ORIGINAL ARTICLE

Value of Texture Analysis of Intravoxel Incoherent Motion Parameters in Differential Diagnosis of Pancreatic Neuroendocrine Tumor and Pancreatic Adenocarcinoma

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Key words: neuroendocrine tumor; pancreatic adenocarcinoma; texture analysis;
intravoxel incoherent motion; differential diagnosis

Objective To evaluate the value of texture features derived from intravoxel incoherent motion (IVIM) parameters for differentiating pancreatic neuroendocrine tumor (pNET) from pancreatic adenocarcinoma (PAC).

Methods Eighteen patients with pNET and 32 patients with PAC were retrospectively enrolled in this study. All patients underwent diffusion-weighted imaging with 10 b values used (from 0 to 800 s/mm²). Based on IVIM model, perfusion-related parameters including perfusion fraction (f), fast component of diffusion (D_{fast}) and true diffusion parameter slow component of diffusion (D_{slow}) were calculated on a voxel-by-voxel basis and reorganized into gray-encoded parametric maps. The mean value of each IVIM parameter and texture features [Angular Second Moment (ASM), Inverse Difference Moment (IDM), Correlation, Contrast and Entropy] values of IVIM parameters were measured. Independent sample t -test or Mann-Whitney U test were performed for the between-group comparison of quantitative data. Regression model was established by using binary logistic regression analysis, and receiver operating characteristic (ROC) curve was plotted to evaluate the diagnostic efficiency.

Results The mean f value of the pNET group were significantly higher than that of the PAC group (27.0% vs. 19.0%, $P = 0.001$), while the mean values of D_{fast} and D_{slow} showed no significant differences between the two groups. All texture features (ASM, IDM, Correlation, Contrast and Entropy) of each IVIM parameter showed

significant differences between the pNET and PAC groups ($P=0.000-0.043$). Binary logistic regression analysis showed that texture ASM of D_{fast} and texture Correlation of D_{slow} were considered as the specific imaging variables for the differential diagnosis of pNET and PAC. ROC analysis revealed that multiple texture features presented better diagnostic performance than IVIM parameters (AUC 0.849-0.899 vs. 0.526-0.776), and texture ASM of D_{fast} combined with Correlation of D_{slow} in the model of logistic regression had largest area under ROC curve for distinguishing pNET from PAC (AUC 0.934, cutoff 0.378, sensitivity 0.889, specificity 0.854).

Conclusion Texture analysis of IVIM parameters could be an effective and noninvasive tool to differentiate pNET from PAC.

PANCREATIC adenocarcinoma (PAC) and pancreatic neuroendocrine tumor (pNET) are the first and second in the incidence for pancreatic tumor respectively.^[1-2] Management and prognosis for these two tumors are entirely different. For pNET patients with liver metastasis, resection may achieved improved overall survival if lesions can be completely removed,^[3-5] and for patients with small-sized tumor, partial pancreatectomy may gain a lower complication rate and a significantly higher overall survival when compared with aggressive surgery approach.^[4, 6] In addition, follow-up with surveillance may be an alternative for patients with nonfunctioning tumor less than 2 cm in diameter.^[3-4] Given the fact that pNET had a higher resectability and relatively better prognosis, it would be important to differentiate pNET from PAC prior to surgical treatment.^[7]

The characterized imaging feature of pNET is hyper-enhancement, whereas PAC often shows hypovascular and desmoplastic. Dynamic MR imaging or CT is frequently performed to observe the difference of vascular perfusion for the two neoplasms in clinical practice.^[8] However, enhancement patterns of pNET or PAC on images are very sensitive to changes in tumor size, degree of differentiation and extent of necrosis, resulting in great difficulty in distinguishing them.^[9] Moreover, contrast agents are likely to give rise to renal damage to patients, therefore contrast enhanced MR imaging cannot be performed sometimes, especially for people with renal insufficiency.

Diffusion-weighted imaging (DWI) is a proven, noninvasive MR imaging modality to have been applicable to getting perfusion and diffusion characteristics of tumors without using contrast media, carried out with sufficient b values by using biexponential fitting based on intravoxel incoherent motion (IVIM) model.^[10-12] Quantitative IVIM parameters have been increasingly used to diagnose and differentiate pancreatic lesions

recently.^[13-21] Owing to the difference of the two tumors in spatial distribution of cellularity and vascularity, texture analysis would be superior to describing pancreatic lesions. Previous studies have used texture or histogram analysis of MR imaging or DWI to differentiate pancreatic lesions.^[21-23] However, there have been rare literature reports describing texture features of IVIM parameters to differentiate pancreatic tumors. Therefore, we performed this study for the purpose of evaluating diagnostic efficiency of texture features derived from IVIM parameters to distinguish between pNET and PAC.

PATIENTS AND METHODS

Patients

We retrieved image database of our hospital and identified 132 patients who were suspected of pancreatic tumor and underwent MR examinations including multi-b-value DWI in the period of Jun 2015 to Mar 2018. According to the following exclusion criteria, 82 patients were excluded from this study: (1) patients who had accepted treatment before MR examination; (2) those with pathologically confirmed other pancreatic diseases or without pathological results; (3) The imaging quality was inadequate for analysis. Finally, 18 pNET patients including 10 males and 8 females and 32 PAC patients including 20 males and 12 females were enrolled in our study. The mean age of pNET patients and PAC patients was 47 (range 26-59) and 54 (range 37-68) years. The distributions of gender ($\chi^2=0.231$, $P=0.630$) and age ($t=2.013$, $P=0.052$) of the two groups were similar. There were no significant differences in tumor diameter between the pNET and PAC groups [3.68 (range 1.3-5.7) vs. 4.45 (range 2.9-6.7) cm; $t=0.938$, $P=0.367$].

The ethics committee of Chinese PLA general hospital granted this retrospective study, and informed

consent was waived.

MR imaging

All patients underwent MR examination with 3-T MR scanner (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) with a 32-channel body array coil. The pancreatic MR imaging protocols were as follows: axial respiratory triggering fat-suppressed fast spin echo (FSE) T2WI, 3D liver acquisition with volume acceleration flex (LAVA-Flex) with breath-hold before contrast media injection and arterial, portal venous, equilibrium and delay phases after contrast media administration.

DWI was performed prior to contrast media administration. Spectral presaturation attenuated by inversion recovery was used for fat suppression. DW images were acquired by using axial single-shot echo-planar imaging pulse sequence in a free-breathing manner with following parameters: repetition time 5000 ms; echo time 52 ms; echo-planar imaging factor 136; bandwidth 250 kHz per pixel; field of view 380 mm × 380 mm; matrix size 160 × 160; slice thickness 6 mm; intersection gap 1 mm; numbers of section 22; numbers of excitation 4; 10 b values (0, 25, 50, 75, 100, 150, 200, 400, 600, 800 s/mm²); acquisition time 284 s.

Imaging analysis

DWI data were imported into an AW4.5 Workstation (GE Healthcare) for IVIM analysis. Based on IVIM model, IVIM parameters including perfusion fraction (f), fast component of diffusion (D_{fast}) and true diffusion parameter slow component of diffusion (D_{slow}) were calculated on a voxel-by-voxel basis and reorganized into gray-encoded parametric maps by using MADC program. The parametric maps were transferred into an open source software ImageJ (1.41v, <https://imagej.nih.gov/ij/>) to perform texture analysis using Gray-level Co-occurrence Matrix (GLCM) method by its plugin. The setting of GLCM was as follows: the size of the step in pixels 1 and the direction of the step 0 degree. The texture features including Angular Second Moment (ASM), Inverse Difference Moment (IDM), Correlation, Contrast and Entropy were measured.

Quantitative analysis of IVIM parameters was performed by an experienced radiologist with 8 years of experience in abdominal MRI, who was blinded to the pathological results. Using conventional pancreatic MR images as anatomic references to identify the extent of the lesion, freehand regions of interest (ROIs)

were drawn on the enhancing solid portion of tumors with maximal area on DW images at a b -value which best revealed the tumor margin, while avoiding the vessels, pancreatic duct, necrosis and cystic components. Well-matched copies of the ROIs were automatically and synchronously generated on each IVIM parametric map on corresponding locations (**Figure 1**) to obtain the mean value of each parameter by using built-in software (MADC programs on AW4.5 Workstation). Furthermore, the similar ROIs were manually drawn on the same locations of IVIM parametric maps to obtain texture features of each parameter by using the software ImageJ. To improve the accuracy of the measurement, ROIs were placed for three times by the same radiologist on the same image, and the average value was regarded as the final result.

Statistical analysis

Statistical analyses were performed using the SPSS Statistics Software Version 22.0 (SPSS Inc., Chicago, IL, USA). Normally distributing quantitative data were presented as mean ± SD and compared with independent t test, while non-normally distributing data presented as median (quantile range) and compared with Mann-Whitney U test. Qualitative data were compared with Chi-square test.

The Binary Logistic regression analysis was performed using forwards method with pNET and PAC as dependent factors, and IVIM parameters and their texture features showing statistically significant difference between the two groups as independent factors. The variables enrolled in the logistic regression equation were determined by *Wald* χ^2 value.^[24]

To evaluate the diagnostic efficiency of IVIM parameters and their texture features in differentiating pNET from PAC, receiver operating characteristic (ROC) curve was built and pathological diagnosis was regarded as gold standard. To evaluate diagnostic performance of logistic regression model with combined variables in differentiating pNET from PAC, ROC curve was drawn and the probability derived from the logistic regression equation was regarded as the state variable. Areas under ROC curve (AUC) and cutoff values with the largest Youden index (the sum of sensitivity and specificity) were calculated from ROC curves and were regarded as the optimal diagnostic point. A rough guide for assessing the diagnostic efficiency based on AUC was as follows: excellent, AUC ≥ 0.9; good, 0.9 > AUC ≥ 0.8; fair, 0.8 > AUC ≥ 0.7; poor, 0.7 > AUC

Figure 1. IVIM parameters measurement of the lesion. A ROI was drawn on the lesion with maximal area on DW image (A), and the mimic ROI was automatically generated on parameter f map (B), D_{fast} map (C) and D_{slow} map (D) on the corresponding location.

IVIM: intravoxel incoherent motion; ROI: region of interest; f : perfusion fraction; D_{fast} : fast component of diffusion; D_{slow} : true diffusion parameter slow component of diffusion.

≥ 0.6 ; fail, $0.6 > AUC \geq 0.5$.^[25] Statistically significant difference was set at a P value of less than 0.05.

RESULTS

IVIM parameters

The mean value of parameter f in the pNET group was significantly higher than that in the PAC group (27.0% vs. 19.0%; $P=0.001$, $U=-3.214$), while no significant differences were found in parameter D_{fast} [median (quantile range), 30.6×10^{-3} (11.8×10^{-3}) mm^2/s vs. 28.4×10^{-3} (17.3×10^{-3}) mm^2/s ; $P=0.196$, $U=-1.294$] and D_{slow} [$(1.21 \pm 0.13) \times 10^{-3}$ mm^2/s vs. $(1.20 \pm 0.19) \times 10^{-3}$ mm^2/s ; $P=0.913$, $t=-0.110$].

Texture features

As illustrated in **Table 1**, all texture features of each IVIM parameter showed significant differences between the two groups. Values of ASM, IDM and Correlation were significantly higher in the pNET group (all

$P < 0.01$), while values of Contrast and Entropy were significantly higher in the PAC group (all $P < 0.01$).

Binary Logistic regression analysis revealed both ASM of D_{fast} and Correlation of D_{slow} manifested significantly statistical difference between the two groups ($P < 0.05$) and were regarded as independent variables (**Table 2**), and then were incorporated into the regression equation: $P = 1/1 + e^{-(-22.112 + 35.251 \times \text{ASM-}D_{fast} + 33247.943 \times \text{Correlation-}D_{slow})}$.

As shown in **Table 3** and **Figure 2**, ASM and Correlation of each IVIM parameter, Entropy of D_{fast} and D_{slow} , and IDM of D_{fast} demonstrated good diagnostic efficiency for differentiating pNET from PAC (AUC 0.849-0.899), while IVIM parameters failed to show fair diagnostic efficiency (AUC 0.526-0.776). The combined texture features (ASM of D_{fast} plus Correlation of D_{slow}) were enrolled in the regression equation and showed a larger AUC than single texture feature did (**Figure 2D**), and presented the excellent diagnostic performance (AUC 0.934, cutoff 0.378, sensitivity 0.889, specificity 0.854).

Table 1. Comparisons of texture features of IVIM parameters between the pNET and PAC groups

Parameters	PAC (n=32)	pNET (n=18)	U/t value	P value
<i>f</i>				
ASM	0.398 (0.047)	0.468 (0.079)	-4.224	0.000
IDM	0.779±0.032	0.806±0.033	-2.810	0.007
Correlation (×10 ⁻³)	0.065±0.007	0.076±0.009	-4.954	0.000
Contrast	4367.155 (1740.747)	3785.633 (1.70.172)	-2.021	0.043
Entropy	2.294±0.173	2.080±0.234	3.687	0.001
<i>D_{fast}</i>				
ASM	0.350±0.049	0.450±0.623	-6.283	0.000
IDM	0.701 (0.069)	0.740 (0.045)	-3.456	0.001
Correlation (×10 ⁻³)	0.083±0.007	0.102±0.016	-5.905	0.000
Contrast	2961.827±514.595	2469.961±618.127	3.016	0.004
Entropy	3.398 (0.587)	2.947 (0.534)	-4.143	0.000
<i>D_{slow}</i>				
ASM	0.315±0.049	0.407±0.053	-6.169	0.000
IDM	0.589±0.048	0.659±0.044	-5.129	0.000
Correlation (×10 ⁻³)	0.198±0.034	0.269±0.057	-5.562	0.000
Contrast	483.639±97.783	422.838±97.344	2.114	0.040
Entropy	4.570±0.441	3.833±0.421	5.768	0.000

Normal distribution data were presented as mean ± SD and compared with independent *t* test. Non-normal distribution data were presented as median (quantile range) and comparisons were performed with Mann-Whitney *U* test.

ASM: Angular Second Moment; IDM: Inverse Difference Moment.

Table 2. Binary Logistic regression analysis of texture features between the pNET group and PAC group

Independent variables	Regression coefficient	Standard error	Wald χ^2	P value
ASM of <i>D_{fast}</i>	35.251	13.929	6.405	0.011
Correlation of <i>D_{slow}</i>	33 247.973	14 163.943	5.510	0.019
Constant	-22.112	7.255	9.289	0.002

DISCUSSION

IVIM DWI can substantially distinguish perfusion effects from true tissue diffusion on images,^[18] making it possible to obtain perfusion-related parameters (*f* and *D_{fast}*) reflecting microcirculation and true water molecule diffusion parameter (*D_{slow}*) reflecting cell density of tissues.^[26] Our study showed that mean *f* value was valuable for distinguishing pNET from PAC, while mean values of *D_{fast}* and *D_{slow}* did not present helpful in differentiating them, which was consistent with the results of previous studies, which reported that the characteristic IVIM manifestation of PAC was significantly lower *f* value than pNET.^[18-21] Nevertheless, there were inconsistent in regard to *D_{fast}*. In the two studies of them, the researchers found *D_{fast}* was significantly lower in PAC than pNET;^[18, 21] in the other two studies, while they revealed no significant difference in *D_{fast}* val-

ue between the two tumors,^[19-20] which may be related with limited measurement reliability of *D_{fast}*.^[19]

GLCM is a common method of texture analysis to be used to display the relationship of two selected points in distance, direction and change magnitude on image.^[27] Texture features derived from GLCM have been applied to diagnose multiple disorders, as the parameters can intuitively offer information on spatial attribute of pixels on images.^[22, 28-30] In this study 5 texture features were extracted from IVIM perfusion-related or true diffusion parameter maps to show the spatial profiles of cells and blood vessels of tumors. The 5 texture features ASM, IDM, Correlation, Contrast and Entropy respectively represent texture homogeneity, regularity, similarity, variation and complexity of an image. The results showed all the texture features of each IVIM parameter were significant difference between the pNET and PAC groups. pNET was

Table 3. ROC analysis of mean value of IVIM parameters, texture features and combined texture features (ASM of D_{fast} and Correlation of D_{slow}) with logistic regression for differentiating pNET from PAC

Parameters	AUC	95%CI	Cut-off value	Sensitivity	Specificity
f					
Mean value	0.776	0.636-0.882	25.700 ^a	0.772	0.812
ASM	0.863	0.736-0.944	0.439 ^a	0.778	0.875
IDM	0.715	0.570-0.834	0.802 ^a	0.611	0.781
Correlation	0.849	0.719-0.934	0.069 ^a	0.778	0.812
Contrast	0.674	0.526-0.799	4675.279 ^b	1.000	0.406
Entropy	0.762	0.621-0.871	2.313 ^b	0.833	0.594
D_{fast}					
Mean value	0.611	0.463-0.746	28.000 ^a	0.833	0.500
ASM	0.899	0.781-0.966	0.389 ^a	0.889	0.844
IDM	0.797	0.659-0.897	0.727 ^a	0.778	0.750
Correlation	0.887	0.766-0.959	0.094 ^a	0.833	0.937
Contrast	0.724	0.579-0.841	2224.521 ^b	0.444	0.937
Entropy	0.856	0.718-0.939	3.231 ^b	0.944	0.656
D_{slow}					
Mean value	0.526	0.380-0.669	0.900	1.000	0.125
ASM	0.898	0.779-0.965	0.348 ^a	0.889	0.812
IDM	0.858	0.730-0.940	0.636 ^a	0.722	0.875
Correlation	0.856	0.728-0.939	0.245 ^a	0.778	0.937
Contrast	0.667	0.519-0.794	401.811 ^b	0.500	0.812
Entropy	0.880	0.757-0.955	4.218 ^b	0.889	0.750
Combined texture features	0.934	0.826-0.985	0.378 ^a	0.889	0.854

ROC: receiver operating characteristic; AUC: area under ROC curve.

The case should be diagnosed as pNET when the variable value above (a) or below (b) the cut-off value.

characterized by significantly higher values of texture features ASM, IDM and Correlation, and lower values of Contrast and Entropy, which indicated image texture of pNET had greater homogeneity and less variation and complexity compared with PAC. These findings manifested that the arrangement of cells and the distribution of blood vessels of pNET are more homogeneous than those of PAC.

In the clinical practice, DWI has been routinely used to observe the signal changes of the lesion and apparent diffusion coefficient (ADC) value is measured to evaluate molecular diffusion. Shindo *et al.*^[23] performed texture analysis of ADC map and demonstrated that only one texture parameter Entropy had diagnostic value and fair diagnostic efficiency (AUC 0.76-0.78) for differentiating pNET from PAC. In the current study, only one IVIM parameter mean f value showed limited value for the differentiation of PAC and pNET. However, the texture analysis demonstrated that all the texture features of each IVIM param-

eter presented significant differences between the two tumors, and multiple texture features presented good diagnostic efficiency (AUC 0.849-0.899) for differentiating pNET from PAC, while IVIM parameters failed to show fair diagnostic efficiency (AUC 0.526-0.776). Therefore, texture analysis could provide much more diagnostic information than mean value measurement of IVIM parameters and might be considered as an effective tool for differentiating pNET from PAC.

Furthermore, binary logistic regression analysis showed texture ASM of D_{fast} and Correlation of D_{slow} were independent variables for differentiating pNET from PAC. ROC analysis showed that texture features ASM of D_{fast} plus Correlation of D_{slow} had an excellent diagnostic efficiency (AUC 0.899), while single texture feature merely presented good diagnostic efficiency. Therefore, multiple texture features with logistic regression analysis would be more valuable for the differentiation between pNET and PAC.

Figure 2. ROC curves of IVIM parameters and their texture features of the logistic regression model for differentiating pNET from PAC. A: f_i ; B: D_{fast} ; C: D_{slow} ; D: ASM of D_{fast} , Correlation of D_{slow} and combined texture features.

There are some limitations for this study. Firstly, this is a retrospective study, and likely subjects to selection and verification biases. Secondly, size of sample is relatively small, especially for the pNET group. Thirdly, quantitative analysis was based on single-slice measurement, which may omit potential information from the rest of volume. Whole volume measurement may better represent heterogeneity of lesion. However, whole-tumor analysis is too complicated to be carried out in clinical practice.

In summary, texture features of IVIM parameters provided more valuable diagnostic information than mean value measurement of IVIM parameters, and texture ASM of D_{fast} combined with Correlation of D_{slow} both enrolled in regression analysis might improve diagnostic performance. Texture analysis of IVIM parameters could be a noninvasive tool to differentiate pNET from PAC.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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