Dynamic contrast-enhanced magnetic resonance imaging, diffusion kurtosis imaging, and intravoxel incoherent motion diffusion-weighted imaging: MRI functional parameters in the assessment of pancreatic cancer

Vincenza Granata1; Roberta Fusco1; Mario Sansone2; Roberto Grassi1; Francesca Maio1; Raffaele Palaia1; Fabiana Totangelo5; Gerardo Botti5; Robert Grimm7; Steven Curley6; Francesco Izzo4; Antonella Petrillo1

1 Radiology Unit, Istituto Nazionale Tumori IRCCS “Fondazione G. Pascale”, Naples, Italy
2 Department of Information Technology and Electrical Engineering (DIETI), Naples, Italy
3 Radiology Unit, Second University of Naples, Italy
4 Hepatobiliary Surgical Oncology Unit, Istituto Nazionale Tumori IRCCS “Fondazione G. Pascale”, Naples, Italy
5 Diagnostic Pathology Unit, Istituto Nazionale Tumori IRCCS “Fondazione G. Pascale”, Naples, Italy
6 Department of Surgery, Baylor College of Medicine, Houston, TX, USA
7 Siemens Healthineers, Erlangen, Germany

Abstract

Purpose
To evaluate the diagnostic potential of perfusion parameters derived from dynamic contrast-enhanced MR imaging (DCE-MRI), diffusion kurtosis imaging (DKI), and parameters derived from the intravoxel incoherent motion model (IVIM)-based diffusion-weighted imaging (DWI) in differentiating between pancreatic tumors and normal pancreatic parenchyma.

Methods
We analyzed 24 patients with a histopathological pancreatic tumor diagnosis (median age: 71 years) and 24 patients without pancreatic lesions (median age: 56 years). For each voxel, DCE-MRI, IVIM, and DKI parameters were extracted. Accuracy was assessed using a non-parametric test and a receiver operating characteristic (ROC) curve.

Results
Based on a Kruskal-Wallis test, statistically significant differences were observed in the median values among the groups for the DKI mean diffusivity (MD), IVIM perfusion fraction (fp), and IVIM diffusion coefficient (Dt). In distinguishing between normal pancreatic parenchyma and pancreatic tumors, MD had an accuracy of 78%.

Conclusions
IVIM and DKI-derived parameters, as well as some of the DCE-MRI semi-quantitative parameters could be helpful in the differentiation of normal pancreatic parenchyma and pancreatic tumors.
Introduction

Pancreatic adenocarcinomas (PDACs) account for 90% of cancers of the pancreas and are the fourth most common cause of cancer-related death in the United States. In contrast to the steady improvement in survival for most cancers, advances in the field of pancreatic cancer have been slow. The five-year relative survival rate is currently just 8%. This low rate is partly because more than half of all cases are diagnosed at a distant stage, for which the five-year survival rate is 3% [1].

Despite significant technical advances in imaging, such as multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI), the correct diagnosis of solid pancreatic lesions remains challenging. This is related to the overlapping imaging features with benign lesions [2]. Yet proper detection and characterization of pancreatic lesions is essential, since therapeutic approaches and the associated prognoses are considerably different, depending on the tumor type and grade [3]. Reliable, accurate imaging is critical for proper tumor staging: in fact, pancreatic adenocarcinoma infiltrates lymphatic vessels early and local infiltrative disease can be manifest as subtle infiltration of peripancreatic tissue. This local invasion can result in the true extent and stage of the tumor to be underestimated and can be a cause of aborted surgical resection if not identified preoperatively [4]. The best hope for patients is in earlier detection of pancreatic adenocarcinomas. Thus, a noninvasive imaging modality that provides higher tumor conspicuity would be invaluable in improving clinical outcomes [5, 6]. How to analyze organ-specific vascularity to differentiate between malignant and benign pancreatic lesions remains an unsolved problem. Quantitative analysis of enhancement patterns and perfusion parameters using dynamic contrast-enhanced MR imaging (DCE-MRI) has been shown to be both objective and helpful in the evaluation of pancreatic lesions [7, 8]. In recent years, we have seen unprecedented use of abdominal MR imaging in the evaluation of pancreatic lesions, with diffusion-weighted imaging (DWI) attracting much attention as a tool for detecting malignancies [9–12]. DWI can provide additional information on focal pancreatic lesions by demonstrating more restricted diffusion in solid malignant tumors than in benign inflammatory or cystic lesions. This can be indicated by a decreased apparent diffusion coefficient (ADC) [13–16]. However, the diffusion-weighted signal and ADC values may be influenced not only by molecular diffusion but also by microcirculation or blood perfusion, and ADC values may therefore be contaminated by perfusion effects. This limits the reliability of ADC in characterizing pancreatic lesions [17, 18]. Microcirculation or perfusion effects can be distinguished from true tissue diffusion by using sufficient b-value sampling and a bi-exponential curve fit analysis with the intravoxel incoherent motion (IVIM) model [17–21].

Previous studies on IVIM in the pancreas have demonstrated that the reduced ADC in PDACs can be attributed to a difference in perfusion fraction (fp), which is reduced in PDACs [20], and that fp is a better DW imaging-derived parameter for differentiating mass-forming pancreatitis and PDACs than ADC values [21]. To date, however, there has only been a small number of studies which have explored the value of IVIM in differentiating between malignant pancreatic tumors and benign lesions. Also, the conventional DWI model is based on the assumption that water diffusion within a voxel has a single component and exhibits Gaussian behavior where water molecules freely diffuse [18, 19]. However, due to the presence of microstructures (i.e., two tissue types or components within one voxel, organelles, and cell membranes), random motion or diffusion of thermally agitated water molecules within biological tissue exhibits non-Gaussian behavior [22]. In 2005, Jensen and colleagues proposed a non-Gaussian diffusion model called diffusion kurtosis imaging (DKI) [22]. This model includes the kurtosis coefficient (K), which measures the deviation of tissue diffusion from a Gaussian model, and the diffusion coefficient (D) with the non-Gaussian bias correction. DKI performed better than conventional ADC in tumor detection and staging [23–29].

The purpose of this study is to evaluate the diagnostic potential of perfusion parameters obtained by DCE-MRI, DKI and IVIM-derived parameters in DWI for the differentiation of pancreatic tumors and normal pancreatic parenchyma.

Materials and methods

Study population
The Scientific Institutional Review Board at the Istituto Nazionale Tumori approved this retrospective study, and the required informed consent was obtained for each patient. We conducted a search of the Institute’s surgical database from January 2011 to October 2017 and selected 42 patients with pancreatic cancer who had undergone surgical resection. The inclusion criteria for the study population were as follows:

A. Patients who had pathologically proven pancreatic cancer;
B. Patients who had undergone both DCE-MRI and DWI;
C. Patients who had an interval of less than one month between imaging and pathologic diagnosis;
D. Availability of diagnostic-quality pictures of the cut sections of the resected specimens in patients who had undergone surgical resection for the matching of imaging and pathology findings. The exclusion criteria were as follows:

1. Conflict between the imaging-based diagnosis and the pathologically confirmed diagnosis;
2. Limitations of pathologic imaging correlation owing to poor image quality;
3. No available DCE-MRI and DWI.

Based on these criteria the study group consisted of 24 patients (14 men and 10 women with a median age of 71 years; age range: 53–85 years). We also conducted a search of the Institute’s radiological database during the study period and selected a control group of patients without pancreatic lesions that had undergone DCE-MRI and DWI upper abdomen studies to reduce spectrum bias. A total of 24 patients (13 men, 11 women with a median age of 56 years; age range: 33–78 years) who fitted these criteria were enrolled for the study.

MR protocol
The MR protocol consisted of morphological and functional imaging including DCE-MRI and DWI sequences. Imaging was performed with a 1.5T scanner (MAGNETOM Symphony, Siemens Healthcare, Erlangen, Germany) equipped with a phased-array body coil. Patients were placed in a supine, head-first position.

A morphological pre-contrast axial T2-weighted (T2w) 2D half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence was performed with and without fat suppression. The acquisition parameters were: TR/TE = 1500/90 ms, slice thickness = 5 mm, gap between slice = 0 mm, flip angle = 180°, matrix = 320 x 320, field of view (FOV) = 380 x 380 mm². Morphological pre-contrast axial T1-weighted (T1w) fast low angle shot (FLASH) 2D in- and out-of-phase images were obtained with the following acquisition parameters: TR/TE = 160/4.87 ms, slice thickness = 5 mm, gap between slice = 0 mm, flip angle = 70°, matrix = 192 x 256, FOV = 285 x 380 mm². Morphological pre-contrast axial T1w fat-suppressed FLASH 2D out-of-phase imaging was completed with the following acquisition parameters: TR/TE = 178/2.3 ms, slice thickness = 3 mm, gap between slice = 0 mm, flip angle = 80°, matrix = 416 x 512, FOV = 325 x 400 mm². Morphological post-contrast axial and coronal fat-suppressed T1w volumetric interpolated breath-hold examination (VIBE) images were recorded with the following acquisition parameters: TR/TE = 4.89/2.38 ms, slice thickness = 3 mm, gap between slice = 0 mm, flip angle = 10°, matrix = 320 x 260, FOV = 325 x 400 mm².

A free breathing axial single-shot echoplanar DWI pulse sequence was performed with the parameters: TR/TE = 7500/91 ms, slice thickness = 3 mm, flip angle = 90°, matrix = 192 x 192, FOV = 340 x 340 mm²; tri-directional diffusion gradients with b-values of 0, 50, 100, 150, 400, and 800 s/mm².

As regards the DCE-MRI imaging, we obtained one sequence before and 120 sequences (with no delay) after intravenous injection of 2 mL/kg of a positive, gadolinium-based paramagnetic contrast medium (Gadobutrol Gd-DTPA, Bayer Pharma AG, Berlin, Germany). The contrast medium was injected using a Spectris Solaris® EP MR pump (MEDRAD Inc., Indianola, PA), with a flow rate of 2 mL/s, followed by a 10 mL saline flush at the same rate. DCE-MRI T1w time-resolved angiography with stochastic trajectories (TWIST) 3D axial images were acquired in order to increase temporal resolution. Acquisition parameters were: TR/TE = 3.01/1.09 ms, flip angle = 25°, matrix = 256 x 256, slice thickness = 2 mm, gap = 0, FOV = 300 x 300 mm²; temporal resolution = 3 seconds, pA: 0.20, pB: 0.20.

MR image analysis
Regions of interest (ROIs) were manually drawn by two expert radiologists in consensus, while simultaneously avoiding encircling any distortion artefacts. One radiologist with over 20 years of clinical experience and one with 8 years of clinical experience in interpreting abdominal MR imaging studies drew ROIs on DCE images with virtual fat suppression obtained by subtracting the pre-contrast from the post-contrast image and on the DWI image with the highest b-value. For patients with pancreatic cancer, the tumor was contoured slice by slice to obtain the neoplastic volume of interest. For patients without pancreatic cancer, we selected 4 regions of interest in the pancreas parenchyma (head, neck, body, and tail) to obtain the median value of pancreatic parenchyma tissue.

Features from DCE-MRI and DWI data were computed pixel by pixel to obtain the median value of the ROIs.

DCE-MRI features
For each voxel, 8 TIC shape descriptors were computed using an approach previously reported in [30]: maximum signal difference (MSD), the time to peak (TTP), the WI slope (WIS), the WO slope (WOS), the WI intercept (WII), the WO intercept (WOI), the WOS/WIS ratio, and the WOI/WII ratio.

DCE-MRI parameters were obtained using in-house prototype software developed within MATLAB R2007a (The MathWorks Inc., Natick, MA, USA)1.

1 The information shown herein refers to products of 3rd party manufacturers and thus are in their regulatory responsibility. Please contact the 3rd party manufacturer for further information.
**DWI features**

For each voxel, 6 features were extracted from DWI data using the mono-exponential model, the diffusion kurtosis imaging model, and the intra-voxel incoherent motion model [17, 18; 31–39].

DWI signal decay is most commonly analyzed using the monoexponential model [17, 18]:

Equation 1

\[
ADC = \frac{\ln \left( \frac{S_0}{S_b} \right)}{b}
\]

where \( S_b \) is the MRI signal intensity with diffusion weighting \( b \), \( S_0 \) is the non-diffusion-weighted signal intensity, and ADC is the apparent diffusion coefficient.

For a voxel with a large vascular fraction, the MRI data decay can deviate from a monoexponential form, in particular showing a rapid decay in the range of low \( b \)-values generated by the IVIM effect [17, 18, 33]. Thus, in addition to the monoexponential model, a biexponential model was used to estimate the IVIM-related parameters of pseudo-diffusivity (\( D_p \) indicated also with \( D^* \)), perfusion fraction (\( fp \)), and tissue diffusivity (\( Dt \)):

Equation 2

\[
\frac{S_b}{S_0} = fp \cdot \exp (-b \cdot D_p) + (1 - fp) \cdot \exp (-b \cdot D_t)
\]

Moreover, diffusion kurtosis imaging was included in the analysis in order to obtain the final fitted images (mean of diffusion coefficient (MD) and mean of diffusional kurtosis (MK)).

Multi-b DW images were obtained through voxel-by-voxel fitting using the diffusion kurtosis signal decay equation (3) by applying a two-variable linear least squares algorithm as used in a previous study [22]:

Equation 3

\[
S_b(b) = S_0 \exp \left( -b \cdot D + \frac{1}{6} b^2 \cdot D^2 \cdot K \right)
\]

In this equation, \( D \) is a corrected diffusion coefficient; and \( K \) is the excess diffusion kurtosis coefficient. \( K \) describes the degree of deviation of molecular motion from the perfect Gaussian distribution. When \( K \) is equal to 0, equation (3) evolves into a conventional monoexponential equation (1):

The difference between \( D \) and ADC is that \( D \) is a corrected form of ADC for use in non-Gaussian circumstances.

The parameters of conventional DWI (ADC), IVIM (\( fp \), \( Dt \), and \( Dp \)), and DKI (MK and MD) were obtained from the multi-b DWI data with all measured \( b \) values using the prototype post-processing software Body Diffusion Toolbox\(^2\) (Siemens Healthcare, Erlangen, Germany).

**Statistical analysis**

Continuous variables were presented as the median ± standard deviation (SD). All parameters that had been subdivided into the three groups were compared using the nonparametric Kruskal-Wallis test. Receiver operating characteristic (ROC) curves were also calculated to determine each parameter value with the aim of assessing the ability to differentiate between pancreatic tumors and pancreatic parenchyma tissue. The optimal cut-off values (obtained according to the maximal Youden index = sensitivity + specificity -1), the corresponding sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated.

A \( P \) value of < 0.05 was considered statistically significant. The Statistics Toolbox produced by MATLAB R2007a (The MathWorks Inc., Natick, MA, USA)\(^1\) was used to perform statistical analysis.

**Results**

Table 1 shows the median value and standard deviation (SD) value for pancreatic tumor and pancreatic parenchyma tissue.

Based on a Kruskal-Wallis test, statistically significant differences were observed in median values among the groups for MD, \( fp \), and \( Dt \), while there were no significant differences among these groups for dynamic parameters. Table 2 shows the diagnostic accuracy of MR-extracted parameters in distinguishing between normal pancreatic parenchyma and pancreatic tumors. WII, MD, \( fp \), and \( Dp \) showed an accuracy of ≥ 68%. MD had the best results with an accuracy of 78%.

**Discussion**

The purpose of this study is to evaluate the diagnostic potential of perfusion parameters obtained by DCE-MRI, DKI, and IVIM-derived parameters in DWI for the differentiation of pancreatic tumors and normal pancreatic parenchyma.

---

1. The information shown herein refers to products of 3rd party manufacturers and thus are in their regulatory responsibility. Please contact the 3rd party manufacturer for further information.
2. WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.
The accuracy of DCE-MRI in the assessment of pancreatic cancer remains unclear. One reason for this is that in pancreatic ductal adenocarcinoma the microvascular component is poorly represented. This can probably be explained by the functional impairment of vessels, often observed in tumors, as they are characteristically leaky, fragile, and incompletely formed, and also by the presence of a prominent stromal matrix embedding the vessels. Moreover, activated pancreatic stellate cells produce increasing fibrous stroma in the central areas of the tumor, which compresses the blood vessels, leading to changes in vascularity and perfusion [7, 8]. Several studies have evaluated the feasibility of DCE-MRI for the characterization of solid pancreatic diseases [7, 8, 11].

Kim et al. [7] evaluated 24 patients with pancreatic cancers, eight with pancreatic neuroendocrine tumors (PNETs), three with chronic pancreatitis, and 10 with a normal pancreas. For the different groups, they assessed $K_{\text{trans}}$, $k_{\text{ep}}$ (flow of contrast agent to the plasma from the EES), and the initial area under the concentration curve (iAUC). They showed that $K_{\text{trans}}$, $k_{\text{ep}}$, and iAUC values in patients with pancreatic cancer ($0.042 \text{ min}^{-1} \pm 0.023$, $0.761 \text{ min}^{-1} \pm 0.529$, and $2.841 \text{ mmol/sec} \pm 1.811$, respectively) were significantly lower than in patients with a normal pancreas ($0.387 \text{ min}^{-1} \pm 0.176$, $6.376 \text{ min}^{-1} \pm 2.529$, and $7.156 \text{ mmol/sec} \pm 3.414$, respectively) ($P < 0.05$ for all). In addition, the $k_{\text{ep}}$ values of PNETs and normal pancreases also differed ($P < 0.0001$), and $K_{\text{trans}}$, $k_{\text{ep}}$, and iAUC values of pancreatic cancers and PNETs differed significantly ($P < 0.0001$, $P = .038$, and $P < 0.0001$, respectively).

Bali et al. [8] evaluated 28 patients with surgically resectable focal pancreatic lesions. DCE-MRI quantitative parameters derived from one-compartment ($K_{\text{trans}}$ and distribution fraction [$f$]) and two-compartment ($K_{\text{trans}}$ and tissue volume fraction occupied by vascular space [$v_p$]) pharmacokinetic models were correlated with fibrosis content and microvascular density (MVD) counts in focal lesions and nontumoral tissue. The pharmacokinetic parameters were compared with tumoral and nontumoral tissue. The study also assessed the diagnostic performance of DCE-MRI fibrosis detection. It showed that $K_{\text{trans}}$ values were significantly lower in primary malignant tumors compared with benign lesions ($P = .023$) and nontumoral pancreatic tissue downstream ($P < .001$) and upstream ($P = .006$); $f$ and $v_p$ were also significantly higher in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal pancreatic parenchyma tissue</th>
<th>Pancreatic cancer</th>
<th>$P$ value from Kruskal-Wallis test</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSD [A.U.]</td>
<td>39.20</td>
<td>42.70</td>
<td>0.71</td>
</tr>
<tr>
<td>TTP [A.U.]</td>
<td>36.25</td>
<td>25.00</td>
<td>0.97</td>
</tr>
<tr>
<td>WOS [A.U.]</td>
<td>-0.42</td>
<td>-1.10</td>
<td>0.99</td>
</tr>
<tr>
<td>WOI [A.U.]</td>
<td>60.27</td>
<td>38.43</td>
<td>0.10</td>
</tr>
<tr>
<td>WIS [A.U.]</td>
<td>3.75</td>
<td>20.91</td>
<td>0.57</td>
</tr>
<tr>
<td>WII [A.U.]</td>
<td>35.95</td>
<td>15.47</td>
<td>0.15</td>
</tr>
<tr>
<td>WOS_WIS [A.U.]</td>
<td>-0.03</td>
<td>-0.01</td>
<td>0.82</td>
</tr>
<tr>
<td>WOI_WII [A.U.]</td>
<td>1.04</td>
<td>-0.94</td>
<td>0.21</td>
</tr>
<tr>
<td>ADC [mm$^2$/s x $10^{-6}$]</td>
<td>1397.50</td>
<td>1196.50</td>
<td>0.17</td>
</tr>
<tr>
<td>MK [x $10^{-3}$]</td>
<td>1193.85</td>
<td>1399.30</td>
<td>0.33</td>
</tr>
<tr>
<td>MD [mm$^2$/s x $10^{-4}$]</td>
<td>2843.20</td>
<td>1849.50</td>
<td>0.00</td>
</tr>
<tr>
<td>fp [% x $10^{-3}$]</td>
<td>225.00</td>
<td>144.20</td>
<td>0.00</td>
</tr>
<tr>
<td>Dt [mm$^2$/s x $10^{-4}$]</td>
<td>1263.00</td>
<td>1018.60</td>
<td>0.75</td>
</tr>
<tr>
<td>Dp [mm$^2$/s x $10^{-4}$]</td>
<td>135.60</td>
<td>112.80</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 1: Median and standard deviation (SD) value for each MR-extracted parameter in two groups: normal pancreatic parenchyma and pancreatic tumor.
primary malignant tumors compared with nontumoral pancreatic tissue downstream (P = .012 and .018, respectively). Fibrosis was negatively correlated with $K_{\text{trans}}$ and positively with $f$ and $v_p$. MVD was positively correlated with $f$ and $v_p$. Sensitively and specificity in detecting fibrosis were 65% (24 of 37) and 83% (10 of 12) for $K_{\text{trans}}$ one-compartment (cut-off value: 0.35 min$^{-1}$) and 76% (28 of 37) and 83% (10 of 12) for $K_{\text{trans}}$ two-compartment (cut-off value: 0.29 min$^{-1}$), respectively.

We evaluated semi-quantitative descriptors of the contrast agent time course, such as MSD, TTP, WIS, WOS, WII, WOI, the WOS/WIS ratio, and the WOI/WII ratio. Our findings showed that there were no differences in the dynamic parameters among the groups with the exception of a statistically not significant difference between WIS and $K_{\text{trans}}$ [30].

Diffusion parameters can be assessed using DWI [39]. The IVIM model provides a theoretical framework that allows for the separate extraction of a flowing blood volume fraction (perfusion) and microstructural information from DWI. Thus, IVIM is gaining interest in oncological applications of DWI as it allows a combined quantification of a flowing blood volume fraction, a perfusion-free diffusion coefficient (microstructural parameter), and a pseudodiffusion coefficient. This is associated with the blood movement in the capillary network without a contrast agent [36, 37].

Several studies have reported that IVIM is a promising tool in identifying pancreatic cancer, since IVIM-derived parameters are useful in the characterization of solid focal lesions [22, 40, 41].

Kang et al. [40] evaluated the diagnostic performance of ADC and IVIM-derived parameters for distinguishing between common pancreatic tumors, chronic pancreatitis, and normal pancreases and for the characterization of the malignancy potential of intraductal papillary mucinous neoplasms. Ninety-three patients with surgically resected pancreatic tumors (39 PDACs, 17 NETs, and 37 IPMNs), seven patients with chronic pancreatitis, and 26 patients with a normal pancreas were included in their study. The ADC, slow component of diffusion ($D_{\text{slow}}$), incoherent microcirculation ($D_{\text{fast}}$), and perfusion fraction ($f_p$) were calculated. They showed that the $D_{\text{fast}}$ and $f_p$ values of PDACs were significantly lower than those of normal

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC</th>
<th>SEN</th>
<th>SPEC</th>
<th>PPV</th>
<th>NPV</th>
<th>ACC</th>
<th>CUT-OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSD</td>
<td>0.47</td>
<td>0.14</td>
<td>0.96</td>
<td>0.75</td>
<td>0.54</td>
<td>0.56</td>
<td>92.21</td>
</tr>
<tr>
<td>TTP</td>
<td>0.54</td>
<td>0.59</td>
<td>0.61</td>
<td>0.59</td>
<td>0.61</td>
<td>0.60</td>
<td>31.02</td>
</tr>
<tr>
<td>WOS</td>
<td>0.51</td>
<td>0.64</td>
<td>0.48</td>
<td>0.54</td>
<td>0.58</td>
<td>0.56</td>
<td>-1.54</td>
</tr>
<tr>
<td>WOI</td>
<td>0.68</td>
<td>0.86</td>
<td>0.48</td>
<td>0.61</td>
<td>0.79</td>
<td>0.67</td>
<td>30.87</td>
</tr>
<tr>
<td>WIS</td>
<td>0.36</td>
<td>1.00</td>
<td>0.04</td>
<td>0.50</td>
<td>1.00</td>
<td>0.51</td>
<td>-44.80</td>
</tr>
<tr>
<td>WII</td>
<td>0.67</td>
<td>0.55</td>
<td>0.91</td>
<td>0.86</td>
<td>0.68</td>
<td>0.73</td>
<td>33.49</td>
</tr>
<tr>
<td>WOS_WIS</td>
<td>0.47</td>
<td>0.36</td>
<td>0.78</td>
<td>0.62</td>
<td>0.56</td>
<td>0.58</td>
<td>0.17</td>
</tr>
<tr>
<td>WOI_WII</td>
<td>0.59</td>
<td>0.77</td>
<td>0.52</td>
<td>0.61</td>
<td>0.71</td>
<td>0.64</td>
<td>-0.92</td>
</tr>
<tr>
<td>ADC</td>
<td>0.61</td>
<td>0.55</td>
<td>0.78</td>
<td>0.71</td>
<td>0.64</td>
<td>0.67</td>
<td>1330.99</td>
</tr>
<tr>
<td>MK</td>
<td>0.42</td>
<td>0.82</td>
<td>0.30</td>
<td>0.53</td>
<td>0.64</td>
<td>0.56</td>
<td>997.00</td>
</tr>
<tr>
<td>MD</td>
<td>0.83</td>
<td>0.86</td>
<td>0.70</td>
<td>0.73</td>
<td>0.84</td>
<td>0.78</td>
<td>2168.48</td>
</tr>
<tr>
<td>$f_p$</td>
<td>0.79</td>
<td>0.82</td>
<td>0.70</td>
<td>0.72</td>
<td>0.80</td>
<td>0.76</td>
<td>167.81</td>
</tr>
<tr>
<td>$D_f$</td>
<td>0.59</td>
<td>0.55</td>
<td>0.74</td>
<td>0.67</td>
<td>0.63</td>
<td>0.64</td>
<td>1197.58</td>
</tr>
<tr>
<td>$D_p$</td>
<td>0.67</td>
<td>1.00</td>
<td>0.39</td>
<td>0.61</td>
<td>1.00</td>
<td>0.69</td>
<td>68.91</td>
</tr>
</tbody>
</table>

Table 2: Diagnostic accuracy of MR-extracted parameters in distinguishing between normal pancreatic parenchyma and pancreatic tumors. Parameters with high accuracy and the area under the curve were underlined in bold.

Note: AUC = area under curve; SEN = sensitivity; SPEC = specificity; NPV = negative predictive value; ACC = accuracy
pancreases, chronic pancreatitis, and NETs (all $P < .05$). To differentiate between PDACs and NETs, $f_p$ and $D_{fast}$ showed a significant difference ($P < .0001$ for both) and were more useful parameters than ADC and $D_{slow}$ in ROC analysis (all $P < .05$). Malignant IPMNs had significantly lower ADC and $D_{slow}$ values and higher $D_{fast}$ and $f_p$ values compared to benign IPMNs (all $P < .05$). In ROC analysis, $f_p$ showed the highest area under the ROC curve for distinguishing malignant from benign IPMNs [40]. They concluded that perfusion might be a more important factor than diffusion in differentiating between PDAC, normal pancreases, chronic prostatitis, and NETs. In addition, $f_p$ showed the highest area under the ROC curve for differentiating between malignant and benign IPMNs among ADC and IVIM-derived parameters. We therefore believe that IVIM DWI is a valuable tool for characterizing the most common solid or cystic malignant tumors in the pancreas, owing to its ability to provide information not only on cellularity ($D_{slow}$) but also on perfusion ($D_{fast}$ and $f_p$) [40].

Klauss et al. [41] investigated the correlation between parameters derived from the IVIM model and histologically determined microvasculature in pancreatic ductal adenocarcinomas (PDACs) and pancreatic neuroendocrine tumors (PNETs). In their study, intravoxel incoherent motion parameters were extracted from two types of volume of interest (VOIs), one VOI that encompassed the total tumor volume (TTV) and another VOI that corresponded to the histological regional tumor location.

Figure 1: Boxplot of WIS, MD, $f_p$, and $D_p$ parameters.
(RTV). They showed that blood volume fraction fp was significantly lower in PDACs than in PNETs (9.9% ± 5.4% vs. 15.5% ± 5.2%; P < 0.0001) and the diffusion coefficient Dt was significantly higher (1.2 ± 0.18 x 10⁻³ vs 1.03 ± 0.15 x 10⁻³ mm²/s; P = 0.001) in PDACs. There was no significant difference in the pseudodiffusion coefficient Dp (44.9 ± 52.9 x 10⁻³ vs. 53.8 ± 51.2 x 10⁻³ mm²/s). Microvessel density was significantly lower in PDACs (36.8 ± 25.9/mm² vs. 80.0 ± 26.1/mm²; P = 0.0005) than in PNETs. When derived from the RTV, the flowing blood volume fraction fp and MVD of PDACs and PNETs showed excellent correlation (r = 0.85). The correlation using the TTV was moderate (0.64). The fp (RTV and TTV) and microvessel area showed moderate correlation (r = 0.54/0.47).

In our study we evaluated the ADC and the IVIM-related parameters (Dp, fp, and Dt), the kurtosis coefficient that signifies the deviation of tissue diffusion from a Gaussian model, and the diffusion coefficient with the correction of non-Gaussian bias by DKI. Recently, DKI has been used to assess therapy response in different kinds of tumors [42–44].

To the best of our knowledge there is no recent study analyzing perfusion and diffusion features (ADC, IVIM, and DKI-derived parameters) to differentiate between pancreas cancer tissue and normal tissue. According to our findings, based on a Kruskal-Wallis test, there were statistically significant differences in the median values among the groups for MD, fp, and Dt. In distinguishing between normal pancreatic parenchyma and pancreatic tumors, MD had the best results with an accuracy of 78%.

In our study, the perfusion-related factors of PDACs (fp and Dp) and the MD of diffusion kurtosis imaging differed from those seen in patients with normal pancreatic parenchyma and showed better diagnostic performance than ADC. Although the differential diagnosis of PDACs and normal pancreatic parenchyma is usually easily assigned, there can be enough overlap in imaging features to cause occasional problems with differentiation. Therefore, the significantly different perfusion-related factors of PDACs and normal pancreatic parenchyma could help clinicians make the most accurate diagnosis. Moreover, these parameters should also help in assessing response to systemic and pancreatic-directed therapies by identifying responders and non-responders as quickly as possible.

**Conclusion**

An accurate diagnosis of pancreatic cancer is essential to facilitate accurate staging which, in turn, enables proper therapeutic management. Parameters derived from IVIM and diffusion kurtosis, as well as semi-quantitative parameters from DCE-MRI could be helpful in distinguishing between normal pancreatic parenchyma and pancreatic tumors. The parameters that allow the best classification of normal pancreatic parenchyma tissue and pancreatic tumors are MSD, WOI_WII, MD of diffusion kurtosis imaging, and fp.

**References**


Contact
Roberta Fusco
Department of Radiology
"Istituto Nazionale Tumori - IRCCS Fondazione G. Pascale"
Via Mariano Semmola
80131 Naples
Italy Tel.: +3908 1590 3738
r.fusco@institutotumori.na.it

siemens.com/magnetom-world