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Application Progress of Intravoxel Incoherent Motion Diffusion Weighted Magnetic Resonance Imaging in Pancreatic Cancer

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Abstract

Intravoxel incoherent motion imaging (IVIM), on the traditional diffusion weighted imaging (DWI) technology, uses the biexponential model and adopts the multi-b-value analysis to obtain the perfusion information of water molecule diffusion and microcirculation without the use of contrast agent. It is more and more used in pancreatic diseases, which is of great significance for the diagnosis and identification of pancreatic cancer. This article will review the principles of IVIM imaging and its application in pancreatic diseases, especially in pancreatic cancer diagnosis, the prediction of pathological grade of pancreatic ductal adenocarcinoma, the judgment of lymph node metastasis, and differentiation of pathological classification.

Keywords

Magnetic Resonance Imaging, Intravoxel Incoherent Motion, Diffusion Weighted Imaging, Pancreatic Disease

1. Introduction

Pancreatic cancer is known as "the king of cancers" and is the most malignant gastrointestinal tumor with occult onset, rapid progression and poor prognosis [1]. According to the data released by the American cancer society in 2019, the incidence of pancreatic cancer among male and female malignant tumors ranks 10th and 9th respectively, the mortality rate ranks 4th, and the 5-year survival rate is only 9% [2] [3]. Early symptoms of pancreatic cancer are not typical. Once the cancer is found to be late, it is very likely, so early diagnosis is of great significance for the prognosis of patients with pancreatic cancer. Diffusion weighted imaging (DWI), which was first used in the diagnosis of brain diseases,

is the only non-invasive imaging technique that can reflect the diffusion of water molecules *in vivo* without the need of contrast medium injection and quantify water molecules diffusion and the pathological characteristics of tumors by measuring apparent diffusion coefficient (ADC) [4]. The traditional DWI imaging technology is based on the single exponential model, and the ADC value is the combined effect of diffusion of water molecules in tissues and microcirculation perfusion, which is higher than the diffusion coefficient of pure water molecules [5] [6]. It cannot really reflect the characteristics of the microstructure of the organization. Le Bitan *et al.* [7] put forward the intravoxel incoherent motion imaging technology in 1986, which is based on a dual exponential model with multiple *b*-values for analysis, enabling to separately reflect pure tissue diffusion and information about microcirculation perfusion. IVIM-DWI can simultaneously provide quantitative analysis to more accurately assess the movement of water molecules in the tissue. In recent years, intravoxel incoherent motion has been widely used in the pancreas. This article will review the principles of IVIM imaging and its application in pancreatic diseases.

2. Basics of IVIM DWI Imaging

The traditional DWI uses the single exponential model whose formula is

$$S_b = S_0 \exp\left(-b\mathrm{ADC}\right) \tag{1}$$

to calculate ADC value, where b value is the diffusion sensitivity coefficient in the unit of s/mm^2, reflecting the sensitivity degree of water molecule dispersion, the ADC is the apparent diffusion coefficient whose unit is mm^2/s. S_0 refers to the signal strength in voxel on the $b = 0$, S_b refers to the signal strength in voxel at a specific b value. This formula assumes that DWI signals show a single exponential attenuation, and at least two scans with different b values are required for linear fitting to obtain the regression slope. However, the tissue contains not only the water molecule diffusion effect but also the capillary microcirculation perfusion effect. In order to distinguish the two, the biexponential IVIM model is used to describe the relationship between the attenuation of signals in the tissue and the b-value. According to the equation proposed by Le Bitan [8]

$$S_b/S_0 = \left(1-f\right)\cdot\exp\left(-bd\right) + f\cdot\exp\left[-b\left(D+D^*\right)\right] \tag{2}$$

where S_b refers to the signal intensity in voxel at a specific b value, S_0 refers to the signal intensity in voxel on the $b = 0$, f is the perfusion fraction (%), which represents the proportion of the diffusion effect of voxel microcirculation perfusion in the overall diffusion effect, D^* (mm^2/s) is a false diffusion coefficient, which reflects the blood perfusion diffusion effect; D (mm^2/s) is a true diffusion coefficient, which indicates the pure water molecule diffusion effect. Since D^* is significantly higher than D [5], when b takes a high b value (>200 mm^2/s), the microcirculation perfusion is not sensitive to the signal intensity. The formula can be simplified as

$$S_b/S_0 = \left(1-f\right)\cdot\exp\left(-bD\right) \tag{3}$$

the perfusion coefficient D of pure water molecules can be obtained and then the values of D^* and f can be obtained through the nonlinear regression algorithm by substituting D into Equation (2). Conversely, when b takes a low value, the attenuation of tissue signals is mainly caused by microcirculation perfusion. The closer b is to 0, the more it can be considered that the attenuation of tissue signals is caused by microcirculation perfusion [9].

3. Clinical Application of IVIM in Pancreatic Diseases

3.1. Application of IVIM in Pancreatic Cancer

Pancreatic ductal adenocarcinoma has the characteristics of late detection, easy recurrence, and resistance to chemotherapeutic drugs, with a high mortality rate. Yoon *et al.* [10] found that with the increase of pancreatic fibrosis, IVIM (ADC, D, f, and D^*) related parameters all showed a downward trend, but only D^* and f have significant difference between different stages of fibrosis. Hecht *et al.* [11] used IVIM-DWI related parameters to study the histopathology of pancreatic ductal adenocarcinoma (PDAC) and found that D value was negatively correlated with matrix fibrosis (pooled $r = -0.46$, $p = 0.04$) and positively correlated with f ($r = 0.44$, $p = 0.05$) suggesting that both perfusion and diffusion could lead to interstitial fibrosis hyperplasia. This is consistent with the fact that PDAC is a tumor with deficient blood supply, it is possible that pancreatic cancer cells are rich in fibrous matrix, which limits their diffusion. ADC values (derived by single index and double index fitting) were significantly reduced in tumors with dense fibrosis and could be used as a biomarker for fibrosis hyperplasia of pancreatic ductal adenocarcinoma, which was similar to the results of previous studies [10] [12] [13]. However, the variation trend of f value in Hecht *et al.*'s study is different from that of Yoon *et al.* [10]. It is possible that the study of Hecht *et al.* selected non-tumor tissue adjacent to the lesion rather than normal healthy pancreatic tissue. In the study of Zhang [14] *et al.*, it was believed that diffusion parameters such as ADC and D value were valuable for the evaluation of pancreatic fibrosis stage, and D value decreased with the increase of fibrosis degree, which was consistent with the relationship between D value and fibrosis in the previous two studies. The FDA believes that gemcitabine can significantly improve the quality of life of patients with pancreatic cancer and prolong the life of patients. It can be used as the gold standard for the treatment of pancreatic cancer [15]. The mechanism is that gemcitabine can inhibit the growth of cancer cells and promote cell apoptosis. Studies [16] [17] have shown that gemcitabine has different efficacy in the treatment of pancreatic cancer, and drug resistance may occur in some patients. Therefore, early evaluation of chemotherapy effect is of great significance for the treatment of pancreatic cancer. Li *et al.* [18] established 24 nude mice model of pancreatic cancer and divided them into gemcitabine group ($n = 12$) and normal saline group ($n = 12$). Three b values of DWI ($b = 50$, 400 and 800 s/mm^2) and multiple b values of IVIM-DWI ($b = 0$, 25, 50, 80, 100, 300, 500, 800 s/mm) were used to compare ADC, D, f and D^* values of the

two groups. The results showed that compared with normal saline group, ADC and D values in the tumor area of the guitar gemcitabine group were significantly increased. There was no significant difference between D^* and f values, suggesting that ADC values and D values could be early imaging indicators of chemotherapy response of pancreatic cancer.

3.2. Application of IVIM in the Prediction of Pathological Grade of Pancreatic Ductal Adenocarcinoma and the Judgment of Lymph Node Metastasis

ADC derived from DWI can be used to evaluate the microstructure of early disease tissues and is widely used in the diagnosis of pancreatic diseases (PC). However, there have been different reports on the role of ADC values in the diagnosis of pancreatic cancer. Report [19] indicated that the ADC value of PC was higher than that of the normal pancreas group, while some studies showed the ADC value of PC is much lower than the normal pancreas [20] [21]. The ADC value includes not only pure water molecular diffusion but also microcirculation effects, making the results inaccurate in these studies, in addition the ADC value calculated by traditional DWI is greatly affected by b value, so different b value selection will also affect the final result. Ma *et al.* [22] used IVIM technology to predict the grading of pancreatic ductal adenocarcinoma with 15 b values (0, 10, 20, 40, 60, 80, 100, 150, 200, 400, 800, 1000, 1200, 1500, and 2000 s/mm^2). The ADC values, D values, f values, and D^* values were measured for 38 pathologically confirmed PDAC. The results showed that the mean D value of well/moderately differentiated PDAC was lower than that of poorly differentiated PDAC and there was a statistical difference. However, the mean f value of well/moderately differentiated PDAC was higher than that of poorly differentiated PDAC, and the f value was higher than that of the D value (0.894 > 0.865) when differentiating the area under the subject curve of well/moderately differentiated pancreatic cancer from poorly differentiated pancreatic cancer. Matrix reaction and fibrosis are the main histopathological features in pancreatic cancer, well/moderately differentiated PDAC shows abundant fibrosis and glandular formation characterized by neoplastic tubular and duct-like structures which contain massive mucus rich in macromolecular protein restraining diffusion of water molecules [23]. The f value represents the perfusion information of the tissue and has shown significant positive correlation with microvascular density (MVD) [24]. Study has shown that well/moderately differentiated PDAC contains higher MVD than poorly differentiated group, which may explain the higher f value of the former than the latter. It is concluded that IVIM technique can be used as a potential non-invasive tool to predict PDAC pathological grading to some extent.

In the study of PDAC lymph node metastasis, Rong *et al.* [25] found that IVIM parameters (ADC, D value, f value and D^* value) were correlated with lymph node metastasis. This study used ROC curve analysis on 59 lymph nodes of 15 patients with pancreatic cancer. The IVIM parameters of metastatic and

non-metastatic lymph nodes were measured. The average value of each parameter in the metastatic group was significantly lower than that in the non-metastatic group. The *D* value was the highest in identifying the metastasis of lymph nodes, followed by ADC (0.940), D^* (0.867) and *f* (0.855), the AUC increased to 0.997 when the parameters *D* and *f* were combined, suggesting that the combination of IVIM parameters may be more helpful in diagnosing lymph node metastasis. So far, there have been few studies on the pathological grade and lymph node metastasis of pancreatic cancer with IVIM technology, so it is necessary to expand the sample size to further study the clinical significance of IVIM derived parameters.

3.3. Application of IVIM in Differentiating Pathological Classification of Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumor (pNET) are the first and second most common cases of pancreatic cancer [26], and the treatment and prognosis of the two tumors are completely different. Compared with PDAC, pNET has better response to chemotherapy, higher resectability and longer overall survival. In view of the high resectability and relatively good prognosis of pNET, it is significant to distinguish pNET from PDAC before surgical treatment [27].

By retrospectively analyzing the clinical data of 18 pNET patients and 32 PAC patients, Wang *et al.* [28] discussed the value of texture analysis of IVIM parameters in differentiating pancreatic neuroendocrine tumor (pNET) from pancreatic adenocarcinoma (PAC). The study showed that the mean f value of pNET group was significantly higher than that of PAC group (27.0% vs 19.0%, P = 0.001), while the mean D^* value and mean D value had no significant difference between the two groups. The author believed that *f* value is beneficial to distinguish PNET and PAC, which is similar to previous research results [29] [30]. It also shows that multi-texture analysis of IVIM parameters can provide more diagnostic information than IVIM parameters and can be used as an effective tool to distinguish pNET and PDAC. However, because of the small number of subjects and the complexity of tumor analysis, it is difficult to perform in clinical practice. Ma *et al.* [31] studied 37 cases of PDAC and 17 cases of high-grade pNET by using IVIM-DWI model. The D^* value of pNET was significantly higher than PDAC, which was the same with the results of Kang *et al.* [32]. The *D* value is significantly lower than PDAC, which is consistent with the conclusion of Ma *et al.* [33]. However, it is different from Kang *et al.* [32]'s conclusion that *D* value has no effect in distinguishing PDAC and PNET, which may be related to the number of *b* value selection. Kang *et al.* [32] used 9 *b* values in the study, while 15 *b* values were used in the Ma's study. The more *b* is selected, the better the image quality is, which may affect the measurement results. The combination of *D* value and D^* value can achieve the highest diagnostic efficiency, and the specificity and sensitivity for the identification of high-level pNET and PDAC are 76.9% and 100%, respectively. Taken together, these re-

sults indicate that IVIM-DWI is likely to be a very valuable biomarker for the identification of pancreatic tumors. Kim *et al.* [34] performed pancreatic ductal adenocarcinoma (n = 60), neuroendocrine tumors (n = 15), and solid pseudopapillary tumors (n = 9), 20 cases of pancreatitis [13 cases of acute pancreatitis, 7 patients with AIP (autoimmune pancreatitis)] and 30 healthy volunteers (normal pancreas) underwent 10 b-value IVIW-DWI examination, and the f-values and D^* values of PDAC, ACP, AIP, and SPT were significantly reduced compared with normal pancreas which is similar to previous research [35]. In terms of pNET, f-values are higher than PDAC, SPT, ACP, and AIP, but usually only pay attention to the statistical differences between pNET and PDAC. The f-value in IVIM parameters has the best diagnostic performance among all the parameters that distinguish PDAC from NP. Compared with pNET, the decrease in f-value of PDCA is consistent with the results of Klau *et al.* [30]. Since PDAC is pathologically a tumor with insufficient blood supply and rich in fiber matrix, and there is a good correlation between perfusion related parameter f value and microvascular density (MVD), the f value and MVD of PDAC group are significantly lower than that of pancreatic neuroendocrine tumor group. Study [36] showed that the f value of AIP and PDAC group was significantly lower than that of the normal control group, while the f value of PDAC group was lower than that of AIP group, which was consistent with the results of De Robertis *et al.* [37]. The above research results show that IVIM-DWI perfusion-related parameters (D^*, f-values) are helpful in determining the degree of internal blood supply of the tumor and in the diagnosis and differential diagnosis of pancreatic neoplastic diseases. Some recent research results related to IVIM are summarized in **Table 1**.

4. Advantages and Disadvantages of IVIM

IVIM-DWI can obtain and distinguish the perfusion information of water molecules and microcirculation by using the dual-exponential model with multiple

Table 1. Different researches on IVIM derived parameters and its diagnostic performance.

The first author	Subject	IVIM derived parameters				Statistic difference				Diagnostic efficacy
		ADC	D	f	D^*	ADC	D	f	D^*	
Wangling Ma *et al.* [23]	pNET vs PDAC	↑	↓	↑	↑	N	Y	N	Y	Combined D and $D^* > D^* > D$
Yingwei Wang *et al.* [20]	pNET vs PAC		↑	↑	↑		N	Y	N	
Wangling *et al.* [16]	well/moderately differentiated PDAC vs poorly differentiated PDAC	↑	↓	↑	↓	N	Y	Y	N	f > D
Riccardo De Robertis *et al.* [27]	PDAC vs NP		↑	↓	↓		Y	Y	Y	f > D^* > D
Andreas Lemke *et al.* [28]	PAC vs NP	↓	↑	↓		Y	N	Y		f > ADC
Lu Ma *et al.* [29]	pNET vs PAC		↓	↑		N	Y	Y	N	D > f

a: PDAC = pancreatic ductal adenocarcinoma; PAC = pancreatic adenocarcinoma; NP = normal pancreatic; pNET = pancreatic neuroendocrine neoplasms.

different *b* values, to provide more accurate and comprehensive diagnostic information. Various studies have shown that the quantitative analysis of IVIM parameters can not only reflect the histopathological characteristics of the tissue, but also play an important role in the classification of pancreatic tumors. Moreover, there is no need to use contrast agent in IVIM-DWI, which has an absolute advantage for patients with renal insufficiency. However, there is no unified international standard for the size and quantity of *b* value, and the difference of *b* value may lead to slight differences in different research results, which may affect the repeatability of parameters. The image signal-to-noise ratio (SNR) will decrease while the selected *b* value is higher than 1000 s/mm^2, which directly affects the image quality. Poor quality of image would affect the accuracy of measurement. However, with a smaller *b* value, the image with a high SNR can be obtained, but it is not sensitive to the detection of water molecule diffusion motion, and it is easy to miss the lesions. The more and higher *b* values would increase scanning time, causing motion artifacts and affecting the post-processing of the parameters. Therefore, more in-depth clinical studies are needed to explore and improve the optimal size and quantity of *b* value, the optimal fitting model and the accurate post-processing measurement, so as to obtain a unified scanning parameter scheme, which can better reflect the technical value of IVIM-DWI and obtain a more comprehensive understanding of the disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Zhang, S., Jin, W., Liu, L. and Yu, X. (2018) Recent Advances in Basic Research, Clinical Diagnosis and Treatment of Pancreatic Cancer in 2017. *China Oncology*, **28**, 1-10.

[2] Zheng, R., Sun, K. and Zhang, S., *et al.* (2019) Report of Cancer Epidemiology in China, 2015. *Chinese Journal of Oncology*, **41**, 19-28.

[3] Siegel, R.L., Miller, K.D. and Jemal, A. (2019) Cancer Statistics, 2019. *CA: A Cancer Journal for Clinicians,* **69,** 7-34. https://doi.org/10.3322/caac.21551

[4] Yin, Y. and Gan, J. (2013) Intravoxel Incoherent Motion Imaging. *Journal of China Clinic Medical Imaging*, **24**, 353-356.

[5] Le Bihan, D., Breton, E., Lallemand, D., Aubin, M.-L., Vignaud, J. and Laval-Jeantet, M. (1988) Separation of Diffusion and Perfusion in Intravoxel Incoherent Motion MR Imaging. *Radiology*, **168**, 497-505. https://doi.org/10.1148/radiology.168.2.3393671

[6] Mami, I. and Denis, L.B. (2016) Clinical Intravoxel Incoherent Motion and Diffusion MR Imaging: Past, Present, and Future. *Radiology*, **278**, 13-32. https://doi.org/10.1148/radiol.2015150244

[7] Le Bihan, D., Breton, E., Lallemand, D., Grenier, P., Cabanis, E. and Laval-Jeantet, M. (1986) MR Imaging of Intravoxel Incoherent Motions: Application to Diffusion and Perfusion in Neurologic Disorders. *Radiology*, **161**, 401-407.

https://doi.org/10.1148/radiology.161.2.3763909

[8] Le Bihan, D. and Turner, R. (1992) The Capillary Network: A Link between IVIM and Classical Perfusion. *Magnetic Resonance in Medicine*, **27**, 171-178. https://doi.org/10.1002/mrm.1910270116

[9] Dyvorne, H.A., Galea, N., Nevers, T., Fiel, M.I., Carpenter, D., Wong, E., *et al.* (2013) Diffusion Weighted Imaging of the Liver with Multiple b Values: Effect of Diffusion Gradient Polarity and Breathing Acquisition on Image Quality and Intravoxel Incoherent Motion Parameters: A Pilot Study. *Radiology*, **36**, 270. https://doi.org/10.1148/radiol.12120686

[10] Yoon, J.H., Lee, J.M., *et al.* (2016) Pancreatic Steatosis and Fibrosis: Quantitative Assessment with Preoperative Multiparametric MR Imaging. *Radiology*, **279**, 140-150. https://doi.org/10.1148/radiol.2015142254

[11] Hecht, E.M., Liu, M.Z., Prince, M.R., *et al.* (2017) Can Diffusion-Weighted Imaging Serve as a Biomarker of Fibrosis in Pancreatic Adenocarcinoma? *Journal of Magnetic Resonance Imaging*, **46**, 392-402. https://doi.org/10.1002/jmri.25581

[12] Wang, Y., Chen, Z.E., Nikolaidis, P., McCarthy, R.J., Merrick, L., Sternick, L.A., *et al.* (2011) Diffusion-Weighted Magnetic Resonance Imaging of Pancreatic Adenocarcinomas: Association with Histopathology and Tumor Grade. *Journal of Magnetic Resonance Imaging*, **33**, 136-142. https://doi.org/10.1002/jmri.22414

[13] Klauss, M., Gaida, M.M., Lemke, A., Grunberg, K., Simon, D., Wente, M.N., *et al.* (2013) Fibrosis and Pancreatic Lesions: Counterintuitive Behavior of the Diffusion Imaging-Derived Structural Diffusion Coefficient D. *Investigative Radiology*, **48**, 129-133. https://doi.org/10.1097/RLI.0b013e31827ac0f1

[14] Zhang, T.T., *et al.* (2019) Diffusion Metrics for Staging Pancreatic Fibrosis and Correlating with Epithelial-Mesenchymal Transition Markers in a Chronic Pancreatitis Rat Model at 11.7T MRI. *Journal of Magnetic Resonance Imaging*, **15**. https://doi.org/10.1002/jmri.26995

[15] Burris, H.A., Moore, M.J., Andersen, J., *et al.* (1997) Improvements in Survival and Clinical Benefit with Gemcitabine as First-Line Therapy for Patients with Advanced Pancreas Cancer: A Randomized Trial. *Journal of Clinical Oncology*, **15**, 2403-2413. https://doi.org/10.1200/JCO.1997.15.6.2403

[16] Zhang, X., Ma, Y., Sun, Y., Cao, Y.-B., Li, Q. and Xu, C.-A. (2017) Gemcitabine in Combination with a Second Cytotoxic Agent in the First-Line Treatment of Locally Advanced or Metastatic Pancreatic Cancer: A Systematic Review and Meta-Analysis. *Targeted Oncology*, **12**, 309-321. https://doi.org/10.1007/s11523-017-0486-5

[17] Panebianco, C., Adamberg, K., *et al.* (2018) Influence of Gemcitabine Chemotherapy on the Microbiota of Pancreatic Cancer Xenografted Mice. *Cancer Chemotherapy and Pharmacology*, **81**, 773-782. https://doi.org/10.1007/s00280-018-3549-0

[18] Wu, L., Li, J., Fu, C., Kühn, B. and Wang, X. (2019) Chemotherapy Response of Pancreatic Cancer by Diffusion-Weighted Imaging (DWI) and Intravoxel Incoherent Motion DWI (IVIM-DWI) in an Orthotopic Mouse Model. *Magma* (*New York, NY*), **32**. https://doi.org/10.1007/s10334-019-00745-3

[19] Yoshikawa, T., Kawamitsu, H., *et al.* (2006) ADC Measurement of Abdominal Organs and Lesions Using Parallel Imaging Technique. *American Journal of Roentgenology*, **187**, 1521-1530. https://doi.org/10.2214/AJR.05.0778

[20] Kim, H., Arnoletti, P.J., Christein, J., Heslin, M.J., Posey, J.A., Pednekar, A., *et al.* (2014) Pancreatic Adenocarcinoma: A Pilot Study of Quantitative Perfusion and Diffusion-Weighted Breath-Hold Magnetic Resonance Imaging. *Abdominal Imaging*, **39**, 744-752. https://doi.org/10.1007/s00261-014-0107-z

[21] Yao, X.Z., Yun, H., Zeng, M.S., Wang, H., Sun, F., Rao, S.X., *et al.* (2013) Evaluation of ADC Measurements among Solid Pancreatic Masses by Respiratory-Triggered Diffusion-Weighted MR Imaging with Inversion-Recovery Fat-Suppression Technique at 3.0T. *Magnetic Resonance Imaging*, **31**, 524-528. https://doi.org/10.1016/j.mri.2012.09.006

[22] Ma, W.L., Zhang, G.W., *et al.* (2018) Quantitative Parameters of Intravoxel Incoherent Motion Diffusion Weighted Imaging (IVIM-DWI): Potential Application in Predicting Pathological Grades of Pancreatic Ductal Adenocarcinoma. *Quantitative Imaging in Medicine and Surgery*, **8**, 301-310. https://doi.org/10.21037/qims.2018.04.08

[23] Erkan, M., Hausmann, S., Michalski, C.W., Schlitter, A.M., Fingerle, A.A., Dobritz, M., *et al.* (2012) How Fibrosis Influences Imaging and Surgical Decisions in Pancreatic Cancer. *Frontiers in Physiology*, **3**, 389. https://doi.org/10.3389/fphys.2012.00389

[24] Lee, H.J., Rha, S.Y., Chung, Y.E., Shim, H.S., Kim, Y.J., Hur, J., *et al.* (2014) Tumor Perfusion-Related Parameter of Diffusion-Weighted Magnetic Resonance Imaging: Correlation with Histological Microvessel Density. *Magnetic Resonance in Medicine*, **71**, 1554-1558. https://doi.org/10.1002/mrm.24810

[25] Rong, D.L., Mao, Y.Z., Hu, W.M., *et al.* (2018) Intravoxel Incoherent Motion Magnetic Resonance Imaging for Differentiating Metastatic and Non-Metastatic Lymph Nodes in Pancreatic Ductal Adenocarcinoma. *European Radiology*, **28**, 2781-2789. https://doi.org/10.1007/s00330-017-5259-0

[26] Dasari, A., Shen, C., Halperin, D., *et al.* (2017) Trends in the Incidence, Prevalence, and Survival Outcomes in Patients with Neuroendocrine Tumors in the United States. *JAMA Oncology*, **3**, 1335-1342. https://doi.org/10.1001/jamaoncol.2017.0589

[27] Ville, S. (2016) Recent Advances in Pancreatic Surgery. *Scandinavian Journal of Surgery*, **105**. https://doi.org/10.1177/1457496916673801

[28] Wang, Y.W., Zhang, X.H. and Wang, B.T., *et al.* (2019) Value of Texture Analysis of Intravoxel Incoherent Motion Parameters in Differential Diagnosis of Pancreatic Neuroendocrine Tumor and Pancreatic Adenocarcinoma. *Chinese Medical Sciences Journal*, **34**, 1-9. https://doi.org/10.24920/003531

[29] Li, J.L., Liang, L.L., Yu, H., *et al.* (2018) Whole-Tumor Histogram Analysis of Non-Gaussian Distribution DWI Parameters to Differentiation of Pancreatic Neuroendocrine Tumors from Pancreatic Ductal Adenocarcinomas. *Magnetic Resonance Imaging*, **55**, 52-59. https://doi.org/10.1016/j.mri.2018.09.017

[30] Klau, M., Mayer, P., Bergmann, F., *et al.* (2015) Correlation of Histological Vessel Characteristics and Diffusion-Weighted Imaging Intravoxel Incoherent Motion-Derived Parameters in Pancreatic Ductal Adenocarcinomas and Pancreatic Neuroendocrine Tumors. *Investigative Radiology*, **50**, 792-797. https://doi.org/10.1097/RLI.0000000000000187

[31] Ma, W.L., Wei, M.Q., Han, Z.W., *et al.* (2019) The Added Value of Intravoxel Incoherent Motion Diffusion Weighted Imaging Parameters in Differentiating High-Grade Pancreatic Neuroendocrine Neoplasms from Pancreatic Ductal Adenocarcinoma. *Oncology Letters*, **18**, 5448-5458. https://doi.org/10.3892/ol.2019.10863

[32] Kang, K.M., Lee, J.M., Yoon, J.H., Kiefer, B., Han, J.K., Choi, B.I., *et al.* (2014) Intravoxel Incoherent Motion Diffusion-Weighted MR Imaging for Characterization of Focal Pancreatic Lesions. *Radiology*, **37**, 173-174. https://doi.org/10.1148/radiol.13122712

[33] Ma, L., He, W. and Liu, J. (2019) Differentiation of Avascular Pancreatic Neuroendocrine Tumors from Pancreatic Ductal Adenocarcinomas Using Apparent Diffusion Mono-Exponential Model and Intravoxel Incoherent Motion. *Chinese Journal of Medical Imaging*, **27**, 487-490.

[34] Kim, B., Lee, S.S., Yu, S.S., Cheong, H. and Jin, H.K. (2016) Intravoxel Incoherent Motion Diffusion-Weighted Imaging of the Pancreas: Characterization of Benign and Malignant Pancreatic Pathologies: IVIM DWI of the Pancreas. *Journal of Magnetic Resonance Imaging*, **45**, 260-269. https://doi.org/10.1002/jmri.25334

[35] Lemke, A., Laun, F.B., Klauss, M., Re, T.J., Simon, D., Delorme, S., Schad, L.R. and Stieltjes, B. (2009) Differentiation of Pancreas Carcinoma from Healthy Pancreatic Tissue Using Multiple b-Values: Comparison of Apparent Diffusion Coefficient and Intravoxel Incoherent Motion Derived Parameters. *Investigative Radiology*, **44**, 769-775. https://doi.org/10.1097/RLI.0b013e3181b62271

[36] Klau, M., Maier-Hein, K., Tjaden, C., Hackert, T., Grenacher, L., Stieltjes, B., *et al.* (2016) IVIM DW-MRI of Autoimmune Pancreatitis: Therapy Monitoring and Differentiation from Pancreatic Cancer. *European Radiology*, **39**, 582.

[37] De Robertis, R., Cardobi, N., *et al.* (2019) Intravoxel Incoherent Motion Diffusion-Weighted MR Imaging of Solid Pancreatic Masses: Reliability and Usefulness for Characterization. *Abdominal Radiology* (*New York*), **44**, 131-139. https://doi.org/10.1007/s00261-018-1684-z