flip-angle method (29-30); and a population-averaged arterial input function (AIF) was included where the blood inflow effect was largely suppressed and B1 field inhomogeneity was corrected (31-32). An extended Tofts pharmacokinetic model (33-34), implemented with an efficient matrix-based computation algorithm (35), was used to generate three DCE-MRI parameters, i.e. the volume transfer constant (K\text{\text{trans}}), fractional volume of extravascular-extracellular space (v_e), and fractional volume of blood plasma
(v_p), for the same ROIs used in the previous DW-MRI analysis. All image visualization and analysis was performed on in-house software developed in IDL 6.3 (ITT Visual Information Solutions, Boulder, CO).

**Statistical Analysis**

The mean and coefficient of variation (%) of diffusion coefficients (D) and perfusion fractions (f) derived from the specific combination of b-values for all 33 patients are tabulated in Table 1, similarly, the same statistics were applied for DCE-MRI-derived parameters: K^{trans}, v_e and v_p in Table 2. Student’s paired t-test with a two-tail distribution was used to determine the separation between normal and tumor tissues for each measure, and statistical significance was considered at p <0.05. Also included was the ratio (N/T) of a parameter’s population-average in normal (N) and tumor (T) ROIs. Scatter plot matrix were used to show the correlations among the different parameters. With the calculated values of centroid position, area and orientation, two error ellipses (95% confidence level) were generated for each parameter pair in tumor and normal tissues, to visually demonstrate data clustering in two-dimensional space (36-37). The area of an error ellipse is considered as a figure of merit for data compactness.

**RESULTS**

Two exemplary ROIs are drawn in tumor (in red) and normal tissues (in green) on a diffusion-weighted image in Figure 2a, and the matching ROI-based curve-fittings are shown in a semi-log graph in Figure 2b. These clearly demonstrate that the diffusion coefficient (D), i.e. the fitted line’s slope, is lower in tumor (red solid line) compared
with normal (blue dashed line) tissue; while the perfusion fraction \( f \), i.e. fitted line’s \( y \)-intercept, is higher in tumor. The histopathology image in Figure 2c highlights (in dashed green line) the lesion location in the right peripheral zone.

There are nine different combinations of 4 \( b \)-values excluding zero in Table 1. For each group, \( D \) was determined using a mono-exponential model; and \( f \) was derived afterward from the extrapolated and measured pixel values at zero \( b \)-value. In Figure 3, the relationship between \( D \) and \( f \) for each combination of \( b \)-values is shown in the corresponding bivariate scatter plot, where error ellipses (95% confidence level) are overlaid to underline the differences in this parameter pair between normal (filled blue triangle) and tumor (filled red circle) ROIs.

Overall, \( D \) is always significantly lower (\( p < 0.05 \)) in tumor than in normal tissues in every group of \( b \)-values. There are noticeable variations (\( \approx 14-17\% \)) in \( D \)’s mean depending on which \( b \)-values are used; however, the N/T ratios of \( D_{\text{ave}} \) between normal and tumor ROIs are almost the same (\( \approx 1.8 \)). Interestingly, exclusion of higher \( b \)-values led to reduced coefficient of variations for \( D \), decreasing from a high of 40\% (Group 9) to a low of 28\% (Groups 3 and 5) in tumor regions.

In contrast, the ratios of averaged \( f \) in normal and in tumor ROIs vary considerably depending on which \( b \)-values are used, ranging from 0.5 (Group 4) to 1.0 (Group 9). When the highest \( b \)-value of 750 s/mm\(^2\) was excluded (Group 3-5), \( f \) was significantly increased (\( p < 0.05 \)) in tumor compared to normal; in other words, it was negatively correlated with the corresponding \( D \) (Figure 3). These results contradict prior literature (18,20), where \( f \) is reported to be paradoxically lower in tumor. However, these increased
perfusion values are more consistent with what is known about angiogenesis within tumors and observations made on DCE-MRI (12-13,38).

Table 2 depicts the tabulated averaged DCE-parameters ($K^{\text{trans}}$, $v_c$ and $v_p$) on the same 33 subjects derived from an extended pharmacokinetic model, and the matching $f$ excluding the highest $b$-value of 750 s/mm$^2$ (Group 3). Statistically, all three DCE-parameters are significantly larger ($p < 0.05$) in tumor than in normal regions; in particular, $K^{\text{trans}}$ and $v_p$ are more than twofold higher compared to normal, and positively correlated with $f$ with Pearson’s correlation coefficients ($r$) of 0.51 and 0.46, respectively (Figure 4). This positive correlation is exemplified in Figure 5, where the lesion is clearly recognized in the right PZ on both $K^{\text{trans}}$ and $f$ maps; by comparison, the same lesion is hypointense on the T2W image.

$D$ and $f$ are more clustered (Groups 3 and 5) when derived from data excluding the highest $b$-value. This is revealed by the relatively smaller areas of their error ellipses (see Figure 3). Parenthetically, removing the highest $b$-value from the DW-MRI would reduce acquisition time because a larger number of scan averages (NSA) is generally required with higher $b$-values to boost the signal-to-noise ratio. Among all the discussed parameters, only $D$ (in units of $10^{-3}$ mm$^2$/s) is capable of differentiating high grade ($0.85 \pm 0.25$) from low grade ($1.13 \pm 0.27$) tumors, consistent with the literature (8-10).

In summary, IVIM-derived diffusion coefficients were extremely robust as a tumor biomarker independent of the choice of $b$-values used in this study; in contrast, the perfusion fractions were heavily dependent on the exclusion of higher $b$-values.
DISCUSSION

DW-MRI has been accepted as an imaging biomarker of cancer and is regarded as a key tool for the detection and characterization of cancers, as well as a method for monitoring the effects of treatment (7). Derived from a simple mono-exponential decay model, apparent diffusion coefficients (ADC) in prostate are significantly lower in tumors than in normal tissues (39); more importantly, ADC has a negative correlation with the degree of tumor aggressiveness as determined by the Gleason scoring system (8-10,40). Although similar correlations have been observed in many studies, the absolute mean ADC values are somewhat disparate even for the same Gleason score. For instance, in tumors with Gleason Scores of 3+4, the mean ADC value (in units of $10^{-3}$ mm$^2$/s) was 1.10 and 0.88 in two different studies (8,40). As stated in one of the two studies (8), the ADC value was not independent of the choice of b-values, and the mean value of ADC for both tumor and healthy prostatic regions was lower when it was calculated using b-values of 0 and 1000 s/mm$^2$ rather than 0 and 700 s/mm$^2$. This variability clearly demonstrates that the simple mono-exponential model for prostate ADC quantification is limited.

In a recent report (20), Riches et al. compared bi-exponential to mono-exponential modeling for diffusion coefficients (D) using 11 b-values (0, 1, 2, 4, 10, 20, 50, 100, 200, 400 and 800 s/mm$^2$) and concluded that the diffusion signals in prostate were better described by the bi-exponential model based on IVIM theory. Specifically, D (in units of $10^{-3}$ mm$^2$/s) values were statistically significantly lower ($0.82 \pm 0.45$ vs. $1.34 \pm 0.28$) in tumors than in healthy prostatic tissues in the PZ; however, perfusion coefficients (D*) and fractions ($f$) were highly variable within the fifty subjects. Nonetheless, the median for D* was about 19 and 16 times larger than of D, and the median of $f$ was 15% and 13
23%, in tumors and normal PZ, respectively. Notably, \( f \) was relatively smaller while \( D^* \) was larger in tumors compared to normal tissues.

Dopfert, et al. reported another IVIM study in 13 patients with prostate cancer using 4 \( b \)-values (0, 50, 500 and 800 s/mm\(^2\)) and a full bi-exponential data analysis (18). \( D \) (in units of \( 10^{-3} \) mm\(^2\)/s) and \( f \) (%), but not \( D^* \) (in units of \( 10^{-3} \) mm\(^2\)/s), was significantly lower in tumors (0.84±0.19, 14.3±7.1% and 7.52±4.77, respectively) compared to benign tissues (1.21±0.22, 21.3±8.3% and 6.82±2.78, respectively). Although similar trends were observed in IVIM-derived parameters in another previous study (20), \( D^* \) was much smaller.

In the current study, an asymptotic rather than a full bi-exponential curve-fitting was employed to model 5 \( b \)-values. The minimal non-zero \( b \)-value (188 s/mm\(^2\)) was large enough to ignore the perfusion contribution to the diffusion signal decay. According to the simulation (28), \( f \) would be underestimated when using an asymptotic fitting for moderate signal-to-noise ratios data. Our study showed that \( D \) was significantly reduced in tumors independent of the choice of \( b \)-values between 0 and 750 (s/mm\(^2\)), in line with the literature (8-10,20,39). However, \( f \) varied dramatically depending on different combinations of \( b \)-values.

When \( f \) was able to differentiate tumor and benign tissues (in Group 1, 3-6), it was significantly increased in tumors compared to benign tissues; this contradicts prior reports (18,20). However, our result is more in keeping with the known increases in perfusion within most prostate cancers based on DCE MRI (12-13,41). Ludemann, et al. reported that the blood volume in prostate tumors was approximately two times higher than benign tissue (41), corresponding to what we observed in \( f \) (7% ± 39% vs. 4% ± 14)
61%). We have shown that both $K^{\text{trans}}$ and $v_p$ are positively correlated with $f$ with Pearson’s correlation coefficients ($r$) of 0.51 and 0.46. It is worth noting that the Tofts model used in DCE-MRI is only valid for the tissues containing small blood volumes (42); in other words, the kinetic parameters reported here may be inaccurate especially for high grade tumors with large vascular spaces. Nonetheless, it is interesting that comparable perfusion fractions could be obtained from two different MRI techniques based on two completely different mechanisms.

IVIM was originally formulated as a bi-exponential model, assuming only one type of diffusion process (11). However, “fast” and “slow” diffusion components have been reported in the prostate based on diffusion data with 15 b-values between 200 to 3000 (s/mm$^2$) (24-25). The physiologic basis for these two kinds of diffusion, assuming they indeed exist, is not yet accounted for. Non-Gaussian noise distribution in the diffusion magnitude images, especially with higher b-values (i.e. lower SNR), could lead to the observed apparent bi-exponential diffusion decay (43). In any event, it would be invalid to apply IVIM to diffusion data acquired with higher b-values where the contribution due to “slow” diffusion was appreciable.

When the highest b-value of 750 (s/mm$^2$) was included in our study (Group 2, 8-9), $D$ and $f$ demonstrated larger coefficient of variations in both malignant and benign tissues (see Table 1) and correspondingly larger areas of the error ellipses (see Figure 3). The highest and lowest $D$ in tumor (1.04±0.32 vs. 0.88±0.35) or benign tissues (1.83±0.36 vs. 1.60±0.39) were from b-values of 188 and 375 s/mm$^2$ (Group 4), and 563 and 750 s/mm$^2$ (Group 9) respectively, indicating that the pure diffusion signal is not modeled well as a mono-exponential decay. Despite the limitations at higher b-values, the results at lower 15
and intermediate b-values were encouraging. In Group 3 (b-values = 0, 188, 375 and 563 s/mm²), D and f had a significant negative correlation with each other.

To extract both diffusion and perfusion information from a single diffusion acquisition based on IVIM is of potential clinical relevance. One appealing feature of this data is that perfusion information might be obtained without the need for intravenous contrast media. This is especially relevant in patients with compromised renal function or severe allergies who cannot receive intravenous gadolinium-based contrast media. However, the inclusion of IVIM in addition to T2 weighting raises the possibility of a highly efficient, multiparametric (T2, D, f) screening method that does not require gadolinium chelate injection. Moreover, use of IVIM with diffusion scanning could shorten protocols while retaining the ability to multiparametrically characterize prostate lesions based on their likelihood of containing cancer.

One limitation of our work is that we used MR-TRUS fusion guided biopsy results as a reference for validating our imaging as whole mount histopathology was not available in all patients. Criticisms of studies conducted using conventional TRUS biopsy are probably deserved since they are well known to be inaccurate. However, unlike conventional blind TRUS biopsies, these biopsies were guided by MR-TRUS fusion which allows direct sampling of each MRI positive lesion and assures that the lesion identified by MRI was the lesion evaluated histologically. This method has been previously validated and has been successfully used in over 100 patients (3,44).

**Conclusion**
In this study, we have shown that IVIM measurements can be obtained in endorectal coil MRI studies of the prostate at 3T. Low and intermediate b-values result in more accurate estimates of the perfusion fraction, whereas high b-values result in higher standard deviations due to incorporation of the “slow” component of diffusion. IVIM measurements could be incorporated into the current multi-parametric paradigm for diagnosing prostate cancer with MRI and could reduce or eliminate the need for gadolinium enhanced DCE-MRI. Studies are underway to assess the impact of IVIM on the diagnostic performance of MRI for prostate cancer

ACKNOWLEDGEMENTS

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REFERENCES

20. Riches SF, Hawtin K, Charles-Edwards EM, de Souza NM. Diffusion-weighted imaging of the prostate and rectal wall: comparison of biexponential and


### Tables

#### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Scan Parameters</th>
<th>Perfusion Fraction (%)</th>
<th>Diffusion Coefficient (10⁻³ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b-values (s/mm²)</td>
<td>Time (m)</td>
<td>Normal (N)</td>
</tr>
<tr>
<td>1</td>
<td>0, 188, 375, 563, 750</td>
<td>5.9</td>
<td>5% ± 52%</td>
</tr>
<tr>
<td>2</td>
<td>0, 375, 563, 750</td>
<td>5.0</td>
<td>9% ± 54%</td>
</tr>
<tr>
<td>3</td>
<td>0, 188, 375, 563</td>
<td>4.0</td>
<td>4% ± 61%</td>
</tr>
<tr>
<td>4</td>
<td>0, 188, 375</td>
<td>2.0</td>
<td>3% ± 74%</td>
</tr>
<tr>
<td>5</td>
<td>0, 188, 563</td>
<td>3.0</td>
<td>4% ± 59%</td>
</tr>
<tr>
<td>6</td>
<td>0, 188, 750</td>
<td>3.0</td>
<td>5% ± 50%</td>
</tr>
<tr>
<td>7</td>
<td>0, 375, 563</td>
<td>3.0</td>
<td>7% ± 64%</td>
</tr>
<tr>
<td>8</td>
<td>0, 375, 750</td>
<td>3.0</td>
<td>9% ± 54%</td>
</tr>
<tr>
<td>9</td>
<td>0, 563, 750</td>
<td>4.0</td>
<td>13% ± 53%</td>
</tr>
</tbody>
</table>

Table 1: Comparison of perfusion fraction (f) and diffusion coefficient (D) separation between normal and tumor using different b-values combinations. The values of f (%) and D are tabulated as the mean ± coefficient of variation (%); the f and D ratios between normal and tumor (N/T) are calculated with their corresponding mean values, and the p-values in Student’s t-test are also included.

#### Table 2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal</th>
<th>Tumor</th>
<th>t-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>D (10⁻³ mm²/s)</td>
<td>1.79 ± 19%</td>
<td>1.02 ± 28%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>f (%)</td>
<td>3.7% ± 61%</td>
<td>7.2% ± 39%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>K&lt;sub&gt;trans&lt;/sub&gt; (min⁻¹)</td>
<td>0.18 ± 55%</td>
<td>0.39 ± 56%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>v&lt;sub&gt;e&lt;/sub&gt; (%)</td>
<td>26% ± 42%</td>
<td>32% ± 44%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>v&lt;sub&gt;p&lt;/sub&gt; (%)</td>
<td>3.4% ± 75%</td>
<td>8.4% ± 78%</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Table 2: IVIM-derived diffusion coefficients (D) and perfusion fractions (f) excluding b-value of 750 (s/mm²), and K<sup>trans</sup>, v<sub>e</sub> and v<sub>p</sub> from DCE-MRI are tabulated for normal and
tumor tissues, with all measures expressed as mean ± coefficient of variation (%). The separation between normal and tumor tissues for each parameter is characterized by the p-values from Student’s t-test.
Figure 1: Simulation of diffusion signal attenuation. Mono-exponential diffusion decay without any perfusion contributions is represented by a straight-line (in dashes and dots) in a semi-log graph, with the slope indicating the diffusion coefficient ($D = 1.0 \times 10^{-3}$ mm$^2$/s). IVIM-based bi-exponential diffusion decay (contributed by perfusion with $f = 20\%$, $D^* = 20 \times 10^{-3}$ mm$^2$/s) is shown as a solid line with circles indicating the 5 b-values used in this study. Based on the mono-exponential model using only 4 b-values excluding zero, the fitted straight-line (in dashes) is extrapolated to intersect with the y-axis (y-intercept), leading to an approximate perfusion fraction ($f$) of 20\%.
Figure 2: On a DW-MRfI image (a), two regions of interest (ROIs) are defined in tumor (in red) and normal tissues (in green), respectively; on a semi-log graph (b), the curve-fitting line (solid red) for tumor ROI has smaller slope (D) and larger y-intercept (f) than that (dashed blue) for normal ROI.
Figure 3: Bivariate scatter plots of diffusion coefficients (D) vs. perfusion fractions (f) with different b-values (see Table 1) in tumor (filled red circle) and normal (filled blue triangle) ROIs, respectively. The error ellipses representing 95% confidence level are to highlight the separation of the parameter pairs (D and f) in tumor and normal ROIs.
Figure 4: Scatter plot matrix for diffusion coefficients (D) and perfusion fractions (f) obtained without the b-value of 750 s/mm² (Group 3 in Table 1), and $K_{\text{trans}}$, $v_c$ and $v_p$ in normal (filled blue triangle) and tumor (filled red circle) tissues. Correlations among different pairs of parameters are indicated by the Pearson’s coefficients (r) inserted in each scatter plot.
Figure 5: T2W image (a) with the same location used in DWI in Figure 2, perfusion fraction $f$ (b) and $K^{\text{trans}}$ (c) maps. The lesion is shown by hypo-intensity in T2W and hyper-intensities in both $f$ and $K^{\text{trans}}$ maps in the same lower right peripheral zone area (white arrows).