Intravoxel Incoherent Motion Diffusion-weighted MR Imaging for Characterization of Focal Pancreatic Lesions

Koung Mi Kang, MD
Jeong Min Lee, MD
Jeong Hee Yoon, MD
Berthold Kiefer, PhD
Joon Koo Han, MD
Byung Ihn Choi, MD

Purpose:
To evaluate the diagnostic potential of apparent diffusion coefficient (ADC) and intravoxel incoherent motion (IVIM)--derived parameters for differentiation of common pancreatic tumors, chronic pancreatitis, and normal pancreas and for characterization of the malignancy potential of intraductal papillary mucinous neoplasms (IPMNs).

Materials and Methods:
The institutional review board approved this retrospective study, and informed consent was waived. Ninety-three consecutive patients with surgically resected and pathologically confirmed pancreatic tumors (39 pancreatic adenocarcinomas [PACs], 17 neuroendocrine tumors [NETs], and 37 IPMNs), seven patients with chronic pancreatitis, and 26 patients with a normal pancreas were included in this study. All patients underwent pancreatic 3.0-T magnetic resonance imaging, including IVIM diffusion-weighted imaging with 10 $b$ values used (from 0 to 1000 sec/mm$^2$). The ADC, slow component of diffusion ($D_{\text{slow}}$), incoherent microcirculation ($D_{\text{fast}}$), and perfusion fraction ($f$) were calculated. Steel-Dwass and Mann-Whitney U tests were used for comparison. The diagnostic performance of the parameters was evaluated by using receiver operating characteristic (ROC) analysis with Bonferroni correction.

Results:
Among ADC- and IVIM-derived parameters, $D_{\text{fast}}$ and $f$ values of PACs were significantly lower than those of normal pancreas, chronic pancreatitis, and NETs (all $P < .05$ in post hoc analyses). For differentiation of PACs from NETs, $f$ and $D_{\text{fast}}$ showed a significant difference ($P < .0001$ for both) and were more useful parameters than ADC and $D_{\text{slow}}$ in ROC analysis (all $P < .05$). Malignant IPMNs had significantly lower ADC and $D_{\text{slow}}$ values and higher $D_{\text{fast}}$ and $f$ values when compared with benign IPMNs (all $P < .05$). In ROC analysis, $f$ showed the highest area under the ROC curve value for distinguishing malignant from benign IPMNs.

Conclusion:
IVIM-derived perfusion-related parameters could be helpful for the differentiation of common malignant tumors in the pancreas and for distinguishing malignant from benign IPMNs. $D_{\text{fast}}$ and $f$ were more valuable parameters in the differentiation of PACs from NETs than were ADC and $D_{\text{slow}}$.

© RSNA, 2013

Online supplemental material is available for this article.
With the increasingly widespread use of cross-sectional imaging for the evaluation of abdominal diseases, it has become more commonplace for radiologists to encounter small pancreatic tumors, including various solid tumors and cystic tumors (1–3). Among them, pancreatic adenocarcinomas (PACs) account for 90% of cancers of the pancreas and are the fourth most common cause of cancer-related death in the United States (4). Neuroendocrine tumors (NETs) are the second most common malignant neoplasm of the pancreas (5) and have been shown to be a common cause of gastrointestinal cancer–related mortality (6,7). In addition, intraductal papillary mucinous neoplasms (IPMNs) are the most common cystic neoplasm of the pancreas, which are thought to progress from benign adenomas to invasive cancer in a manner similar to colon polyps (8). However, despite great technical advances in imaging, such as multidetector computed tomography (CT) and magnetic resonance (MR) imaging, assigning the correct diagnosis of pancreatic neoplasms on the basis of those anatomic imaging tests still remains challenging, owing to overlapping imaging features (9). Considering that the therapeutic approaches for focal pancreatic lesions and the associated prognoses are considerably different, depending on the tumor type and grade (4), radiologic tests must offer high sensitivity for the early detection of pancreatic malignancies and high specificity for the appropriate choice of treatment.

Recently, abdominal MR imaging has been used more widely for the evaluation of pancreatic lesions than ever before, with diffusion-weighted (DW) imaging garnering much attention as a tool for the detection of abdominal malignancies in various organs, including the liver, pancreas, and kidney (10–13). Several previous studies have shown that DW imaging can provide additional information for focal pancreatic lesions by demonstrating more restricted diffusion in solid malignant tumors than in benign inflammatory or cystic lesions, which can be indicated by a decreased apparent diffusion coefficient (ADC) (14–17).

However, earlier studies have also demonstrated that the diffusion-weighted signal and ADC values can be influenced not only by molecular diffusion but also through microcirculation, or blood perfusion, and, therefore, ADC values containing perfusion effect may limit the reliability of ADC in characterizing pancreatic lesions (18,19). It has also been shown that microcirculation or perfusion effects can be distinguished from true tissue diffusion by using sufficient b value sampling and a biexponential curve fit analysis with the intravoxel incoherent motion (IVIM) model (18,20–23). In addition, previous studies on IVIM DW imaging in the pancreas have demonstrated that the reduced ADC in PACs can be attributed to a difference in perfusion fraction (f), which is also reduced in PACs (22), and that f is a better DW imaging–derived parameter for differentiating mass-forming pancreatitis and PACs than are ADC values (23). Until now, however, there have been only a few studies in which the value of IVIM DW imaging was explored for differentiation between malignant pancreatic tumors and benign lesions.

Thus, the purpose of this study was to evaluate the diagnostic potential of ADC- and IVIM-derived parameters for the differentiation of common pancreatic tumors, chronic pancreatitis (CP), and normal pancreas (NP) and for characterization of the malignancy potential of IPMNs.

### Materials and Methods

Our institutional review board approved the study protocol, and informed consent was waived. Technical support was

---

**Advances in Knowledge**

- Intravoxel incoherent motion (IVIM) imaging enables the separate assessment of perfusion- and diffusion-related parameters, of which perfusion-related parameters may be helpful for differentiating pancreatic adenocarcinomas (PACs) from normal pancreas, chronic pancreatitis, and neuroendocrine tumors (NETs) (all P < .05).

- Perfusion fraction (f) and incoherent microcirculation (Dslow) showed better diagnostic performance than the apparent diffusion coefficient (ADC) (P = .0001 and P = .0006, respectively) and the slow component of diffusion (P < .0001 and P < .0001, respectively) in distinguishing PACs from NETs.

- ADC- and IVIM-derived parameters were significantly different between malignant intraductal papillary mucinous neoplasms (IPMNs) and benign IPMNs (all P < .05).

**Implication for Patient Care**

- The IVIM-derived perfusion-related parameters Dslow and f may be helpful for the characterization of focal pancreatic lesions, potentially improving the care of patients with pancreatic tumors.
provided by a Siemens employee (B.K.) for IVIM DW imaging sequence modifications and implementation with our MR imaging devices. Authors not associated with Siemens maintained full control of the data at all times.

**Study Population**

After a review of our radiology database for the period of June 2010 to July 2012, we identified 882 patients suspected of having pancreatic or biliary diseases who underwent biliary-pancreatic-protocol MR examinations, including unenhanced MR imaging, MR cholangiopancreatography, IVIM DW imaging, and dynamic imaging. Among them, patients who did not have pathologic confirmation of their pancreatic lesion and patients with biliary obstruction due to stone or cancer were excluded from this study (n = 700). Fifty-six patients were additionally excluded for several reasons (Fig 1). Finally, 126 patients, including those with NP (n = 26), CP (n = 7), PAC (n = 39), NETs (n = 17), or IPMNs (n = 37; benign IPMNs, n = 22; malignant IPMNs, n = 15) were enrolled in our study (Table 1).

For the control group, the diagnosis of NP was assigned on the basis of a combination of no abnormal radiologic signs in the pancreas at MR imaging, no clinical features of pancreatic disease, and normal-range results from several laboratory studies, including amylase, lipase, and alkaline phosphatase. In addition, the NP group had no documented history of pancreatic disease. All patients in the CP group were known to have CP or were suspected of having CP on the basis of previous imaging studies, laboratory findings, and/or the results from endoscopic retrograde cholangiography or endoscopic ultrasound (US). In the pancreatic tumor group, the mean interval between MR examination and surgery was 10 days (range, 0–64 days). The pathologic diagnosis of PAC was assigned by means of surgical resection (n = 37) or percutaneous US-guided gun biopsy (n = 2). The pathologic diagnosis of NETs and IPMNs was confirmed by means of surgical resection in all patients.

Mean size of the pancreatic tumors was 3.3 cm ± 1.1 (range, 1.4–7.0 cm) for PAC, 3.4 cm ± 0.79 (range, 2.3–4.5 cm) for NETs, and 3.4 cm ± 1.1 (range, 2.5–7.0 cm) for IPMNs.

**MR Examination**

All patients underwent MR examination with 3-T MR imager (Magnetom Verio; Siemens Healthcare, Erlangen, Germany) by using a 32-channel phased-array coil. MR parameters of each sequence are summarized in Table 2. Unenhanced T2- and T1-weighted images were obtained by using the half-Fourier rapid acquisition with relaxation enhancement sequence and the dual-echo in- and opposed-phase fast low–angle shot, or FLASH, sequence, respectively. MR cholangiopancreatography images were obtained by using two techniques: (a) breath-hold single-section rapid acquisition with turbo spin echo and (b) respiratory-triggered multisection three-dimensional turbo spin echo. Dynamic images were obtained by using two techniques: (a) breath-hold single-section rapid acquisition with turbo spin echo and (b) respiratory-triggered multisection three-dimensional turbo spin echo. Dynamic images were obtained by using fat-suppressed three-dimensional FLASH sequences; volume interpolation with breath-hold examinations (or VIBE; Siemens Medical Solutions, Erlangen, Germany) was performed before and after administration of gadobutrol (Gadovist; Bayer Healthcare, Leverkusen, Germany) at a dose of 0.1 mmol/mL with an injection rate of 1 mL/
sec. Arterial phase images were obtained 8 seconds after the gadolinium-enhanced bolus was detected in the abdominal aorta. Acquisition of three-dimensional VIBE images for each phase was completed during a single breath hold at the end of expiration (18–20 seconds). Arterial, portal venous, and equilibrium-phase images were obtained at approximately 20–40 seconds, 45–65 seconds, and 3–5 minutes, respectively, after injection of the contrast agent.

**IVIM DW Imaging**

DW imaging was performed in addition to the routine MR imaging protocol for both the patient group and the control group. DW images were obtained prior to contrast material administration. Spectral saturation attenuated by inversion recovery was used for fat suppression. DW images were acquired by using the single-shot echo-planar imaging sequence in free breathing with parallel imaging, with an acceleration factor of two and $b$ values of 0, 25, 50, 75, 100, 150, 200, 500, 800, and 1000 sec/mm². Although a larger number of $b$ values would have provided more data support for the estimates of IVIM-derived parameters, this was not possible because of imaging time restrictions. Therefore, referencing the recommendations of Koh et al (21) and Lenke (24) that a minimum number of $b$ values used for IVIM DW imaging could be eight and 10, respectively, we used 10 $b$ values in total and six $b$ values lower than 200 sec/mm². Diffusion weighting was accomplished by using three orthogonal gradient directions. The ADC was obtained by using all $b$ values (0–1000 sec/mm²) fitted to the following equation: $S_b = S_0 \exp(-bD_{\text{ADC}})$, where $S_b$ is the signal intensity at a given $b$ value and $S_0$ is the signal intensity observed in the absence of a diffusion gradient.

**Image Analysis**

In the IVIM model, the relationship between signal variation and $b$ factors is expressed as (20):

$$S_b/S_0 = (1 - f)\exp(-bD_{\text{slow}}) + \{ f \cdot \exp[-b(D_{\text{fast}} + D_{\text{slow}})] \},$$

where $f$ is the volume fraction of the protons linked to the intravascular component, $D_{\text{slow}}$ is the slow component of diffusion, and $D_{\text{fast}}$ represents incoherent microcirculation. More specific details on IVIM DW imaging are provided in Appendix E1 (online).

Quantitative analysis of IVIM DW imaging in the patient group was performed by a radiologist (K.M.K, with 3 years of experience in biliary-pancreatic MR imaging interpretation) who was blinded to the pathology results. Conventional biliary-pancreatic MR images were used as the anatomic reference to identify the extent of a lesion. MR cholangiopancreatography was used to evaluate the anatomic relationship of the pancreatic duct and cystic mass in IPMNs. A freehand region of interest (ROI) was drawn on the enhancing solid portion of the solid pancreatic tumor on DW images and ADC maps to avoid vessels and necrosis. For IPMNs, a freehand ROI was drawn to encompass as much of the lesion as possible. All ROIs were directly co-localized on all parameter maps. For quantitative analysis of DW imaging in the control group, the same reviewer placed a freehand ROI that covered the largest area over the pancreas. To assess the reproducibility of measurements with IVIM DW imaging, the measurement of ADC and IVIM parameters was performed three times by the same reader at 2- and 4-week intervals, respectively.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DW</th>
<th>T2-weighted</th>
<th>T1-weighted Gradient-Echo*</th>
<th>Thick-Sub MRCP</th>
<th>3D MRCP</th>
<th>Fat-suppressed 3D T1-weighted Gradient-Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat suppression</td>
<td>SPAIR</td>
<td>SPAIR</td>
<td>None</td>
<td>SPAIR</td>
<td>SPAIR</td>
<td>SPAIR</td>
</tr>
<tr>
<td>Breath hold</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Trigger</td>
<td>Yes</td>
</tr>
<tr>
<td>Acquisition time (sec)</td>
<td>212</td>
<td>50</td>
<td>19</td>
<td>15</td>
<td>138</td>
<td>19</td>
</tr>
<tr>
<td>Repetition time (msec)/echo time (msec)</td>
<td>4500/52</td>
<td>962/93</td>
<td>3.4/1.2</td>
<td>2500/909</td>
<td>1590/710</td>
<td>3.38/1.23</td>
</tr>
<tr>
<td>Flip angle (degree)</td>
<td>NA</td>
<td>130</td>
<td>11</td>
<td>180</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td>Parallel imaging factor</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Field of view (mm)</td>
<td>$380 \times 380$</td>
<td>$380 \times 303$</td>
<td>$380 \times 303$</td>
<td>240</td>
<td>380</td>
<td>380</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>50</td>
<td>1.1</td>
<td>3</td>
</tr>
<tr>
<td>No. of sections acquired</td>
<td>25</td>
<td>25</td>
<td>56</td>
<td>6</td>
<td>88</td>
<td>56</td>
</tr>
<tr>
<td>No. of signals acquired</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bandwidth (Hertz per pixel)</td>
<td>2450</td>
<td>395</td>
<td>723</td>
<td>134</td>
<td>266</td>
<td>720</td>
</tr>
<tr>
<td>Matrix</td>
<td>$256 \times 205$</td>
<td>$384 \times 245$</td>
<td>$384 \times 250$</td>
<td>$256 \times 320$</td>
<td>$388 \times 384$</td>
<td>$307 \times 384$</td>
</tr>
<tr>
<td>Echo-planar imaging factor</td>
<td>136</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* In phase and opposed phase.

Note.—$b$ Values of 0, 25, 50, 75, 100, 150, 200, 500, 800, and 1000 sec/mm² were used for DW imaging. MRCP = MR cholangiopancreatography, NA = not applicable, SPAIR = spectral attenuated inversion recovery, 3D = three dimensional.
We used the median value of the measurements to define the measured parameter.

Statistical Analysis

Intraobserver reliability of the measurements was assessed by using the intraclass correlation coefficient, or ICC. Among the various guidelines for the interpretation of IGC, we have adapted a scale introduced in previous literature: ICC values of less than 0.40 indicate poor reproducibility, ICC values of 0.40–0.75 indicate fair to good reproducibility, and ICC values higher than 0.75 indicate excellent reproducibility (25). Differences in mean age and patient sex between the patient group and the control group were tested by using the independent-sample t test and the χ² test, respectively. The Shapiro-Wilk test was applied to the ADC- and IVIM-derived parameters for normality (P < .05 indicates nonnormal distribution). For the comparison of ADC, Dslow, Dfast, and f values among the NP, CP, PAC, NETs, and IPMNs, data were analyzed by using the Kruskal-Wallis test and Steel-Dwass test of post hoc nonparametric multiple comparison (26). The Mann-Whitney U test was used for the comparison of ADC, Dslow, Dfast, and f values between benign and malignant IPMNs. Multiple logistic regression was used to assess the parameters in terms of differentiating common pancreatic tumors, CP, and NP, and to characterize the malignancy potential of IPMNs. We then performed receiver operating characteristic (ROC) analysis to evaluate the diagnostic performance of the ADC- and IVIM-derived parameters. The areas under the ROC curve (A values) were compared for significant differences between parameters, and the cutoff values with the largest Youden index (the sum of sensitivity and specificity) were calculated from the ROC curves. For the comparison of ROC curves, a P value less than the Bonferroni-corrected significance value of .008 (.05/6) was considered to indicate a significant difference. Otherwise, a P value of less than .05 was considered to indicate a significant difference. The Kruskal-Wallis test and Steel-Dwass test were performed by using Excel Statistics (version 1.12; Social Survey Research Information, Tokyo, Japan). The Mann-Whitney U test, ROC analysis, and pairwise comparison of ROC curves were performed by using MedCalc (MedCalc Software, Mariakerke, Belgium).

Results

Overall intraobserver agreement was fair to excellent. The ICC values were 0.670 for ADC maps, 0.940 for Dslow maps, 0.784 for Dfast maps, and 0.803 for f maps. In ROC analysis, for differentiation of PAC from NP (P = .001) and of PAC from NETs (P = .016) after adjusting for Dfast. In contrast, Dfast was not a significant parameter for the differentiation of PAC from NP (P = .901) and of PAC from NETs (P = .073). For the differentiation of PAC and CP, Dfast (P = .038) and f (P = .048) were both significant factors after adjusting for each other.

ADC and IVIM Analysis in NP, CP, PAC, and NETs

Values and ranges of ADC, Dslow, Dfast, and f values of the NP, CP, PAC, NETs, and IPMNs are described in Table 3. The ADC value of PAC was significantly lower than that of NP (P = .03) but was not different from that of CP (P = .995). In addition, although the Dslow value of PAC was not significantly different from that of NP and CP (P = .344, respectively), Dfast and f values of PAC were significantly lower than those of NP and CP (all P < .05) (Table 3, Fig 2). To the contrary, ADC- and IVIM-derived parameters of NETs were not significantly different from those of NP and CP (all P > .05) (Table 4). Notably, although the ADC and Dslow values of PAC were not significantly different from those of NETs (P = .611 and P = .998, respectively), Dfast and f values of PAC were significantly lower than those of NETs (all P < .0001) (Figs 3, 4). Multiple logistic regression showed that f was an independently significant parameter for the discrimination of PAC from NP (P = .001) and of PAC from NETs (P = .016) after adjusting for Dfast. In contrast, Dfast was not a significant parameter for the discrimination of PAC from CP (P = .981) and of PAC from NETs (P = .733) and of PAC from NETs (P = .073). For the differentiation of PAC and CP, Dfast (P = .038) and f (P = .048) were both significant factors after adjusting for each other.

Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NP (n = 26)</th>
<th>CP (n = 7)</th>
<th>PAC (n = 39)</th>
<th>NET (n = 17)</th>
<th>IPMN (n = 37)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC†</td>
<td>1.34 (0.91–1.67)</td>
<td>1.16 (1.01–1.63)</td>
<td>1.22 (0.66–2.20)</td>
<td>1.32 (0.93–2.23)</td>
<td>2.75 (1.33–3.67)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Dslow†</td>
<td>1.19 (0.81–1.51)</td>
<td>1.41 (1.09–1.53)</td>
<td>1.14 (0.53–2.07)</td>
<td>1.11 (0.83–1.80)</td>
<td>2.84 (1.24–3.94)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Dfast†</td>
<td>36.15 (22.60–80.30)</td>
<td>40.80 (24.20–57.00)</td>
<td>22.30 (5.70–45.00)</td>
<td>43.70 (24.60–75.90)</td>
<td>15.6 (2.10–44.50)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>f†</td>
<td>24.79 (16.60–31.90)</td>
<td>18.60 (15.20–26.10)</td>
<td>11.60 (4.20–23.00)</td>
<td>29.50 (12.70–50.60)</td>
<td>9.65 (2.80–39.70)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Note.—Data are median values. Numbers in parentheses are ranges.

* According to the Kruskal-Wallis test for differences in ADC and IVIM parameters between NP, CP, and pancreatic tumors.
† ADC, Dslow, and Dfast values are expressed as the median value (× 10⁻³ mm²/sec), with ranges in parentheses.
‡ f values are expressed as the median percentage, with ranges in parentheses.
higher $A_z$ values than those of ADC and $D_{slow}$ ($P = .0001$ and $P < .0001$, respectively) between PAC and NP. In addition, for differentiating PAC from NETs, $f$ and $D_{fast}$ showed significantly higher $A_z$ values than those of ADC ($P = .0001$ and $P = .0006$, respectively) and $D_{slow}$ ($P < .0001$ and $P < .0001$, respectively).
GASTROINTESTINAL IMAGING: MR Imaging of Focal Pancreatic Lesions

Kang et al

ADC and IVIM Analysis for the Characterization of IPMNs

IVIM-derived parameters and ADC of IPMNs were markedly different between NP and other solid pancreatic tumors. ADC and $D_{slow}$ values of IPMNs were significantly higher than those of the NP, CP, NETs, and PAC (all $P < .05$). $D_{fast}$ and $f$ values of IPMNs were also significantly lower than those of NP, CP, and NETs (all $P < .05$) (Table 3, Fig 2).

The median values of benign IPMNs were as follows: ADC, $3.04 \times 10^{-3}$ mm$^2$/sec (range, $[2.15–3.67] \times 10^{-3}$ mm$^2$/sec); $D_{slow}$, $3.00 \times 10^{-3}$ mm$^2$/sec (range, $[1.93–3.94] \times 10^{-3}$ mm$^2$/sec); $D_{fast}$, $10.05 \times 10^{-3}$ mm$^2$/sec (range, $[2.10–44.5] \times 10^{-3}$ mm$^2$/sec); and $f$, 7.1% (range, 2.8%–35.8%). Those of malignant IPMNs were as follows: ADC, $1.99 \times 10^{-3}$ mm$^2$/sec (range, $[1.33–3.14] \times 10^{-3}$ mm$^2$/sec); $D_{slow}$, $2.44 \times 10^{-3}$ mm$^2$/sec (range, $[1.24–3.03] \times 10^{-3}$ mm$^2$/sec); $D_{fast}$, $23.10 \times 10^{-3}$ mm$^2$/sec (range, $[3.60–36.8] \times 10^{-3}$ mm$^2$/sec); and $f$, 14.1% (range, 8.3%–39.7%).

With regard to the differentiation of benign from malignant IPMNs, the ADC and $D_{slow}$ values of malignant IPMNs were significantly lower than those of benign IPMNs ($P < .0001$ and $P = .0002$, respectively), and $D_{fast}$ and $f$ values of malignant IPMNs were significantly higher than those of benign IPMNs ($P = .036$ and $P < .0001$, respectively). Multiple logistic regression
Table 5

Table 5 Results of ROC Analysis for IVIM-derived Parameters

<table>
<thead>
<tr>
<th>Comparison</th>
<th>A Value*</th>
<th>Sensitivity (%)†</th>
<th>Specificity (%)†</th>
<th>Accuracy (%)†</th>
<th>Cutoff Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC vs NP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>0.714 (0.588, 0.819)</td>
<td>69.2 (27/39)</td>
<td>76.9 (20/26)</td>
<td>72.3 (47/65)</td>
<td>1.26</td>
<td>.003</td>
</tr>
<tr>
<td>D_fast</td>
<td>0.616 (0.487, 0.734)</td>
<td>38.5 (15/39)</td>
<td>88.5 (23/26)</td>
<td>58.5 (38/65)</td>
<td>1.08</td>
<td>.103</td>
</tr>
<tr>
<td>D_slow</td>
<td>0.891 (0.788, 0.954)</td>
<td>71.8 (28/39)</td>
<td>92.3 (24/26)</td>
<td>80.0 (52/65)</td>
<td>23.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>f</td>
<td>0.986 (0.922, 1.000)</td>
<td>89.7 (35/39)</td>
<td>100 (26/26)</td>
<td>84.6 (55/65)</td>
<td>15.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PAC vs CP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>0.542 (0.389, 0.690)</td>
<td>94.9 (37/39)</td>
<td>42.9 (3/7)</td>
<td>87.0 (40/46)</td>
<td>1.48</td>
<td>.783</td>
</tr>
<tr>
<td>D_fast</td>
<td>0.627 (0.436, 0.793)</td>
<td>92.3 (36/39)</td>
<td>57.1 (4/7)</td>
<td>87.0 (40/46)</td>
<td>1.33</td>
<td>.047</td>
</tr>
<tr>
<td>D_slow</td>
<td>0.936 (0.825, 0.988)</td>
<td>94.9 (37/39)</td>
<td>85.7 (6/7)</td>
<td>93.5 (43/46)</td>
<td>30.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>f</td>
<td>0.947 (0.838, 0.991)</td>
<td>84.6 (33/39)</td>
<td>100 (7/7)</td>
<td>87.0 (40/46)</td>
<td>14.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PAC vs NET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>0.621 (0.482, 0.748)</td>
<td>87.2 (34/39)</td>
<td>47.0 (8/17)</td>
<td>75.0 (42/56)</td>
<td>1.4</td>
<td>.196</td>
</tr>
<tr>
<td>D_fast</td>
<td>0.773 (0.589, 0.962)</td>
<td>87.2 (34/39)</td>
<td>35.3 (6/17)</td>
<td>71.4 (40/56)</td>
<td>1.29</td>
<td>.773</td>
</tr>
<tr>
<td>D_slow</td>
<td>0.946 (0.851, 0.989)</td>
<td>94.9 (37/39)</td>
<td>82.4 (14/17)</td>
<td>91.1 (51/56)</td>
<td>30.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>f</td>
<td>0.964 (0.876, 0.995)</td>
<td>89.7 (35/39)</td>
<td>94.1 (16/17)</td>
<td>91.1 (51/56)</td>
<td>15.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Malignant vs benign IPMN</td>
<td>0.815 (0.653, 0.923)</td>
<td>53.3 (8/15)</td>
<td>100.0 (22/22)</td>
<td>54.0 (20/37)</td>
<td>1.99</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>D_fast</td>
<td>0.838 (0.680, 0.938)</td>
<td>93.3 (14/15)</td>
<td>63.6 (14/22)</td>
<td>75.7 (28/37)</td>
<td>2.93</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>D_slow</td>
<td>0.706 (0.534, 0.844)</td>
<td>66.7 (10/15)</td>
<td>86.4 (19/22)</td>
<td>78.4 (28/37)</td>
<td>22.0</td>
<td>.027</td>
</tr>
<tr>
<td>f</td>
<td>0.885 (0.737, 0.968)</td>
<td>93.3 (14/15)</td>
<td>77.3 (17/22)</td>
<td>83.8 (31/37)</td>
<td>9.4</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are 95% confidence intervals.
† Numbers in parentheses are those used to calculate the percentage.

Discussion

Among the IVIM-derived parameters in our study, the perfusion-related parameters f and D_fast were most useful for distinguishing PAC from NP, CP, and NETs in univariate analysis. In addition, at multiple logistic regression, f was an independently significant parameter for the differentiation of PAC from NP, CP, and NETs. Furthermore, according to ROC analysis, among the ADC- and IVIM-derived parameters, f showed the highest A value in the differentiation of PAC from NP, CP, and NETs. Consistent with the present findings, in previous studies, Lemke et al (22) and Re et al (27) reported that the f value in pancreatic cancer was markedly reduced when compared with healthy pancreatic tissue. Furthermore, our results are similar to those of a previous study by Klaus et al (23), which demonstrated that the perfusion fraction f proved to be a superior DW imaging-derived parameter for differentiation of mass-forming pancreatic tumors and pancreatic carcinoma. Therefore, on the basis of our results, we may suggest that perfusion might be a more important factor than diffusion in differentiating PAC from NP, CP, and NETs. In addition, f showed the highest A value in differentiating malignant from benign IPMs among ADC- and IVIM-derived parameters. Therefore, we believe that IVIM DW imaging has value not only cellularity (D_fast) but also perfusion information (D_fast and f), which has potential as a noninvasive marker of tumor vascularity.

In our study, f and D_fast showed better diagnostic performance than ADC and D_slow for differentiating NETs from PAC (all P < .05). In fact, ADC values and D_slow were not helpful in differentiating PAC and NETs. Considering that hypervascular enhancement can be regarded as a typical imaging feature of NETs of the pancreas, whereas PACs are hypovascular and desmoplastic, the difference in f and D_fast between the two diseases could be explained by the difference in vascular perfusion. Therefore, on the basis of our study results, we believe that tissue perfusion may be a more important factor than diffusion in differentiating the two. In clinical practice, dynamic MR imaging or CT is frequently used to demonstrate this difference in vascular perfusion between the two diseases. Yet, atypical enhancement patterns of PACs or NETs are not rare at dynamic MR imaging or CT (28,29) because of tumor size, degree of differentiation, and...
extent of necrosis, resulting in great difficulty in distinguishing between them (30). Although we believe that dynamic MR imaging still plays a major role for the characterization of focal pancreatic lesions, when focal pancreatic lesions show atypical enhancement patterns at dynamic MR imaging, IVIM-derived perfusion parameters might add helpful information in differentiating PACs from NETs.

In addition, in our study, the perfusion-related factors of PAC—$D_{\text{fast}}$ and $f$—differed from those seen in patients with CP and also showed better diagnostic performance than did ADC or $D_{\text{slow}}$. Although the differential diagnosis of PAC and CP is usually assigned easily, there can be enough overlap in the presenting features and in imaging studies that differentiation may sometimes be extremely difficult. As this confusion may lead to either surgical resection of benign disease or ignorance of curable PAC, the differential diagnosis of these two diseases is important (31,32). Therefore, the significantly different perfusion-related factors of PAC and CP might be helpful for determining the most accurate diagnosis.

In the characterization of IPMNs for malignancy changes, the $D_{\text{fast}}$ and $f$ values of malignant IPMNs were significantly higher than those of benign IPMNs in our study, whereas the ADC and $D_{\text{slow}}$ values of malignant IPMNs were significantly lower than those of benign IPMNs ($P < .05$). Our results regarding ADC values were in good agreement with those of a previous study in which ADC values for low-grade IPMNs were significantly higher than those for high-grade or invasive IPMNs ($P = .03$) (32).

The present study has a number of limitations. First, because our study was a retrospective study, there may have been selection and verification biases. Second, there were a limited number of patients with CP; therefore, we provided preliminary results by using a relatively small sample size. Third, because IVIM diffusion-weighted MR images were acquired by using the free-breathing technique, image misalignment due to organ motion may have been a source of variance. However, in a study on the reproducibility of ADC measurements in breath-hold, respiratory-triggered, and free-breathing acquisitions, ADC measurements of the normal liver parenchyma in respiratory-triggered DW imaging were less reproducible than in breath-hold and free-breathing MR imaging, and there were no significant differences in ADC values among breath-hold and free-breathing DW imaging studies (33). Further studies about the effect of different DW imaging acquisition methods on IVIM-derived parameters are warranted. Fourth, although the IVIM model was originally developed to account for capillary perfusion, it has been recognized that the IVIM measurement may also sometimes be sensitive to flow in all forms. Other bulk flow phenomena, such as tubular flow or glandular secretion, can contribute to the signal attenuation and may be difficult to distinguish from perfusion effects (21). We presumed that this limitation could explain the reason why $D_{\text{fast}}$ and $f$ values of IPMNs were not significantly different from those of PAC ($P = .241$, $P = .531$). Fifth, although we demonstrated that IVIM parameters were helpful in the differentiation of PAC and NETs, we did not analyze whether the addition of IVIM-derived parameter maps to dynamic imaging could provide incremental benefit in differentiating PAC from NETs. Therefore, we believe that additional studies are required to assess the incremental benefits of the IVIM parameters, in addition to the dynamic MR imaging. Sixth, we used the median value of the ROI to define the measured parameter, but a histogram analysis of these heterogeneous lesions may have been more useful to identify differences between lesions. Nevertheless, to reduce variance due to ROI placement, ROI measurements were conducted relatively conservatively. Last, a statistical limitation in our study was that multiple tests were performed on a relatively small data set. However, most of the results were strongly significant. In addition, all of our $P$ values were adjusted by using the Steel-Dwass test and Bonferroni correction.

In conclusion, IVIM-derived perfusion-related parameters could be helpful in assigning the correct diagnosis of common malignant tumors in the pancreas, and $D_{\text{fast}}$ and $f$ were potentially more valuable parameters for the differentiation of PAC from NETs than were ADC and $D_{\text{slow}}$.

Disclosures of Conflicts of Interest: K.M.K. No relevant conflicts of interest to disclose. J.M.L. No relevant conflicts of interest to disclose. J.H.Y. No relevant conflicts of interest to disclose. B.K. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is a Siemens Healthcare employee. Other relationships: none to disclose. J.K.H. No relevant conflicts of interest to disclose. B.J.C. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: received a grant from Samsung Electronics. Other relationships: none to disclose.

References
8. Rainmond M, Tachibana I, Urrutia R, Burgart LJ, DiMagno EP. Invasive cancer and survival of intraductal papillary mucinous