DIAGNOSTIC ADVANCES

Various diffusion magnetic resonance imaging techniques for pancreatic cancer

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Abstract

Pancreatic cancer is one of the most common malignant tumors and remains a treatment-refractory cancer with a poor prognosis. Currently, the diagnosis of pancreatic neoplasm depends mainly on imaging and which methods are conducive to detecting small lesions. Compared to the other techniques, magnetic resonance imaging (MRI) has irreplaceable advantages and can provide valuable information unattainable with other noninvasive or minimally invasive imaging techniques. Advances in MR hardware and pulse sequence design have particularly improved the quality and robustness of MRI of the pancreas. Diffusion MR imaging serves as one of the common functional MRI techniques and is the only technique that can be used to reflect the diffusion movement of water molecules *in vivo*. It is generally known that diffusion properties depend on the characterization of intrinsic features of tissue microdynamics and microstructure. With the improvement of the diffusion models, diffusion MR imaging techniques are increasingly varied, from the simplest and most commonly used technique to the more complex. In this review, the various diffusion MRI techniques for pancreatic cancer are discussed, including conventional diffusion weighted imaging (DWI), multi-b DWI based on intra-voxel incoherent motion theory, diffusion tensor imaging and diffusion kurtosis imaging. The principles, main parameters, advantages and limitations of these techniques, as well as future directions for pancreatic diffusion imaging are also discussed.

Key words: Pancreatic cancer; Magnetic resonance imaging; Diffusion; Diffusion weighted imaging; Diffusion tensor imaging; Diffusion kurtosis imaging

Core tip: Magnetic resonance imaging (MRI) has irreplaceable advantages and can provide valuable information unattainable with other noninvasive or minimally invasive imaging techniques. Diffusion MR imaging serves as one of the common functional MRI

techniques and is the only technique that can be used to reflect the diffusion movement of water molecules *in vivo*. In this review, the various diffusion MR imaging techniques for pancreatic cancer will be discussed, including conventional diffusion weighted imaging (DWI), multi-b DWI based on intra-voxel incoherent motion theory, diffusion tensor imaging and diffusion kurtosis imaging.

INTRODUCTION

Pancreatic cancer is one of the most common malignant tumors with a poor prognosis, of which the 5-year survival rate range is no more than 5%[1] and as low as 0.4% to 2%[2,3]. It is reported that there has been little improvement in survival rate over the past 30 years[4]. Because the pancreas is deep-seated, there is a lack of apparent symptoms in early pancreatic cancer. In most cases, the tumor is diagnosed at an advanced stage, at which point, it does not benefit from radical surgery[2]. The management of pancreatic cancer is still encountered as a significant and unresolved therapeutic challenge.

Currently, the diagnosis of pancreatic neoplasm depends mainly on the imaging, and which methods can be conducive to detecting small lesions. Despite the continuing advances in diagnostic techniques, the early precise diagnosis of pancreatic cancer remains unsatisfactory. Early detection followed by surgical resection offers hope for a cure and is the key to improving pancreatic cancer survival[5]. Unfortunately, only 20% of patients are resectable at the time of diagnosis[6]. Computed tomography (CT), Magnetic resonance imaging (MRI), transabdominal and endoscopic ultrasonography (US and EUS) and endoscopic retrograde cholangiopancreatography (ERCP) also play an important role in the diagnosis of pancreatic cancer[7-10]. Among them, MRI has irreplaceable advantages, especially, the advances in MR hardware and pulse sequence design that have improved the quality and robustness of MRI of the pancreas. Today, MRI is an indispensable tool for pancreatic disorders and can provide valuable information unattainable with other noninvasive or minimally invasive imaging techniques[11-13].

With the rapid development of the MRI, diffusion MR imaging, which is based on the microscopic mobility of water molecules in the tissues without contrast administration, is a promising technique that is widely applied in clinical practice. Diffusion MR imaging is also the only available method that can measure the diffusion properties of tissues noninvasively and quantitatively[14,15], such as the diffusion weighted imaging (DWI), and has been helpful for the detection and characterization of pancreatic conditions[16,17]. The DWI technique serves as an excellent adjunct to routine abdominal MR imaging[13], is noninvasive in contrast to EUS and ERCP, and does not employ ionizing radiation like CT[18].

The changes in the composition and/or cellularity of tissues influences the random thermal diffusion of water molecules[19]. Compared to normal pancreatic tissue, pancreatic cancer has a higher cell density, relatively smaller extracellular space and a different blood supply. Thus, the diffusion of molecules in the cancer would be different from that in the normal pancreatic tissue. DWI, one of the functional MRI techniques based on water molecule movement, can depict this change in diffusion and can quantitatively measure the parameters that can represent these diffusion properties. Thus, DWI can reflect biologic abnormalities at an early stage[20].

In this review, the various diffusion MR imaging techniques for pancreatic cancer will be discussed, including DWI, multi-b DWI based on intra-voxel incoherent motion (IVIM) theory, diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI). The principles, main parameters, advantages and limitations of each technique and the future directions for pancreatic diffusion imaging will also be discussed.

DWI FOR PANCREATIC CANCER

Conventional DWI

Single-shot spin-echo echo-planar (SE-EPI) sequence is the most widely applied in the DW MR imaging (Figure 1). Conventional DWI uses the 2 motion-probing bipolar gradients in 3 directions (x, y, z) and acquires the signal from the 3 directions. The final DW image is derived from the fusion of the 3 images. DWI exploits the random motion of water molecules in biologic tissues. The water molecules diffuse in 3 different compartments: The intracellular, the intravascular, and the interstitial compartment. The diffusion of water molecules depends on the interactions with cell membranes, tissue compartments, and intracellular content[21]. Consequently, the diffusion of water in tissues reflects, to various degrees, a combination of tissue cellularity, tortuosity of extracellular spaces, integrity of cell membranes, and viscosity of fluids[22].

DWI was originally described for the central nervous system[23,24], which is particularly good for the diagnosis of ischemic stroke. In recent years, DWI has presented promising results in the diagnosis of some illnesses of the lower abdomen, such as those of the prostate[25,26]. DWI of the upper abdomen has been a technical challenge due to respiration, bowel peristalsis, blood flow and long acquisition times[18]. The implementation of ultrafast imaging techniques, such as parallel imaging, has made DWI (a combination of pulses and strong gradients) of the upper abdomen
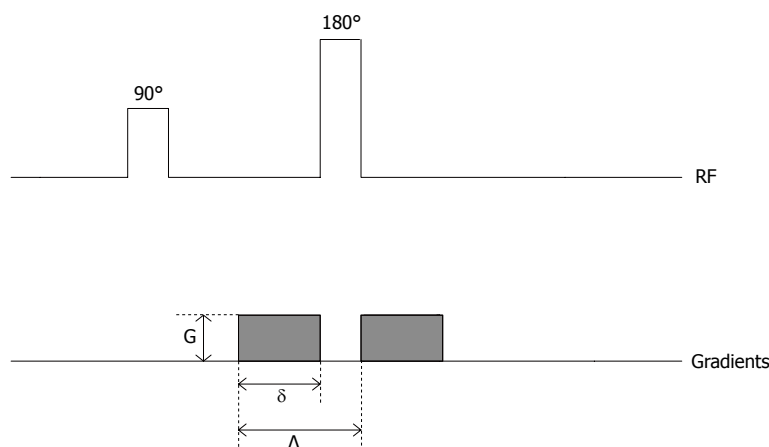
Figure 1 Diffusion weighted imaging sequence. Diffusion weighted imaging (DWI) applies the two motion-probing bipolar gradients on either side of the refocusing 180°pulse. The degree of diffusion weighting depends on the G (the amplitude of the gradients), δ (their duration) and Δ (the interval between gradients). This factor is quantitatively expressed by a parameter b, where $b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$ and γ is a constant of the gyromagnetic ratio. Assuming that the water molecules in tissues are motionless, the effects of the two motion-probing bipolar gradients can cancel each other. Thus, for the free molecular diffusion of water molecules, the displacement can be depicted by the DWI. RF: Radio frequency.

a feasible option. It has also been found to be useful in the differentiation of malignancy from benign liver lesions[27,28].

The three main parameters in the DWI are D value, b value and apparent diffusion coefficient (ADC) value. The D value is the diffusion parameter representing the free molecular diffusion and is defined as the average displacement by molecules in a certain direction, per unit of time. The D value can be affected by a variety of physiological factors, including respiration, perfusion, pulse and movement. The b value is referred to as the gradient factor, which can reflect the effect of the diffusion gradient. In the conventional DWI, the various b values can be selected. The low b value is applied more in water molecules with rapid movement or long diffusion distance, but the high b value is applied more in water molecules with slow movement or a short diffusion distance. Thus, the high b value is good for reducing the effect of the movement of water molecules due to perfusion[29].

In vivo, there are many factors that can affect the diffusion movement of water molecules, including the b value, D value and T2 shine-through effect. The T2 shine- through effect occurs when tissue with a long T2 relaxation time is characterized by hyperintensity on DWI. The ADC results in standardizing by considering the above factors and would be used to reflect the state of diffusion of water molecules *in vivo*.

DWI, which can be used for the qualitative and quantitative assessment of tissue diffusivity, can be routinely applied in clinical practice[16]. Recent studies indicate that DWI is also promising in pancreatic imaging[30-34]. These popular research studies also reflect the value of DWI in the diagnosis of pancreatic cancer. Moreover, compared to the other techniques, the sensitivity and specificity for the diagnosis of pancreatic cancer is valuable. Kartalis *et al*[18] conducted research on the value of DWI for pancreatic cancer, and their

results showed that the qualitative DWI of pancreatic cancer has an accuracy of 96%; further, DWI has been shown to have high sensitivity (92%) and specificity (97%), consistent with the findings of Ichikawa *et al*[30] (96.2% and 98.6%, respectively). Furthermore, a recent study shows that the addition of DWI to conventional MR imaging improves the sensitivity of cancer detection[35]. The sensitivity of DWI was close to that of dynamic gadolinium-enhanced MRI (97.7%), with a higher specificity (85.1%)[36]. Compared to the multidetector CT, positron emission tomography with CT and transabdominal ultrasound, the sensitivity and specificity of DWI are higher[18,37,38]. Although the sensitivity of EUS can reach 100%, it is invasive and has only 50% specificity[39]. Thus, it does not have wide application in clinical practice.

DWI can provide information regarding the cellular density and properties of the extracellular matrix[40,41]. The ADC values seem to reflect not only the underlying tissue microstructure but also the undirected movement of particles in thecapillaries[42]. The ADC value has been shown to be able to serve as a marker of cellularity[41,43]. The ADC value in the normal pancreas has been reported to range from 1.0 to 2.0×10^{-3} mm^2/s[44]. Many studies have shown that the ADC value of pancreatic cancer is lower than that of the normal pancreas[13,31,45-52]. There are three reasons that may explain these results[53]. First, tumor cell growth is rapid with high cellularity. Second, tumor cell atypia and the richness of organelles are positively correlated in the pancreatic tumor cells, and the nucleus and organelles are bulkier than that of normal pancreas cells. Thus, to some extent, tumor cell growth may limit the diffusion of water molecules. Third, the decrease of extracellular space from dense cellularity and extracellular fibrosis may also account for the restricted water diffusion[13,20,54-56]. However, Wang *et al*[54] reported that there is no significant difference in the ADC value between the normal pan-

creas and pancreatic cancer. These different results were most likely due to the application of different DWI experimental protocols and processing means[57]. The most important factor is the choice of b value. Kim *et al*[58] conducted research to determine the effect of the magnitude of b values on the ADC. Their results showed that the calculated ADC value could be affected by the magnitude of the maximum b value and that the higher the maximum b value, the lower the ADC value.

Additionally, the diverse differentiation of pancreatic cancer can be differentiated using DWI. For example, poorly differentiated adenocarcinoma had significantly lower ADCs than those of well/moderately differentiated adenocarcinomas[59].

Recently, DWI techniques have been shown not to be uniform, this controversial conclusion needs further study and differences in the sequence parameters and b values chosen may affect the ADC results. Future prospective studies are required to better determine the most appropriate use of the b value of pancreatic disease. Comparing different b values in a larger series of patients with malignant lesions would probably be of value; the quantification of the ADC of various lesions will be more accurate is feasible b values are used. The ADC values may have considerable overlap between the benign and malignant lesions, indicating that qualitative DWI seems to be more accurate than the quantitative analysis and can be used as an accurate method for the detection of pancreatic cancer[18].

Multi-b DWI based on IVIM theory

The rapid development of DWI monoexponential and biexponential models, of which the theoretical basis of the techniques is that the diffusion of water molecules is characterized by a normal distribution, has been applied to abdominal imaging using DWI. The monoexponential model is the most commonly used in daily practice. However, the biexponential model, which is based on the IVIM theory that was introduced as a technique to reflect both perfusion and diffusion by Le Bihan *et al*[20] can account for separating tissue diffusivity and tissue microcapillary perfusion. The unique feature of the multi-b DWI based on IVIM is the application of the multiple b value (Figures 2-4), which can be used in biexponential models to calculate the IVIM-derived parameters.

Monoexponential models are based on an assumption that the diffusion occurs in a free and unrestricted environment in biologic tissue, that is to say, the distribution of displacements obeys Gaussian law. Biexponential models reflect a combination of tissue perfusion and tissue diffusivity effects. It is now generally accepted that when the b value is relatively low (0-200 s/mm^2), the signal of ADC contains two parts; one is the diffusion of water molecules, and the other is the perfusion of water molecules in the capillary in local microcirculation. Further, the effect of perfusion is more sensitive. When the b value is relatively high (200-1000 s/mm^2), the

attenuation of signal due to the effect of perfusion is slight, at this point, the signal of DWI only approximately reflects the diffusion of water molecules[60]. This is a basic principle of conventional DWI and is the reason that the high b value was selected.

IVIM can accurately describe the relationship between signal attenuation and b values in the DWI and relatively obtain the parameters that present the effect of diffusion and perfusion in tissue.

Standard ADC value (or conventional ADC value) can be obtained from IVIM. Additionally, there are three main parameters in the IVIM, including D value, D* value and f value (perfusion fraction). D value is the true diffusion coefficient, also called the structural diffusion constant D value or slow ADC value, which reflects the tissue microstructure[48] and is the actual diffusion effect of water molecules. The D* value, also referred as the pseudo diffusion coefficient, perfusion-related coefficient or fast ADC value, is the diffusion parameter due to the perfusion effect of the incoherent microcirculation within the voxel[61]. The diffusion and perfusion can affect the signal intensity attenuation on DWI, and the proportion of the perfusion effect is defined as the perfusion fraction (Figure 4).

Diffusion-based IVIM has recently gained interest as a method to detect and characterize pancreatic lesions, and multi-b DWI based on IVIM theory shows very promising results and should be further investigated[48,62]. The f values were reported to make a contribution to distinguishing between normal pancreatic parenchyma and pancreatic neoplasm[45,49,50,63,64], and the f value proved to be the superior DWI-derived parameter for the differentiation of mass-forming pancreatitis and pancreatic carcinoma[50].

Many studies indicated that the IVIM-derived parameter's f value was a superior parameter for differentiating pancreatic tumors from the normal pancreas compared to the conventional ADC values and that the f value is lower in pancreatic cancer[48,51]. Lemke *et al*[63] conducted research to study the vascular contribution to the measured ADC value and to validate the IVIM theory; their results showed that the perfusion fraction f in the blood-suppressed pancreatic tissue decreased, possibly because the normal pancreas has a rich blood supply and will lead to a high f value. However, pancreatic cancer can destroy the normal pancreatic tissue and the vessel, and the decrease of vessel density may lead to the decreased f value, even if research shows that the f value in the IVIM-approach proved to be the best parameter for the differentiation between the normal pancreas and pancreatic cancer[48,51].

Compared to the f value, there is relatively less research on D value and D* value in pancreatic tumors. The structural diffusion constant D value reflects the tissue microstructure. The value of the D value for pancreatic cancer is controversial. Lemke *et al*[48] found that the D value showed no significant difference in pancreatic carcinoma and the healthy pancreas. Concia
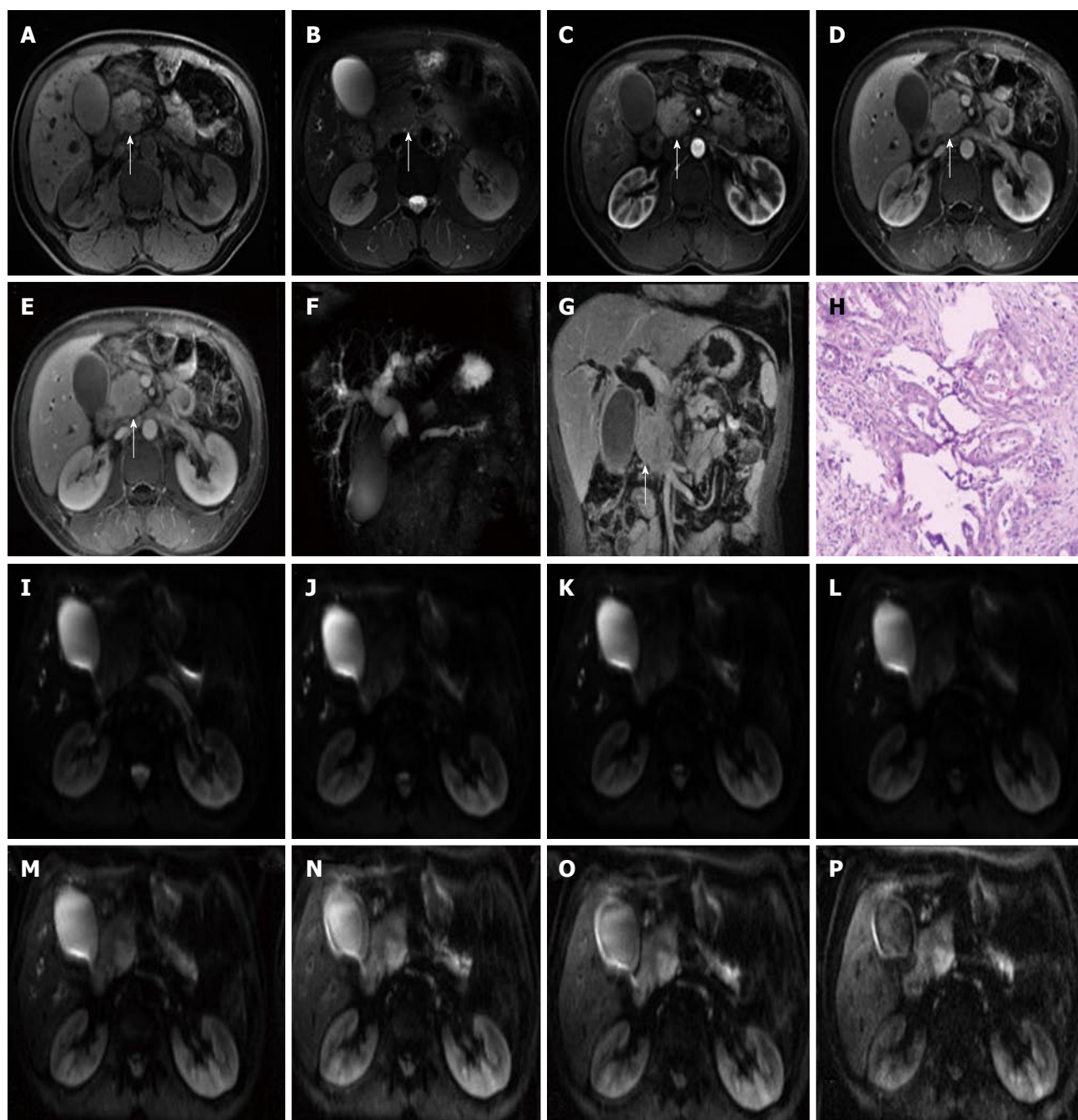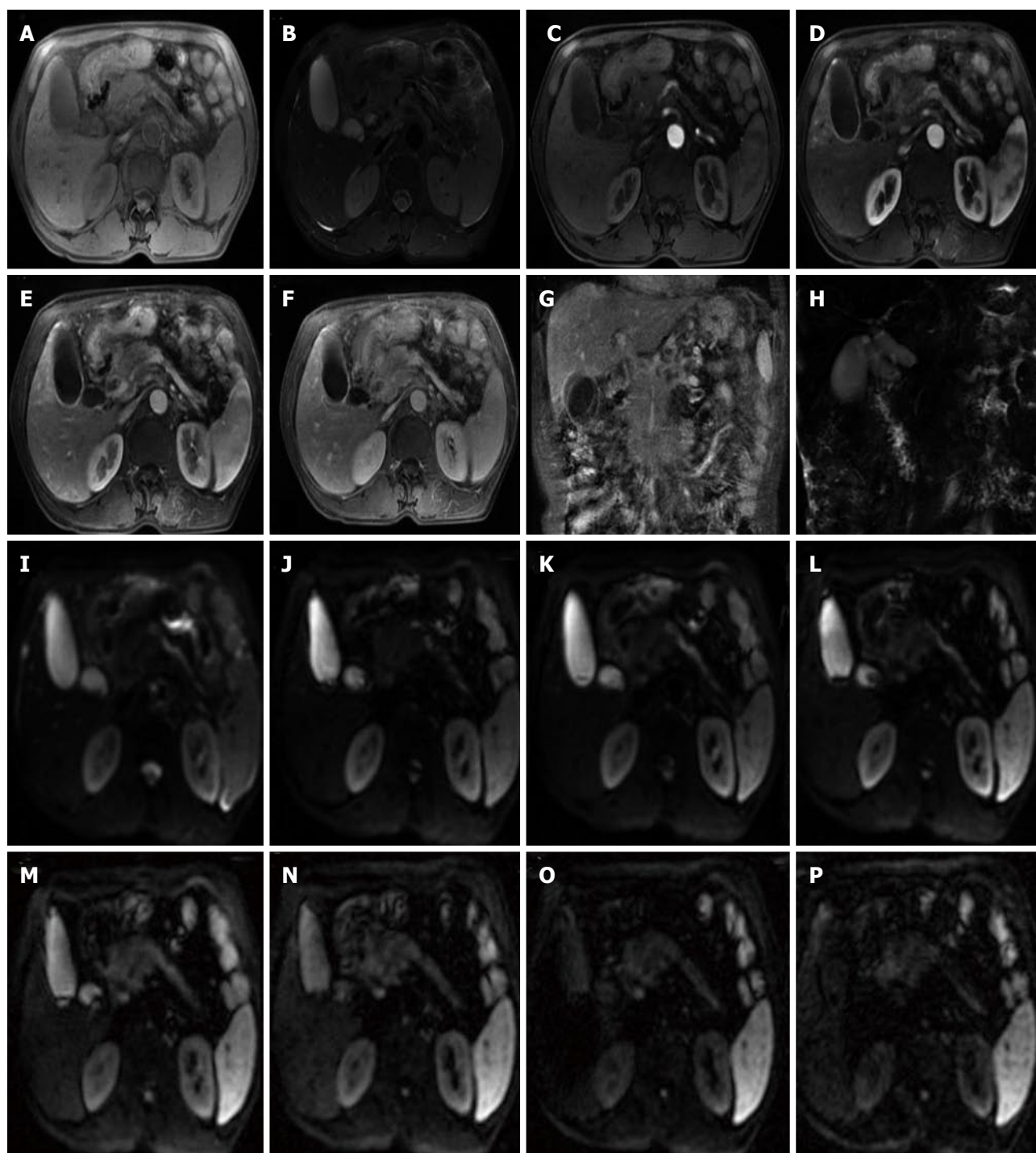
Figure 2 Images in a 47-year-old man with pancreatic moderately differentiated adenocarcinoma in the head of the pancreas (white arrows). A: Axial T1-weighted fat-suppressed gradient-echo MR image; B: Axial T2-weighted fat-suppressed fast spin-echo MR image; C-E and G: Axial and coronal slab three-dimensional liver acquisition with volume acceleration dynamic contrast-enhanced; F: MRCP shows the biliary obstruction; H: The pathology of the lesion is shown as pancreatic moderately differentiated adenocarcinoma; I-P: Multi-b DWI imaging (b = 0, 50, 100, 300, 500, 800, 1000 and 1500). MR: Magnetic resonance; DWI: Diffusion weighted imaging; MRCP: Magnetic resonance cholangiopancreatography.

et al[49] found that the D' value (D value was estimated by D' value) hardly differed in neuroendocrine pancreatic tumors and chronic pancreatitis. Klauss *et al*[50] reported that the D value cannot distinguish pancreatic carcinoma from mass-forming chronic pancreatitis. Klauss *et al*[42] reported that D value correlates with the histopathological grade of fibrosis in pancreatic lesions, which is the most characteristic histopathological feature of pancreatic carcinoma, compared with healthy pancreatic tissue, and concluded that D value can be

used to monitor novel therapy approaches that inhibit the formation of fibrosis. In 2014, Hwang *et al*[65] reported that the D value may be a better marker of cellularity than ADC. Until now, this was the only research on the D* value in pancreatic cancer. In 2014, Kang *et al*[51] used IVIM-derived parameters for the differentiation of common pancreatic tumors and concluded that the D* value and f values were more useful parameters in the differentiation of pancreatic adenocarcinomas from neuroendocrine tumors than were the ADC and D values.

Figure 3 Images in a 63-year-old man with a focal lesion in the head of the pancreas. MR imaging suggests that it is a malignancy. A: Axial T1-weighted fat-suppressed gradient-echo MR image; B: Axial T2-weighted fat-suppressed fast spin-echo MR image; C-G: Axial and coronal slab three-dimensional liver acquisition with volume acceleration dynamic contrast-enhanced; H: MRCP shows the biliary obstruction; I-P: Multi-b DWI imaging (b = 0, 50, 100, 300, 500, 800, 1000 and 1500). MR: Magnetic resonance; DWI: Diffusion weighted imaging; MRCP: Magnetic resonance cholangiopancreatography.

DTI FOR PANCREATIC CANCER

The sequence of DTI is similar to that of the DWI, and both are a SE-EPI sequence. The DTI also applies the two motion-probing bipolar gradients on either side of the refocusing 180° pulse. The difference or the unique feature is that the DTI acquires images from multiple directions. Thus, in clinical practice, a minimum of 6 non-collinear images is needed, but 12 or more images are often collected to increase the accuracy of the measure (Figure 5, Figure 6Q and R).

The DTI based on the diffusion of water molecules is anisotropic, which can be illustrated by the fact that the diffusion can be greater in one direction than in other directions and is termed "anisotropic" due to some factors, such as cell membranes, fibers, and myelin[66].
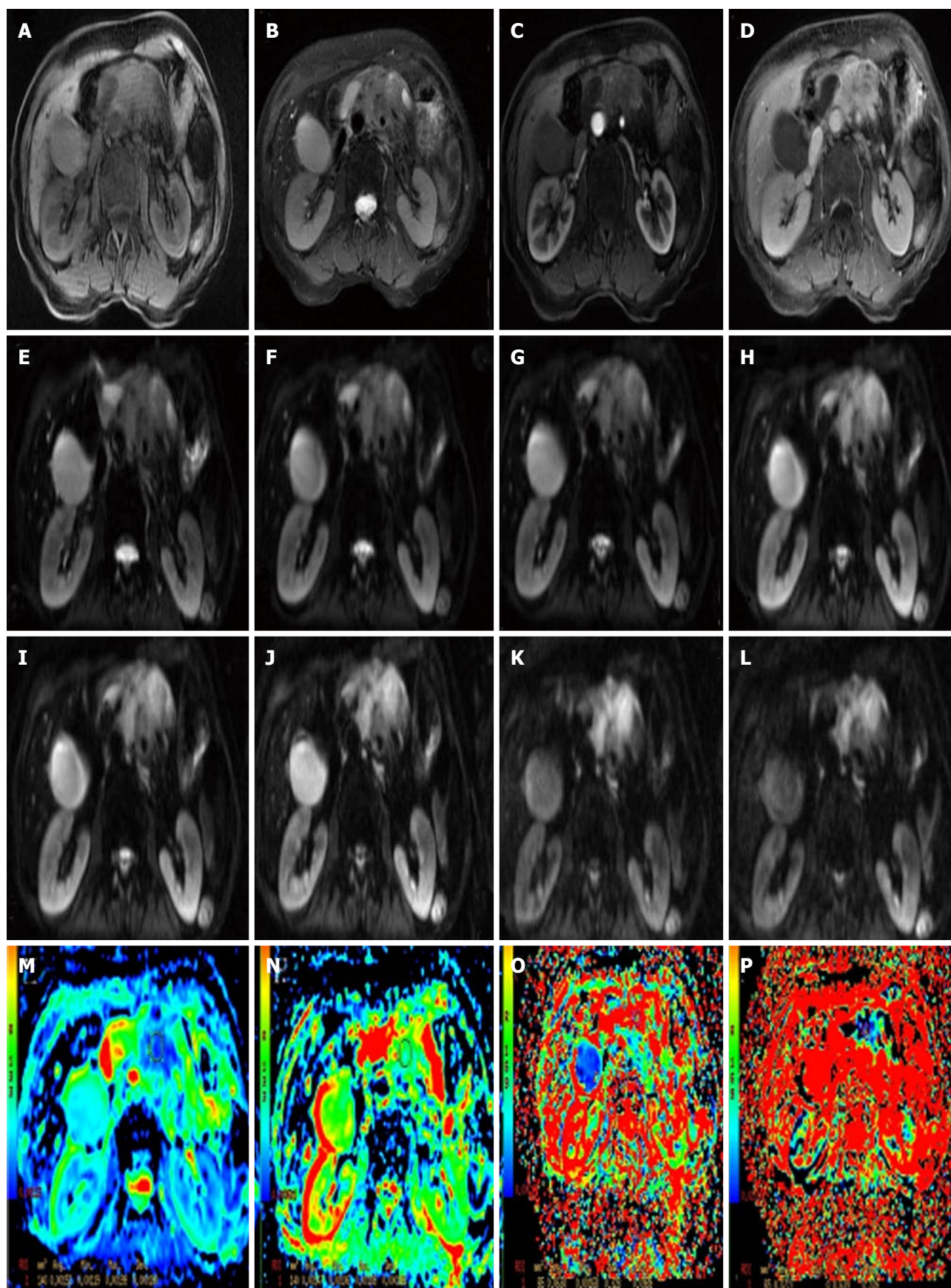
Figure 4 Images in a 65-year-old woman with a focal lesion in the neck of the pancreas. Magnetic resonance (MR) imaging suggests that it is a malignancy. A: Axial T1-weighted fat-suppressed gradient-echo MR image; B: Axial T2-weighted fat-suppressed fast spin-echo MR image; C and D: Axial slab three-dimensional liver acquisition with volume acceleration dynamic contrast-enhanced; E-L: Multi-b DWI (b = 0, 50, 100, 300, 500, 800, 1000 and 1500); M-P: Standard ADC = 1.52 × 10^{-3} mm^2/s, slow ADC = 1.39 × 10^{-3} mm^2/s, fast ADC = 63 × 10^{-3} mm^2/s and f = 7.2% generated by the post-processing from the multi-b DWI. DWI: Diffusion weighted imaging; ADC: Apparent diffusion coefficient.
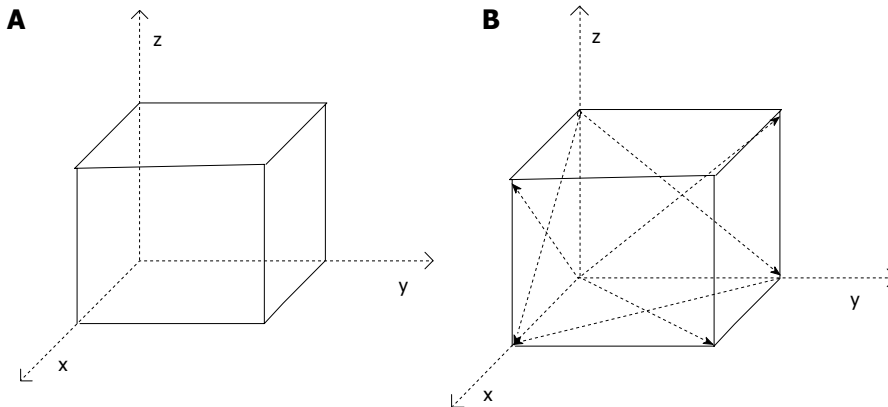
Figure 5 Conventional diffusion weighted imaging (A): The bipolar gradients in three directions; the diffusion tensor imaging bipolar gradients in the six non-collinear directions (solid black arrows) (B).

Conversely, without barriers, the random Brownian movement of water molecules is uniform in all directions or "isotropic". In general, DWI experiments yield an average ADC over three orthogonal directions, ignoring the anisotropy of tissue in the diffusion process[11,67]. Though the DTI model also assumes the diffusion distribution to be Gaussian, the same as the DWI, the DTI can measure the magnitude and directionality of water diffusion in tissue quantitatively[66]. The "tensor" in DTI refers to a mathematical construct for representing the magnitude of directional water diffusion in a three-dimensional volume[17].

DTI can not only reveal the degree of the restriction of water molecules in the diffusion movement but can also evaluate the different direction of diffusion. In a recently popular model, the DTI can provide some details on the microstructure of tissues that are not available in conventional imaging[68-70]. The major advantages of DTI are that it can assess the directionality of the diffusion of water molecules in biological tissue[71]. Thus, the DTI can evaluate more comprehensively and accurately the diffusion movement of water molecules in tissue. DTI also provides another non-invasive characterization of tissue microstructural properties *in vivo*[68].

DTI can demonstrate the subtle abnormalities of some diseases, and degrees of anisotropy have been reported to correlate with the microstructural changes in neural tissues[72,73] and even the peripheral nervous system[70]. DTI is also applied in myocardial infarction[74], prostate cancer[75,76], kidneys[77], liver[78], breast cancer[79], to name just a few. Indeed, it was reported that DTI would provide significant characterization of tissue microstructure and pathophysiology[80-82]. Each voxel in a DTI data set contains vector information that reflects the directionality and magnitude of diffusion in the underlying tissue.

There are five main parameters in the DTI, including mean diffusivity (MD), three eigenvalues $\lambda 1$, $\lambda 2$, $\lambda 3$, and fractional anisotropy (FA). MD is the average of the ADC in all directions and can represent the degree of diffusion. In theory, MD more truly reflects the water molecules' diffusion ability than ADC, but in clinical practice, the mean diffusivity is expressed as ADC. The FA represents the fraction of the magnitude of tensor that is due to anisotropic water diffusion[83]. That is to say, FA represents the diversity of diffusion direction, which is calculated by the three above eigenvalues[84].

In 2014, Nissan *et al*[57] used the DTI for patients with pancreatic-ductal-adenocacinoma, and their results indicated that the parameters of DTI ($\lambda 1$, $\lambda 2$, $\lambda 3$ and the ADC value) were lower than the values of the corresponding diffusion coefficients in the distal normal pancreatic tissue of the patients[57]; this outcome suggested that the fast diffusion component is dominated by the microcapillary perfusion process[63]. The results were consistent with those of previous DWI studies reporting lower ADC values in pancreatic cancer attributed to their higher cellularity[45-47].

DKI FOR PANCREATIC CANCER

The high b value is the most important feature of the DKI (Figure 6S and T). The DWI and IVIM are based on an assumption that the diffusion of water molecules obeys the normal distribution *in vivo*. However, Wu *et al*[85] reported that in biological tissue, complex cellular microstructures make water diffusion a highly hindered or restricted process, especially at high b values, where the distribution of displacements does not obey a Gaussian distribution. DKI was recently reported to be an extension to the Gaussian DT model[14], and it has become more popular in recent years.

DKI uses the same pulse sequences as that of conventional DWI, but with b values that are somewhat larger than those usually selected[86]. DKI is a straightforward extension of DTI, which requires only minor changes in data acquisition and processing[87,88]. The theory of DKI is based on the above principles, which describes the non-Gaussian diffusion behavior in tissues[14]. The literature has even reported that the DKI parameters, such as the radial or axial kurtosis, are more sensitive to brain physiology changes than the well-known DTI parameters in some white and gray matter structures[14]. In the white and gray matter structures,
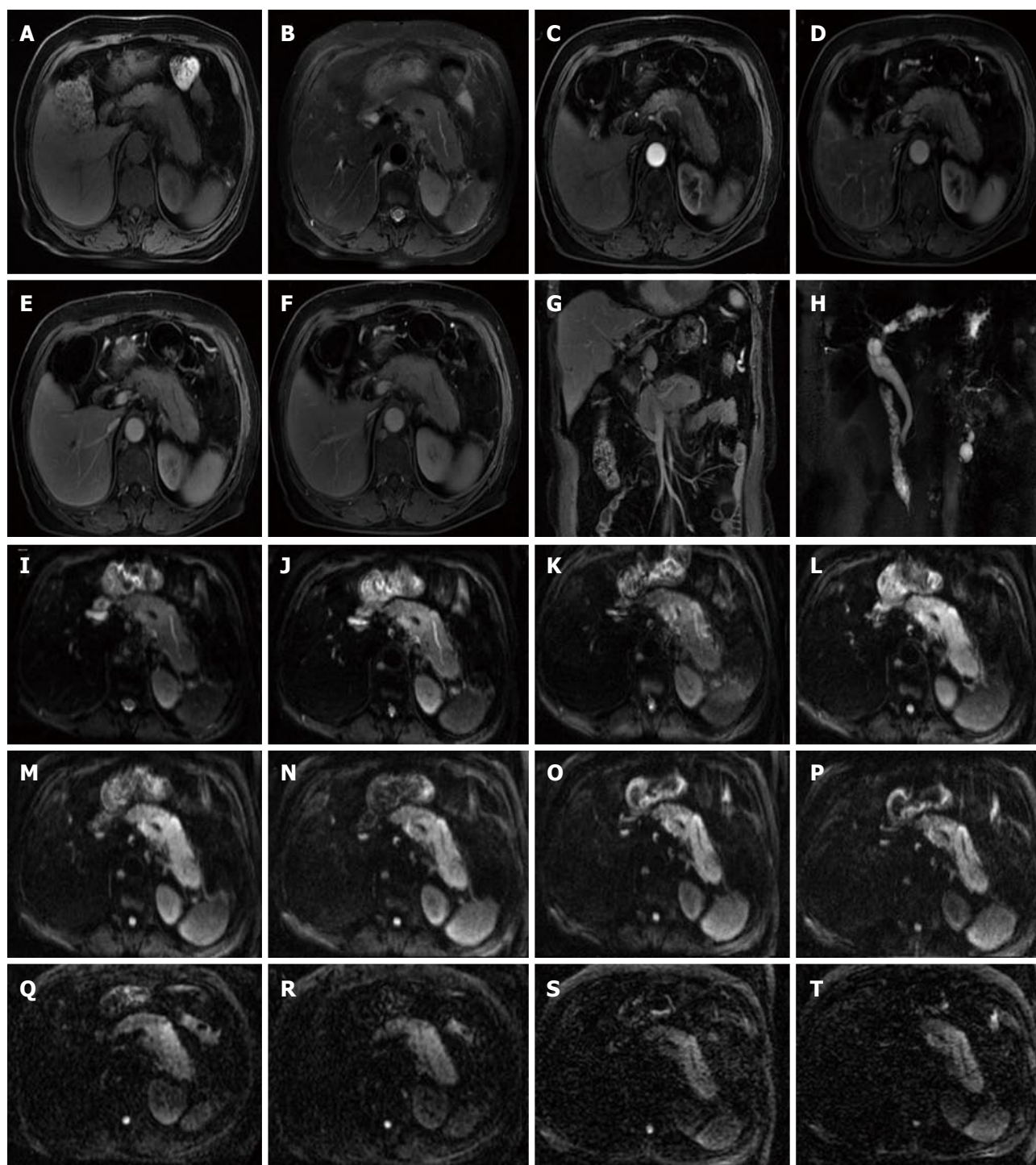
Figure 6 Images in a 52-year-old man with a focal lesion in the body and tail of the pancreas. MR imaging suggests that it is a malignancy. A: Axial T1-weighted fat-suppressed gradient-echo MR image; B: Axial T2-weighted fat-suppressed fast spin-echo MR image; C-G: Axial and coronal slab three-dimensional liver acquisition with volume acceleration dynamic contrast-enhanced; H: MRCP shows the dilated main pancreatic duct in the body and tail of pancreas; I-P: Multi-b DWI imaging (b = 0, 50, 100, 300, 500, 800, 1000 and 1500); Q and R: DTI (b = 500 and 800) using 30 diffusion gradients directions; S and T: DKI (b = 1500 and 2000) using 30 diffusion gradients directions. MR: Magnetic resonance; DWI: Diffusion weighted imaging; DKI: Diffusion kurtosis imaging; MRCP: Magnetic resonance cholangiopancreatography.

the DKI shows a better detection and characterization of various changes[89]. Hence, the DKI, which can measure the kurtosis excess of that distribution, allows for a more accurate description of the diffusion properties of neural tissues than the DTI model[87].

In the model, DKI can obtain the parameters that can also be derived from DWI and DTI, such as ADC and FA. Its main parameter is the mean kurtosis (MK). MK is a complex micro parameter that is associated with the complexity of the tissue structure. The high MK represents the more complex tissue structure[14].

There is less research on DKI for pancreatic cancer. However, in 2012, Rosenkrantz *et al*[90] used DKI in prostate cancer, and their preliminary findings suggest

an increased value for DKI compared with that of standard DWI in prostate cancer assessment. In theory, the pancreatic cancer occurs with tumor cell invasion and the proliferation of interstitial cells and connective tissue. The change in the tissue structure leads to the change of MK value.

ADVANTAGES AND LIMITATIONS FOR THESE DIFFUSION MR IMAGING FOR PANCREATIC CANCER

In pancreatic cancer, tumor cell growth will lead to changes in cellularity, tumor cell atypia, organelles, and extracellular space. All of these factors can change the water molecules' movement and restrict water diffusion. Extending the diffusion MR imaging, the diffusion of water molecules can be described more accurately and comprehensively. The conventional DWI can reflect the diffusion in one direction. The multi-b value DWI is based on the IVIM theory, which is generated by the blood flow in the tortuous microcirculation of the normal pancreatic tissue[51] and thus can reflect both perfusion and diffusion. The DTI can measure the magnitude and directionality of water diffusion in tissue quantitatively. DKI describes the non-Gaussian diffusion behavior in tissues.

However, we should be aware of the limitations of this technique: (1) Generally, in daily work, abdominal MRI suffers from interference and motional artifacts due to breathing[91,92]; (2) The gradient eddy currents in the EPI protocols can lead to the B0 field inhomogeneity and susceptibility differences[93,94]. Using a dielectric pad and a bellows belt for respiratory triggering can reduce geometrical distortions. DWI has been mostly acquired using single-shot echo planar imaging (ss EPI) to minimize motion-induced artifacts[95]; and (3) the choice of b value can also limit the technique. Currently, the ADC of the pancreas still does not reach unanimity; some scholars think the ADC, which was derived from the low b value, presents only a small part of the diffusion movement, which leads to contamination of other forms of IVIM, such as perfusion in the capillary bed. The perfusion will affect the diffusion when the b value is low, even though it can characterize the anatomy and the details of the lesion[55]. Finally, low b values result in increased ADC values[19,20]. Conversely, Kim *et al*[58] indicated that the high b value can be useful in clinical practice. The high b value means that it needs a longer echo time (TE), implying that it will lead to decreasing the SNR and increasing artifacts. Poor image quality will affect observation[18]. Using a high b value, the ADC value may be closer to the real state. In clinical practice, the choice of b value is controversial. As a compromise, a b value of 500 s/mm^2 was chosen[18]; however, the higher b value of 1000 s/mm^2 has been reported as good for malignant abdominal tumors[96] and the detection of pancreatic adenocarcinoma[32,96].

The choice of b value to minimize motion artifacts and to improve the SNR in pancreas is very important. Higher b values may be more sensitive to reflect true diffusion[30,97]. In clinical practice, taking the two factors into the consideration, a feasible b value can be selected depending on your purpose of study.

CONCLUSION

The proposed method may hold great promise for the non-invasive, non-contrast-enhanced imaging of pancreas lesions and may eventually become a screening tool for pancreatic cancer. MR is well suited to the quantitative and non-invasive measurement of diffusion. Diffusion MR imaging techniques are increasingly varied, from the simplest and most commonly used techniques to the more complex, such as from DWI to DKI. The diffusion MR imaging for pancreatic cancer revealed valuable advantages, such as high sensitivity and specificity. Moreover, diffusion MR imaging can aid in differentiating the different type of differentiation. These techniques go beyond traditional macrostructural volumetric methods and provide valuable information about underlying tissue integrity and organization at the microstructural and biochemical levels.

At present, a major issue with diffusion MR imaging is the lack of standardization of the protocol[98]. The IVIM-derived parameters in pancreatic cancer are controversial. For example, it is unknown how fibrosis affects diffusion parameters[42,52]. Further studies evaluating the behavior of IVIM-derived parameters in the diagnosis and treatment of pancreatic cancer are needed for standardization. One important point to bear in mind in future studies is that larger sample sizes, including imaging and histopathological workup are needed. The clinical report of utilization of the DTI and DKI in pancreatic cancer is still rare, and the potential of DTI to reveal the complex microstructure and physiology of the pancreas and detect pathological changes has not been investigated. Much work remains in solving the challenges inherent to tractography, which may certainly be a very promising technique that may be likely to contribute greatly to our understanding of nerve invasion.

In addition to the use of advanced DTI or DKI for pancreatic cancer, future advancements will come from continued study. Further standard diffusion MR imaging can benefit the accurate detection and staging of pancreatic cancer and provide the imaging evidence for clinical treatment.

REFERENCES

1   **Vincent A**, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet* 2011; **378**: 607-620 [PMID: 21620466 DOI: 10.1016/S0140-6736(10)62307-0]
2   **Krechler T**, Horejs J, Ulrych J, Zeman M, Macásek J, Dusková J, Zák A. Current status of pancreatic cancer diagnosis. *Cas Lek Cesk*

2011; **150**: 587-593 [PMID: 22292339]

3   **Singh M**, Maitra A. Precursor lesions of pancreatic cancer: molecular pathology and clinical implications. *Pancreatology* 2007; **7**: 9-19 [PMID: 17449961 DOI: 10.1159/000101873]

4   **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]

5   **Chari ST**, Kelly K, Hollingsworth MA, Thayer SP, Ahlquist DA, Andersen DK, Batra SK, Brentnall TA, Canto M, Cleeter DF, Firpo MA, Gambhir SS, Go VL, Hines OJ, Kenner BJ, Klimstra DS, Lerch MM, Levy MJ, Maitra A, Mulvihill SJ, Petersen GM, Rhim AD, Simeone DM, Srivastava S, Tanaka M, Vinik AI, Wong D. Early detection of sporadic pancreatic cancer: summative review. *Pancreas* 2015; **44**: 693-712 [PMID: 25931254 DOI: 10.1097/MPA.0000000000000368]

6   **Amedei A**, Niccolai E, Prisco D. Pancreatic cancer: role of the immune system in cancer progression and vaccine-based immunotherapy. *Hum Vaccin Immunother* 2014; **10**: 3354-3368 [PMID: 25483688 DOI: 10.4161/hv.34392]

7   **Li D**, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet* 2004; **363**: 1049-1057 [PMID: 15051286 DOI: 10.1016/S0140-6736(04)15841-8]

8   **Klimstra DS**, Pitman MB, Hruban RH. An algorithmic approach to the diagnosis of pancreatic neoplasms. *Arch Pathol Lab Med* 2009; **133**: 454-464 [PMID: 19260750 DOI: 10.1043/1543-2165-133.3.454]

9   **Jang SK**, Kim JH, Joo I, Jeon JH, Shin KS, Han JK, Choi BI. Differential diagnosis of pancreatic cancer from other solid tumours arising from the periampullary area on MDCT. *Eur Radiol* 2015; **25**: 2880-2888 [PMID: 25916385 DOI: 10.1007/s00330-015-3721-4]

10   **Putzer D**, Jaschke W. Radiological evaluation of focal pancreatic lesions. *Dig Dis* 2015; **33**: 91-98 [PMID: 25531502 DOI: 10.1159/000366045]

11   **Heyn C**, Sue-Chue-Lam D, Jhaveri K, Haider MA. MRI of the pancreas: problem solving tool. *J Magn Reson Imaging* 2012; **36**: 1037-1051 [PMID: 23090915 DOI: 10.1002/jmri.23708]

12   **de la Santa LG**, Retortillo JA, Miguel AC, Klein LM. Radiology of pancreatic neoplasms: An update. *World J Gastrointest Oncol* 2014; **6**: 330-343 [PMID: 25232458 DOI: 10.4251/wjgo.v6.i9.330]

13   **O'Neill E**, Hammond N, Miller FH. MR imaging of the pancreas. *Radiol Clin North Am* 2014; **52**: 757-777 [PMID: 24889170 DOI: 10.1016/j.rcl.2014.02.006]

14   **Poot DH**, den Dekker AJ, Achten E, Verhoye M, Sijbers J. Optimal experimental design for diffusion kurtosis imaging. *IEEE Trans Med Imaging* 2010; **29**: 819-829 [PMID: 20199917 DOI: 10.1109/TMI.2009.2037915]

15   **Yao X**, Kuang T, Wu L, Feng H, Liu H, Cheng W, Rao S, Wang H, Zeng M. Optimization of MR diffusion-weighted imaging acquisitions for pancreatic cancer at 3.0T. *Magn Reson Imaging* 2014; **32**: 875-879 [PMID: 24848293 DOI: 10.1016/j.mri.2014.04.011]

16   **Barral M**, Taouli B, Guiu B, Koh DM, Luciani A, Manfredi R, Vilgrain V, Hoeffel C, Kanematsu M, Soyer P. Diffusion-weighted MR imaging of the pancreas: current status and recommendations. *Radiology* 2015; **274**: 45-63 [PMID: 25531479 DOI: 10.1148/radiol.14130778]

17   **Moseley M**, Bammer R, Illes J. Diffusion-tensor imaging of cognitive performance. *Brain Cogn* 2002; **50**: 396-413 [PMID: 12480486]

18   **Kartalis N**, Lindholm TL, Aspelin P, Permert J, Albiin N. Diffusion-weighted magnetic resonance imaging of pancreas tumours. *Eur Radiol* 2009; **19**: 1981-1990 [PMID: 19308414 DOI: 10.1007/s00330-009-1384-8]

19   **Ma C**, Li YJ, Pan CS, Wang H, Wang J, Chen SY, Lu JP. High resolution diffusion weighted magnetic resonance imaging of the pancreas using reduced field of view single-shot echo-planar imaging at 3 T. *Magn Reson Imaging* 2014; **32**: 125-131 [PMID: 24231348 DOI: 10.1016/j.mri.2013.10.005]

20   **Le Bihan D**, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology* 1988; **168**: 497-505 [PMID: 3393671]

21   **Qayyum A**. Diffusion-weighted imaging in the abdomen and pelvis: concepts and applications. *Radiographics* 2009; **29**: 1797-1810 [PMID: 19959522 DOI: 10.1148/rg.296095521]

22   **Koh DM**, Collins DJ, Orton MR. Intravoxel incoherent motion in body diffusion-weighted MRI: reality and challenges. *AJR Am J Roentgenol* 2011; **196**: 1351-1361 [PMID: 21606299 DOI: 10.2214/AJR.10.5515]

23   **Le Bihan D**, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 1986; **161**: 401-407 [PMID: 3763909 DOI: 10.1148/radiology.161.2.3763909]

24   **Robertson RL**, Glasier CM. Diffusion-weighted imaging of the brain in infants and children. *Pediatr Radiol* 2007; **37**: 749-768 [PMID: 17589837 DOI: 10.1007/s00247-007-0515-0]

25   **Morgan VA**, Kyriazi S, Ashley SE, DeSouza NM. Evaluation of the potential of diffusion-weighted imaging in prostate cancer detection. *Acta Radiol* 2007; **48**: 695-703 [PMID: 17611881 DOI: 10.1080/02841850701349257]

26   **Bittencourt LK**, Hausmann D, Sabaneeff N, Gasparetto EL, Barentsz JO. Multiparametric magnetic resonance imaging of the prostate: current concepts. *Radiol Bras* 2014; **47**: 292-300 [PMID: 25741104 DOI: 10.1590/0100-3984.2013.1863]

27   **Bruegel M**, Holzapfel K, Gaa J, Woertler K, Waldt S, Kiefer B, Stemmer A, Ganter C, Rummeny EJ. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. *Eur Radiol* 2008; **18**: 477-485 [PMID: 17960390 DOI: 10.1007/s00330-007-0785-9]

28   **Gourtsoyianni S**, Papanikolaou N, Yarmenitis S, Maris T, Karantanas A, Gourtsoyiannis N. Respiratory gated diffusion-weighted imaging of the liver: value of apparent diffusion coefficient measurements in the differentiation between most commonly encountered benign and malignant focal liver lesions. *Eur Radiol* 2008; **18**: 486-492 [PMID: 17994317 DOI: 10.1007/s00330-007-0798-4]

29   **Szafer A**, Zhong J, Gore JC. Theoretical model for water diffusion in tissues. *Magn Reson Med* 1995; **33**: 697-712 [PMID: 7596275 DOI: 10.1002/mrm.1910330516]

30   **Ichikawa T**, Erturk SM, Motosugi U, Sou H, Iino H, Araki T, Fujii H. High-b value diffusion-weighted MRI for detecting pancreatic adenocarcinoma: preliminary results. *AJR Am J Roentgenol* 2007; **188**: 409-414 [PMID: 17242249 DOI: 10.2214/AJR.05.1918]

31   **Matsuki M**, Inada Y, Nakai G, Tatsugami F, Tanikake M, Narabayashi I, Masuda D, Arisaka Y, Takaori K, Tanigawa N. Diffusion-weighed MR imaging of pancreatic carcinoma. *Abdom Imaging* 2007; **32**: 481-483 [PMID: 17431713 DOI: 10.1007/s00261-007-9192-6]

32   **Takeuchi M**, Matsuzaki K, Kubo H, Nishitani H. High-b-value diffusion-weighted magnetic resonance imaging of pancreatic cancer and mass-forming chronic pancreatitis: preliminary results. *Acta Radiol* 2008; **49**: 383-386 [PMID: 18415779 DOI: 10.1080/02841850801895381]

33   **Jang KM**, Kim SH, Min JH, Lee SJ, Kang TW, Lim S, Choi D. Value of diffusion-weighted MRI for differentiating malignant from benign intraductal papillary mucinous neoplasms of the pancreas. *AJR Am J Roentgenol* 2014; **203**: 992-1000 [PMID: 25341136 DOI: 10.2214/AJR.13.11980]

34   **Lee NK**, Kim S, Kim DU, Seo HI, Kim HS, Jo HJ, Kim TU. Diffusion-weighted magnetic resonance imaging for non-neoplastic conditions in the hepatobiliary and pancreatic regions: pearls and potential pitfalls in imaging interpretation. *Abdom Imaging* 2015; **40**: 643-662 [PMID: 25216848 DOI: 10.1007/s00261-014-0235-5]

35   **Park MJ**, Kim YK, Choi SY, Rhim H, Lee WJ, Choi D. Preoperative detection of small pancreatic carcinoma: value of adding diffusion-weighted imaging to conventional MR imaging for improving confidence level. *Radiology* 2014; **273**: 433-443 [PMID:

24991989 DOI: 10.1148/radiol.14132563]

36 **Birchard KR**, Semelka RC, Hyslop WB, Brown A, Armao D, Firat Z, Vaidean G. Suspected pancreatic cancer: evaluation by dynamic gadolinium-enhanced 3D gradient-echo MRI. *AJR Am J Roentgenol* 2005; **185**: 700-703 [PMID: 16120921 DOI: 10.2214/ajr.185.3.01850700]

37 **Fletcher JG**, Wiersema MJ, Farrell MA, Fidler JL, Burgart LJ, Koyama T, Johnson CD, Stephens DH, Ward EM, Harmsen WS. Pancreatic malignancy: value of arterial, pancreatic, and hepatic phase imaging with multi-detector row CT. *Radiology* 2003; **229**: 81-90 [PMID: 14519871 DOI: 10.1148/radiol.2291020582]

38 **Farma JM**, Santillan AA, Melis M, Walters J, Belinc D, Chen DT, Eikman EA, Malafa M. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. *Ann Surg Oncol* 2008; **15**: 2465-2471 [PMID: 18551347 DOI: 10.1245/s10434-008-9992-0]

39 **Agarwal B**, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol* 2004; **99**: 844-850 [PMID: 15128348 DOI: 10.1111/j.1572-0241.2004.04177.x]

40 **Charles-Edwards EM**, deSouza NM. Diffusion-weighted magnetic resonance imaging and its application to cancer. *Cancer Imaging* 2006; **6**: 135-143 [PMID: 17015238 DOI: 10.1102/1470-7330.2006.0021]

41 **Thoeny HC**, Ross BD. Predicting and monitoring cancer treatment response with diffusion-weighted MRI. *J Magn Reson Imaging* 2010; **32**: 2-16 [PMID: 20575076 DOI: 10.1002/jmri.22167]

42 **Klauss M**, Gaida MM, Lemke A, Grünberg K, Simon D, Wente MN, Delorme S, Kauczor HU, Grenacher L, Stieltjes B. Fibrosis and pancreatic lesions: counterintuitive behavior of the diffusion imaging-derived structural diffusion coefficient d. *Invest Radiol* 2013; **48**: 129-133 [PMID: 23296083 DOI: 10.1097/RLI.0b013e31827ac0f1]

43 **Schnapauff D**, Zeile M, Niederhagen MB, Fleige B, Tunn PU, Hamm B, Dudeck O. Diffusion-weighted echo-planar magnetic resonance imaging for the assessment of tumor cellularity in patients with soft-tissue sarcomas. *J Magn Reson Imaging* 2009; **29**: 1355-1359 [PMID: 19472392 DOI: 10.1002/jmri.21755]

44 **Herrmann J**, Schoennagel BP, Roesch M, Busch JD, Derlin T, Doh LK, Petersen KU, Graessner J, Adam G, Habermann CR. Diffusion-weighted imaging of the healthy pancreas: ADC values are age and gender dependent. *J Magn Reson Imaging* 2013; **37**: 886-891 [PMID: 23086728 DOI: 10.1002/jmri.23871]

45 **Lee SS**, Byun JH, Park BJ, Park SH, Kim N, Park B, Kim JK, Lee MG. Quantitative analysis of diffusion-weighted magnetic resonance imaging of the pancreas: usefulness in characterizing solid pancreatic masses. *J Magn Reson Imaging* 2008; **28**: 928-936 [PMID: 18821618 DOI: 10.1002/jmri.21508]

46 **Fattahi R**, Balci NC, Perman WH, Hsueh EC, Alkaade S, Havlioglu N, Burton FR. Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas. *J Magn Reson Imaging* 2009; **29**: 350-356 [PMID: 19161187 DOI: 10.1002/jmri.21651]

47 **Fukukura Y**, Takumi K, Kamimura K, Shindo T, Kumagae Y, Tateyama A, Nakajo M. Pancreatic adenocarcinoma: variability of diffusion-weighted MR imaging findings. *Radiology* 2012; **263**: 732-740 [PMID: 22623694 DOI: 10.1148/radiol.120111222]

48 **Lemke A**, Laun FB, Klauss M, Re TJ, Simon D, Delorme S, Schad LR, Stieltjes B. Differentiation of pancreas carcinoma from healthy pancreatic tissue using multiple b-values: comparison of apparent diffusion coefficient and intravoxel incoherent motion derived parameters. *Invest Radiol* 2009; **44**: 769-775 [PMID: 19838121 DOI: 10.1097/RLI.0b013e3181b62271]

49 **Concia M**, Sprinkart AM, Penner AH, Brossart P, Gieseke J, Schild HH, Willinek WA, Mürtz P. Diffusion-weighted magnetic resonance imaging of the pancreas: diagnostic benefit from an intravoxel incoherent motion model-based 3 b-value analysis. *Invest Radiol* 2014; **49**: 93-100 [PMID: 24089021 DOI: 10.1097/RLI.0b013e3182a71cc3]

50 **Klauss M**, Lemke A, Grünberg K, Simon D, Re TJ, Wente MN, Laun FB, Kauczor HU, Delorme S, Grenacher L, Stieltjes B. Intravoxel incoherent motion MRI for the differentiation between mass forming chronic pancreatitis and pancreatic carcinoma. *Invest Radiol* 2011; **46**: 57-63 [PMID: 21139505 DOI: 10.1097/RLI.0b013e3181fb3bf2]

51 **Kang KM**, Lee JM, Yoon JH, Kiefer B, Han JK, Choi BI. Intravoxel incoherent motion diffusion-weighted MR imaging for characterization of focal pancreatic lesions. *Radiology* 2014; **270**: 444-453 [PMID: 24126370 DOI: 10.1148/radiol.13122712]

52 **Muraoka N**, Uematsu H, Kimura H, Imamura Y, Fujiwara Y, Murakami M, Yamaguchi A, Itoh H. Apparent diffusion coefficient in pancreatic cancer: characterization and histopathological correlations. *J Magn Reson Imaging* 2008; **27**: 1302-1308 [PMID: 18504750 DOI: 10.1002/jmri.21340]

53 **Sakuma H**, Nomura Y, Takeda K, Tagami T, Nakagawa T, Tamagawa Y, Ishii Y, Tsukamoto T. Adult and neonatal human brain: diffusional anisotropy and myelination with diffusion-weighted MR imaging. *Radiology* 1991; **180**: 229-233 [PMID: 2052700 DOI: 10.1148/radiology.180.1.2052700]

54 **Wang Y**, Chen ZE, Nikolaidis P, McCarthy RJ, Merrick L, Sternick LA, Horowitz JM, Yaghmai V, Miller FH. Diffusion-weighted magnetic resonance imaging of pancreatic adenocarcinomas: association with histopathology and tumor grade. *J Magn Reson Imaging* 2011; **33**: 136-142 [PMID: 21182131 DOI: 10.1002/jmri.22414]

55 **Padhani AR**, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, Hammoud DA, Rustin GJ, Taouli B, Choyke PL. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia* 2009; **11**: 102-125 [PMID: 19186405 DOI: 10.1593/neo.81328]

56 **Wang Y**, Chen ZE, Yaghmai V, Nikolaidis P, McCarthy RJ, Merrick L, Miller FH. Diffusion-weighted MR imaging in pancreatic endocrine tumors correlated with histopathologic characteristics. *J Magn Reson Imaging* 2011; **33**: 1071-1079 [PMID: 21509863 DOI: 10.1002/jmri.22541]

57 **Nissan N**, Golan T, Furman-Haran E, Apter S, Inbar Y, Ariche A, Bar-Zakay B, Goldes Y, Schvimer M, Grobgeld D, Degani H. Diffusion tensor magnetic resonance imaging of the pancreas. *PLoS One* 2014; **9**: e115783 [PMID: 25549366 DOI: 10.1371/journal.pone.0115783]

58 **Kim T**, Murakami T, Takahashi S, Hori M, Tsuda K, Nakamura H. Diffusion-weighted single-shot echoplanar MR imaging for liver disease. *AJR Am J Roentgenol* 1999; **173**: 393-398 [PMID: 10430143 DOI: 10.2214/ajr.173.2.10430143]

59 **Wang Y**, Miller FH, Chen ZE, Merrick L, Mortele KJ, Hoff FL, Hammond NA, Yaghmai V, Nikolaidis P. Diffusion-weighted MR imaging of solid and cystic lesions of the pancreas. *Radiographics* 2011; **31**: E47-E64 [PMID: 21721197 DOI: 10.1148/rg.313105174]

60 **Luciani A**, Vignaud A, Cavet M, Nhieu JT, Mallat A, Ruel L, Laurent A, Deux JF, Brugieres P, Rahmouni A. Liver cirrhosis: intravoxel incoherent motion MR imaging--pilot study. *Radiology* 2008; **249**: 891-899 [PMID: 19011186 DOI: 10.1148/radiol.2493080080]

61 **Zhang JL**, Sigmund EE, Chandarana H, Rusinek H, Chen Q, Vivier PH, Taouli B, Lee VS. Variability of renal apparent diffusion coefficients: limitations of the monoexponential model for diffusion quantification. *Radiology* 2010; **254**: 783-792 [PMID: 20089719 DOI: 10.1148/radiol.09090891]

62 **Grünberg K**, Grenacher L, Klauss M. Diffusion-weighted imaging of the pancreas. *Radiologe* 2011; **51**: 186-194 [PMID: 21305263 DOI: 10.1007/s00117-010-2059-9]

63 **Lemke A**, Laun FB, Simon D, Stieltjes B, Schad LR. An in vivo verification of the intravoxel incoherent motion effect in diffusion-weighted imaging of the abdomen. *Magn Reson Med* 2010; **64**: 1580-1585 [PMID: 20665824 DOI: 10.1002/mrm.22565]

64 **Re TJ**, Lemke A, Klauss M, Laun FB, Simon D, Grünberg K, Delorme S, Grenacher L, Manfredi R, Mucelli RP, Stieltjes B. Enhancing pancreatic adenocarcinoma delineation in diffusion derived intravoxel incoherent motion f-maps through automatic vessel and

duct segmentation. *Magn Reson Med* 2011; **66**: 1327-1332 [PMID: 21437979 DOI: 10.1002/mrm.22931]

65   **Hwang EJ**, Lee JM, Yoon JH, Kim JH, Han JK, Choi BI, Lee KB, Jang JY, Kim SW, Nickel MD, Kiefer B. Intravoxel incoherent motion diffusion-weighted imaging of pancreatic neuroendocrine tumors: prediction of the histologic grade using pure diffusion coefficient and tumor size. *Invest Radiol* 2014; **49**: 396-402 [PMID: 24500090 DOI: 10.1097/RLI.0000000000000028]

66   **Wozniak JR**, Lim KO. Advances in white matter imaging: a review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. *Neurosci Biobehav Rev* 2006; **30**: 762-774 [PMID: 16890990 DOI: 10.1016/j.neubiorev.2006.06.003]

67   **Fukuda Y**, Ohashi I, Hanafusa K, Nakagawa T, Ohtani S, An-naka Y, Hayashi T, Shibuya H. Anisotropic diffusion in kidney: apparent diffusion coefficient measurements for clinical use. *J Magn Reson Imaging* 2000; **11**: 156-160 [PMID: 10713948 DOI: 10.1002/(SICI)1522-2586(200002)11: 2<156: : AID-JMRI12>3.0.CO; 2-8]

68   **Basser PJ**, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 1996; **111**: 209-219 [PMID: 8661285 DOI: 10.1006/jmrb.1996.0086]

69   **Le Bihan D**, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging* 2001; **13**: 534-546 [PMID: 11276097 DOI: 10.1002/jmri.1076]

70   **Hagmann P**, Jonasson L, Maeder P, Thiran JP, Wedeen VJ, Meuli R. Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. *Radiographics* 2006; **26** Suppl 1: S205-S223 [PMID: 17050517 DOI: 10.1148/rg.26si065510]

71   **Basser PJ**, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J* 1994; **66**: 259-267 [PMID: 8130344 DOI: 10.1016/S0006-3495(94)80775-1]

72   **Vandermosten M**, Boets B, Wouters J, Ghesquière P. A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neurosci Biobehav Rev* 2012; **36**: 1532-1552 [PMID: 22516793 DOI: 10.1016/j.neubiorev.2012.04.002]

73   **Kuswanto CN**, Teh I, Lee TS, Sim K. Diffusion tensor imaging findings of white matter changes in first episode schizophrenia: a systematic review. *Clin Psychopharmacol Neurosci* 2012; **10**: 13-24 [PMID: 23429992 DOI: 10.9758/cpn.2012.10.1.13]

74   **Wu MT**, Tseng WY, Su MY, Liu CP, Chiou KR, Wedeen VJ, Reese TG, Yang CF. Diffusion tensor magnetic resonance imaging mapping the fiber architecture remodeling in human myocardium after infarction: correlation with viability and wall motion. *Circulation* 2006; **114**: 1036-1045 [PMID: 16940196 DOI: 10.1161/CIRCULATIONAHA.105.545863]

75   **Uribe CF**, Jones EC, Chang SD, Goldenberg SL, Reinsberg SA, Kozlowski P. In vivo 3T and ex vivo 7T diffusion tensor imaging of prostate cancer: Correlation with histology. *Magn Reson Imaging* 2015; **33**: 577-583 [PMID: 25721995 DOI: 10.1016/j.mri.2015.02.022]

76   **Li L**, Margolis DJ, Deng M, Cai J, Yuan L, Feng Z, Min X, Hu Z, Hu D, Liu J, Wang L. Correlation of gleason scores with magnetic resonance diffusion tensor imaging in peripheral zone prostate cancer. *J Magn Reson Imaging* 2015; **42**: 460-467 [PMID: 25469909 DOI: 10.1002/jmri.24813]

77   **Sigmund EE**, Vivier PH, Sui D, Lamparello NA, Tantillo K, Mikheev A, Rusinek H, Babb JS, Storey P, Lee VS, Chandarana H. Intravoxel incoherent motion and diffusion-tensor imaging in renal tissue under hydration and furosemide flow challenges. *Radiology* 2012; **263**: 758-769 [PMID: 22523327 DOI: 10.1148/radiol.12111327]

78   **Taouli B**, Chouli M, Martin AJ, Qayyum A, Coakley FV, Vilgrain V. Chronic hepatitis: role of diffusion-weighted imaging and diffusion tensor imaging for the diagnosis of liver fibrosis and inflammation. *J Magn Reson Imaging* 2008; **28**: 89-95 [PMID: 18581382 DOI: 10.1002/jmri.21227]

79   **Nissan N**, Furman-Haran E, Shapiro-Feinberg M, Grobgeld D, Degani H. Diffusion-tensor MR imaging of the breast: hormonal regulation. *Radiology* 2014; **271**: 672-680 [PMID: 24533873 DOI: 10.1148/radiol.14132084]

80   **Cauley KA**, Filippi CG. Diffusion-tensor imaging of small nerve bundles: cranial nerves, peripheral nerves, distal spinal cord, and lumbar nerve roots--clinical applications. *AJR Am J Roentgenol* 2013; **201**: W326-W335 [PMID: 23883249 DOI: 10.2214/AJR.12.9230]

81   **Jambawalikar S**, Baum J, Button T, Li H, Geronimo V, Gould ES. Diffusion tensor imaging of peripheral nerves. *Skeletal Radiol* 2010; **39**: 1073-1079 [PMID: 20593175 DOI: 10.1007/s00256-010-0974-5]

82   **Lee JW**, Kim JH, Kang HS, Lee JS, Choi JY, Yeom JS, Kim HJ, Chung HW. Optimization of acquisition parameters of diffusion-tensor magnetic resonance imaging in the spinal cord. *Invest Radiol* 2006; **41**: 553-559 [PMID: 16772848 DOI: 10.1097/01.rli.0000221325.03899.48]

83   **Masutani Y**, Aoki S, Abe O, Hayashi N, Otomo K. MR diffusion tensor imaging: recent advance and new techniques for diffusion tensor visualization. *Eur J Radiol* 2003; **46**: 53-66 [PMID: 12648802 DOI: 10.1016/S0720-048X(02)00328-5]

84   **Basser PJ**, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. 1996. *J Magn Reson* 2011; **213**: 560-570 [PMID: 22152371 DOI: 10.1016/j.jmr.2011.09.022]

85   **Wu EX**, Cheung MM. MR diffusion kurtosis imaging for neural tissue characterization. *NMR Biomed* 2010; **23**: 836-848 [PMID: 20623793 DOI: 10.1002/nbm.1506]

86   **Huang Y**, Chen X, Zhang Z, Yan L, Pan D, Liang C, Liu Z. MRI quantification of non-Gaussian water diffusion in normal human kidney: a diffusional kurtosis imaging study. *NMR Biomed* 2015; **28**: 154-161 [PMID: 25392938 DOI: 10.1002/nbm.3235]

87   **Jensen JH**, Helpern JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magn Reson Med* 2005; **53**: 1432-1440 [PMID: 15906300 DOI: 10.1002/mrm.20508]

88   **Lu H**, Jensen JH, Ramani A, Helpern JA. Three-dimensional characterization of non-gaussian water diffusion in humans using diffusion kurtosis imaging. *NMR Biomed* 2006; **19**: 236-247 [PMID: 16521095 DOI: 10.1002/nbm.1020]

89   **Cheung MM**, Hui ES, Chan KC, Helpern JA, Qi L, Wu EX. Does diffusion kurtosis imaging lead to better neural tissue characterization? A rodent brain maturation study. *Neuroimage* 2009; **45**: 386-392 [PMID: 19150655 DOI: 10.1016/j.neuroimage.2008.12.018]

90   **Rosenkrantz AB**, Sigmund EE, Johnson G, Babb JS, Mussi TC, Melamed J, Taneja SS, Lee VS, Jensen JH. Prostate cancer: feasibility and preliminary experience of a diffusional kurtosis model for detection and assessment of aggressiveness of peripheral zone cancer. *Radiology* 2012; **264**: 126-135 [PMID: 22550312 DOI: 10.1148/radiol.12112290]

91   **Dietrich O**, Reiser MF, Schoenberg SO. Artifacts in 3-T MRI: physical background and reduction strategies. *Eur J Radiol* 2008; **65**: 29-35 [PMID: 18162353]

92   **Riffel P**, Michaely HJ, Morelli JN, Pfeuffer J, Attenberger UI, Schoenberg SO, Haneder S. Zoomed EPI-DWI of the pancreas using two-dimensional spatially-selective radiofrequency excitation pulses. *PLoS One* 2014; **9**: e89468 [PMID: 24594702 DOI: 10.1371/journal.pone.0089468]

93   **Dietrich O**, Biffar A, Baur-Melnyk A, Reiser MF. Technical aspects of MR diffusion imaging of the body. *Eur J Radiol* 2010; **76**: 314-322 [PMID: 20299172 DOI: 10.1016/j.ejrad.2010.02.018]

94   **Jones DK**, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed* 2010; **23**: 803-820 [PMID: 20886566 DOI: 10.1002/nbm.1543]

95   **Yamada I**, Aung W, Himeno Y, Nakagawa T, Shibuya H. Diffusion coefficients in abdominal organs and hepatic lesions: evaluation with intravoxel incoherent motion echo-planar MR imaging. *Radiology* 1999; **210**: 617-623 [PMID: 10207458 DOI: 10.1148/

radiology.210.3.r99fe17617]

96   **Tsushima Y**, Takano A, Taketomi-Takahashi A, Endo K. Body diffusion-weighted MR imaging using high b-value for malignant tumor screening: usefulness and necessity of referring to T2-weighted images and creating fusion images. *Acad Radiol* 2007; **14**: 643-650 [PMID: 17502253 DOI: 10.1016/j.acra.2007.02.006]

97   **Huang WC**, Sheng J, Chen SY, Lu JP. Differentiation between pancreatic carcinoma and mass-forming chronic pancreatitis: usefulness of high b value diffusion-weighted imaging. *J Dig Dis* 2011; **12**: 401-408 [PMID: 21955434 DOI: 10.1111/j.1751-2980.2011.00517.x]

98   **Sandrasegaran K**. Functional MR imaging of the abdomen. *Radiol Clin North Am* 2014; **52**: 883-903 [PMID: 24889176 DOI: 10.1016/j.rcl.2014.02.018]

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