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REVIEW

Diffusion-weighted imaging of pancreatic cancer

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Abstract

Magnetic resonance imaging (MRI) is a reliable and accurate imaging method for the evaluation of patients with pancreatic ductal adenocarcinoma (PDAC). Diffusion-weighted imaging (DWI) is a relatively recent technological improvement that expanded MRI capabilities, having brought functional aspects into conventional morphologic MRI evaluation. DWI can depict the random diffusion of water molecules within tissues (the so-called Brownian motions). Modifications of water diffusion induced by different factors acting on the extracellular and intracellular spaces, as increased cell density, edema, fibrosis, or altered functionality of cell membranes, can be detected using this MR sequence. The intravoxel incoherent motion (IVIM) model is an advanced DWI technique that consent a separate quantitative evaluation of all the microscopic random motions that contribute to DWI, which are essentially represented by molecular diffusion and blood microcirculation (perfusion). Technological improvements have made possible the routine use of DWI during abdominal MRI study. Several authors have reported that the addition of DWI sequence can be of value for the evaluation of patients with PDAC, especially improving the staging; nevertheless, it is still unclear whether and how DWI could be helpful for identification, characterization, prognostic stratification and follow-up during treatment. The aim of this paper is to review up-to-date literature data regarding the applications of DWI and IVIM to PDACs.

Key words: Pancreas; Pancreatic neoplasms; Pancreatic ductal carcinoma; Magnetic resonance imaging; Diffusion magnetic resonance imaging

Core tip: Diffusion-weighted imaging (DWI) plays an important role for the identification of pancreatic adenocarcinoma, even if small in size, thus allowing early diagnosis. The intravoxel incoherent motion model is a promising DWI technique for the characterization of this tumor, with potential usefulness for the differentiation from mass-forming pancreatitis. Thanks to its high negative prognostic value, DWI should be used to assess the presence of liver metastases in patients with pancreatic adenocarcinoma.

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INTRODUCTION

Magnetic resonance imaging (MRI) has a well-established role in the evaluation of patients with pancreatic ductal adenocarcinoma (PDAC). MR diffusion-weighted imaging (DWI) is a relatively recent technological improvement of MRI. DW sequence can evaluate the diffusion of water molecules (Brownian motions) within biological tissues: All factors that tends to narrow the extracellular compartment or modify water exchanges through cell membranes lead to an impairment of the diffusion of water molecules. Tissues with restriction of water diffusion present high signal intensity on DW images and low signal intensity on the apparent diffusion coefficient (ADC) map; diffusion restriction can be also quantified through the calculation of the ADC value within specific regions of interest (ROIs).

Thanks to technological improvements that have shortened the acquisition time and improved the signal-to-noise ratio, DWI sequence has been widely adopted as a part of abdominal MRI examination protocols. Several authors have assessed the usefulness of this technique for the evaluation of PDAC and have reported that the addition of DWI sequence might represent an adjunct value, especially improving the staging. Nevertheless, it is still unclear whether and how DWI could be of value for identification, characterization, prognostic stratification and post-treatment follow-up of these patients.

The aim of this paper is to describe the applications of DWI to the evaluation of patients with PDAC, in particular regarding lesion identification, characterization, prognostication and assessment of response to therapy, through a review of up-to-date literature data.

DWI: TECHNICAL BASES

In 1965, Stejskal and Tanner[1] developed a modified T2-weighted MRI sequence that included motion-probing gradients for the detection of the diffusion of water molecules. DWI enables the visualization of Brownian random molecular motions in the extracellular and intracellular spaces[2]. This technique can provide information on the cellular density and the integrity of cell membranes, since the degree of restriction to water diffusion in biologic tissues is inversely correlated to these features[3-6]. Nevertheless, any factor that modifies the extracellular space (fibrosis, edema, size of the cells, size and density of intratumoral vessels) may also contribute to diffusion restriction.

The first clinical application of DWI has been the evaluation of the hyperacute phase of brain ischemia. Cytotoxic edema induced by ischemia and neuronal death narrows the extracellular space and therefore decreases the diffusion of water molecules. Thereafter, DWI has been proven to be useful for the assessment of a variety of intra-cranial pathologic conditions, as tumors. High cellular density, which is typical of tumors, narrows the extracellular space and determines a high density of hydrophobic cellular membranes[7], leading to impaired diffusion of water molecules.

Technical advances, as the use of parallel imaging techniques, have shortened the acquisition time and have improved the contrast- and signal-to-noise ratio of this sequence, thus leading to an increased use of DWI in the MR evaluation of the abdomen[8].

The acquisition technique and parameters may vary from institution to institution. The choice of acquisition using free-breathing, respiratory-triggering, navigator-tracking, or breath-hold is optional; nevertheless, this selection may influence image quality and acquisition time: Free-breathing acquisition provides lower image quality, but the acquisition time is invariably shorter as compared to respiratory-gated acquisitions. Free-breathing DWI acquisition is therefore more widely used for "work horse" MRI abdominal protocols.

The *b*-value is a technical parameter that regulates the strength, duration and interval of bipolar motion-probing gradients and affects the degree of phase dispersion and the diffusion weighting of the images. DW images are acquired using at least two different *b*-values, both low (for example, 0 or 50 s/mm^2) and high (for example, 800 or 1000 s/mm^2). Changing the *b*-value leads to a variation of the sensitivity of the DW sequence to water motion[2]. At low *b*-values, lesions with high diffusion (*e.g.*, cysts) appear hyperintense compared to the surrounding tissues, since the T2-weighted contrast is still dominant. Increasing the *b*-value leads to a signal loss of tissues with "free diffusion" (*i.e.*, cysts, cerebro-spinal fluid, necrosis), whereas tissues with restricted diffusion, as solid neoplastic areas, will appear hyperintense.

Low *b*-value images have generally higher spatial resolution and better image quality, being comparable to T2-weighted fat-suppressed images, while high *b*-value images have higher contrast resolution, but

lower spatial resolution.

The ADC quantifies the diffusion of water molecules and can be represented with the ADC map. The evaluation of the ADC map is mandatory: Hyperintense areas on both high *b*-value DW image and the ADC map are typical of tissues with "T2-shine through" effect, that occurs because of long T2 decay time in some cases, as for example subacute infarction with vasogenic edema or epidermoid cysts. In contrast, areas with restricted water diffusion will appear hyperintense on high *b*-value DW image and hypointense on ADC map. Beyond the visual assessment there is also the possibility of a quantitative analysis by the calculation of the ADC value, which can be measured drawing ROIs within the target tissue; ADC measurement can be expressed as a mean value or as a histogram representing the distribution of different ADC values within the ROI.

The ADC is a combined measurement of all molecular random movements of water molecules (diffusion) and blood microcirculation in the capillaries (perfusion)[9]. The intravoxel incoherent motion (IVIM) model takes these two sources of signal decay into account, thus providing a separate quantification of diffusion (provided by the diffusion coefficient - D and the pseudodiffusion coefficient - D*) and perfusion (represented by the perfusion fraction - f) parameters[10]. IVIM can therefore quantify the relative contribution of these parameters to the total diffusion restriction and can evaluate perfusional features without the need of contrast medium injection. IVIM acquisition needs in most cases respiratory compensation, and therefore this sequence has a long acquisition time. For this reason, the IVIM model is not completely integrated into clinical practice.

IDENTIFICATION

The sensitivity of computed tomography (CT) in revealing PDAC is high, ranging between 89% and 97%[11]. MRI offers better soft tissue contrast compared with CT; PDACs are usually well recognized on T1-weighted and DW images, owing to differences between the histological components of the tumor and the circumstant parenchyma. There is however no significant diagnostic advantage of MRI over contrast-enhanced CT for the identification of PDAC[12].

Studies on DWI revealed that this sequence might have an important role in the identification of PDAC. Both visual analysis[13-15] and ADC measurement[14,16-21] can reliably distinguish PDAC from the background pancreatic parenchyma. Pancreatic tumors, even if small in size, almost invariably show diffusion restriction, as revealed by studies conducted on neuroendocrine tumors[22], presenting as a focal hyperintense area on high *b*-value DW images with hypointensity on ADC map[13].

Identification of PDAC can be therefore improved by the use of DW images, as tumors are brighter than the circumstant pancreatic parenchyma: The high contrast resolution of high *b*-value DW images usually leads to a clear identification of these tumors.

PDACs present lower ADC values than the circumstant parenchyma. Nevertheless, it is still unclear which is the histological component that mainly contributes to diffusion restriction in PDACs. Lemke[23] reported that the IVIM-derived f value (perfusion fraction), which reflects blood microcirculation, was significantly lower in PDACs than in the healthy pancreas (mean, 8.59% ± 4.6% *vs* 25.0% ± 6.2%, respectively): This may be related to the histological composition of PDAC, which is mainly composed by fibrotic stroma with very few vessels.

The best way to reduce mortality in patients with PDAC is through early diagnosis, that necessary derives from an improvement of the identification of this tumor. This is of particular importance in high-risk patients (*i.e.*, those with familiarity). At this regard, Del Chiaro *et al*[24] reported the efficacy of a MRI-based screening program in individuals at risk. Unfortunately, this study did not report the accuracy of DWI in PDAC detection; nevertheless, it could be argued that the high contrast resolution of DW images may help in the early identification of PDACs in high-risk patients.

Some authors reported that small or well-differentiated PDACs may lack typical CT features, as ill-defined margins and hypovascularity, and could therefore be missed or misdiagnosed[25]. Prokesch *et al*[26] emphasized that indirect signs such as mass effect, atrophic distal parenchyma, and interrupted duct sign were important indicators of the presence of tumors with no visible tumor–pancreas contrast. MRI could be helpful in these cases. Some old studies have suggested that T1-weighted spin-echo images with fat suppression and dynamic gradient-echo MR images enhanced with gadolinium could be superior to CT for detecting small pancreatic carcinomas[27,28]. At present, no single study evaluated the efficacy of DW images in the identification of small PDACs; nevertheless, as high *b*-value DW images provide high contrast resolution, this sequence is probably of value in this regard.

Chronic pancreatitis may represent a confusing factor for PDAC identification, as both T1-weighted and DW images may fail to discriminate between fibrotic parenchyma and the tumor, which typically contains large amount of fibrotic tissue. At this regard, Fukukura[29] reported that visual assessment of DW images might be misleading in these patients, as chronic inflammation frequently appears hyperintense on high *b*-value images. Despite this, the mean ADC value of PDACs ($1.160 \pm 0.22 \times 10^{-3}$ mm^2/s) was significantly lower than that of the pancreatic parenchyma affected by chronic pancreatitis ($1.24 \pm 0.23 \times 10^{-3}$ mm^2/s, $P = 0.004$). ADC quantification can be therefore helpful when the visual assessment is doubtful but clinical setting (presence of painless jaundice, newly onset diabetes or high CA 19.9 serum levels) or MRI features are highly suspicious for a PDAC associated with chronic

Table 1 Comparison of apparent diffusion coefficient values between different solid pancreatic neoplasms

Ref.	No. of patients	Field strength (T)	*b*-values (s/mm^2)	Mean ± SD ADC values (× 10^{-3} mm^2/s)	*P* value
Yao *et al*[18]	30 PDACs	3	0, 600	1.57 ± 0.26	< 0.001
	12 SPTs			1.05 ± 0.35	
	15 PanNETs			1.62 ± 0.41	
Barral *et al*[19]	18 malignant[1]	1.5	0, 400, 800	1.150[2]	< 0.05
	10 benign			2.493[2]	
Lee *et al*[33]	47 PDACs	1.5	0, 500, 1000	1.23 ± 0.18	NS
	6 SPTs			1.16 ± 0.36	
	5 PanNETs			1.30 ± 0.41	

[1]Including 13 PDACs; [2]Median. T: Tesla; ADC: Apparent diffusion coefficient; PDAC: Pancreatic ductal adenocarcinoma; SPT: Solid pseudopapillary tumor; PanNET: Pancreatic neuroendocrine tumor; NS: Not statistically significant.

pancreatitis.

Some technical aspects should be considered regarding PDAC identification using DWI. Respiratory-triggered acquisitions provide higher spatial resolution and signal-to-noise ratio compared to free breathing and breath-hold acquisitions, as reported by Kartalis *et al*[30]. As previously stated, respiratory-gated acquisition of DW images is time-consuming and is not frequently performed during clinical practice. Contrast medium administration does not induce modifications of DWI features: Liu *et al*[31] reported no significant differences in ADC measurements when comparing precontrast to postcontrast DWI acquired 6-7 min after contrast medium administration.

Summarizing, it seems that CT and conventional MRI sequences have a similar accuracy for PDAC identification in most cases; further studies should be performed to assess the efficacy of DW images in identification of small/well differentiated PDACs.

CHARACTERIZATION

Pancreatic adenocarcinoma is usually hypointense to the normal pancreas on T1-weighted fat-suppressed sequences, shows hypoenhancement during arterial phase, and shows progressive enhancement on delayed sequences. These features, and particularly the hypointense appearance on pancreatic phase images, are distinctive of this tumor[32]. Very few studies have focused on the role of DWI for the differential diagnosis of solid pancreatic tumors. Literature data reveal that quantitative analysis of DW images can distinguish between benign and malignant pancreatic lesions[19]. Nevertheless, ADC quantification could fail in the differentiation of solid pancreatic lesions, due to a wide overlap in ADC values[18-20,33]. Details regarding ADC quantification of pancreatic solid neoplasms are reported in Table 1. Yao *et al*[18] reported that ADC measurement using respiratory-triggered DWI at 3. T may aid to disclose the histopathological pattern of normal pancreas and solid pancreatic masses, which may be helpful in characterizing solid pancreatic lesions: statistical difference was noticed in ADC values among PDAC, solid pseudopapillary tumors and neuroendocrine tumors (PanNETs). Barral *et al*[19] and Lee *et al*[33], instead, did not reported significant differences in ADC values between PDACs and other solid pancreatic tumors.

IVIM-derived parameters may be helpful for characterization. Kang *et al*[34] found that perfusion-related parameters as f (perfusion fraction) were significantly lower in PDACs as compared to normal pancreas, chronic pancreatitis, and PanNETs. Concia *et al*[35] reported that PDACs are characterized by very low $ADC_{0,50}$ and *f* values, significantly different from PanNETs and chronic pancreatitis. These findings are consistently related to the histologic nature of PDACs, which are fibrous tumors with very few internal vessels, as compared to the healthy parenchyma and to PanNETs.

The possibility to differentiate mass-forming inflammatory diseases from PDAC by means of DWI is a topic of particular interest. These entities frequently present overlapping features at conventional MRI evaluation. Overall, mass-forming pancreatitis (MFP) and autoimmune pancreatitis (AIP) tend to present lower ADC values than PDACs; nevertheless, literature data are inhomogeneous and controversial[18,36-43]. Details regarding the main published studies dealing with this issue are reported in Table 2. A meta-analysis by Niu *et al*[43], which included 9 studies, reported a pooled sensitivity and specificity of 86% and 82%, with an AUC of 0.91, for the differentiation between PDAC and MFP using DWI alone.

IVIM-derived parameters may be helpful for this differentiation. Lee *et al*[33] reported that ADC_{500}, ADC_{1000}, and D of MFP were all significantly lower than those of pancreatic cancer. Klauss *et al*[41] found that F (perfusion fraction) values were significantly higher in focal pancreatitis (16.3%) compared with PDACs (8.2%): This was explained by the increasing perfusion effects at lower *b*-values, which were correlated with a relatively higher vascularity in pancreatitis.

The comparison of ADC values of focal pancreatitis and pancreatic carcinoma to the remaining pancreas may be helpful for the differentiation of these diseases: Fattahi *et al*[42] reported that ADC values of focal panc-

Table 2 Comparison of apparent diffusion coefficient values between pancreatic ductal adenocarcinomas and mass-forming pancreatitis/autoimmune pancreatitis

Ref.	No. of patients	Field strength (T)	*b*-values (s/mm^2)	Mean ± SD ADC values (× 10^{-3} mm^2/s)	*P* value
Yao *et al*[18]	30 PDACs 15 MFPs	3	0, 600	1.57 ± 0.26 1.19 ± 0.15	< 0.001
Barral *et al*[19]	13 PDACs 8 MFPs	1.5	0, 400, 800	1.150 1.160	NS
Lee *et al*[33]	47 PDACs 13 MFP	1.5	0, 500, 1000	1.46 ± 0.20/1.23 ± 0.18[1] 1.23 ± 0.22 /1.04 ± 0.18[1]	< 0.05
Hur *et al*[36]	28 PDACs 9 AIPs	1.5 or 3	0, 500	1.512 1.086	< 0.05
Ma *et al*[37]	25 PDACs 14 MFPs	3	0, 800	1.39 ± 0.22 1.21 ± 0.23	< 0.05
Huang *et al*[38]	37 PDACs 14 MFPs	3	0, 1000	1.06 ± 0.15 1.35 ± 0.14	< 0.05
Kamisawa *et al*[39]	40 PDACs 13 AIPs	1.5	800	1.249 ± 0.113 1.012 ± 0.112	< 0.001
Wiggermann *et al*[40]	24 PDACs 20 MFPs	1.5	50, 500	0.78 ± 0.11 0.69 ± 0.18	NS
Klauss *et al*[41]	20 PDACs 9 MFPs	1.5	Multiple[2]	2.55 ± 1.09/1.46 ± 0.31[1] 3.17 ± 0.67/1.76 ± 0.19[1]	< 0.05
Fattahi *et al*[42]	10 PDACs 14 MFPs	1.5	0, 600	1.46 ± 0.18 2.09 ± 0.18	NE

[1]Two readers; [2]0, 25, 50, 75, 100, 150, 200, 300, 400, 600, 800 s/mm^2. PDAC: Pancreatic ductal adenocarcinoma; MFP: Mass-forming pancreatitis; AIP: Autoimmune pancreatitis; NE: Not evaluated; NS: Not statistically significant.

Table 3 Data derived from studies that have evaluated apparent diffusion coefficient quantification of pancreatic ductal adenocarcinomas with different degree of differentiation

Ref.	No. of patients	Field strength (T)	*b*-values (s/mm^2)	Mean ± SD ADC (× 10^{-3} mm^2/s)	*P* value
Wang *et al*[20]	21	1.5	0, 500	2.10 ± 0.42 (MD-WD) 1.46 ± 0.17 (PD)	< 0.05
Legrand *et al*[21]	22	1.5 or 3	Multiple[1]	1.43 ± 0.12 (WD) 1.94 ± 0.62 (MD-PD)	0.05
Muraoka *et al*[44]	10	1.5	0, 500	1.88 ± 0.39 (loose fibrosis) 1.01 ± 0.29 (dense fibrosis)	< 0.05
Rosenkrantz *et al*[45]	30	1.5	0, 500	1.78 ± 0.33/1.75 ± 0.49 (MD-WD)[2] 1.69 ± 0.36/1.62 ± 0.33 (PD)[2]	NS
Fukukura *et al*[46]	92	3	0, 1000	1.10 ± 0.09 (high cellularity) 1.25 ± 0.18 (low cellularity)	< 0.05

[1]0, 50, 200, 400, 600, 800 s/mm^2; [2]Two readers. T: Tesla; WD: Well differentiated PDAC; MD: Moderately differentiated PDAC; PD: Poorly differentiated PDAC; ADC: Apparent diffusion coefficient; PDAC: Pancreatic ductal adenocarcinoma; NS: Not statistically significant.

reatitis (2.09 × 10^{-3} mm^2/s) were indistinguishable compared with those of the remaining pancreas (2.03 × 10^{-3} mm^2/s), which suggests that the same inflammatory process may be present both in focal pancreatitis and the remaining pancreas; instead, ADC values of pancreatic carcinoma (1.46 × 10^{-3} mm^2/s) were invariably lower than those of the remaining pancreas (2.11 × 10^{-3} mm^2/s).

Summarizing, it seems that DWI can distinguish between benign and malignant solid pancreatic lesions. Despite this, quantitative analysis of DWI features can fail in the differentiation between solid pancreatic tumors due to a wide overlap of ADC values. DWI may be potentially feasible for differentiating PDAC from MFP, especially using the IVIM technique. However, large-scale randomized control trials are necessary to assess its real clinical value.

PROGNOSTIC STRATIFICATION

Prognosis in patients with PDAC is influenced by the histopathologic grade. Nevertheless, it plays a less important role in clinical management of PDACs as compared to the stage of the disease.

Some studies tried to correlate DWI findings with the histopathologic features of PDACs[20,21,44-48]; literature data dealing with this specific topic are reported in Table 3. Ideally, well-differentiated PDACs should present higher ADC values as compared to low-grade tumors, but some authors reported opposite findings

as well as non-significant results. It is reasonable to believe that the main contribution to the restriction of water diffusion in PDACs is provided by fibrosis, which is the predominant part of this tumor, while the contribution of the cells - even if less differentiated - and the perfusion effect provided by blood vessels should be minimal. Wang *et al*[20] reported that PDACs characterized by dense fibrosis have significantly lower ADC values compared to those characterized by abundant neoplastic tubular structures; moreover, well/moderately differentiated PDACs with dense fibrosis showed also significantly lower ADC values than those with loose fibrosis. Muraoka *et al*[44] reported similar findings: In their study, the mean ADC value was significantly higher in PDACs with loose fibrosis (1.88 ± 0.39 × 10^{-3} mm^2/s) than in those with dense fibrosis (1.01 ± 0.29 × 10^{-3} mm^2/s, $P < 0.05$). Moreover, Rosenkrantz *et al*[45] did not report significant difference in mean ADC between poorly and well/moderately differentiated tumors. Unfortunately, these findings have not been confirmed by other studies. Legrand *et al*[21], for example, reported that mean ADC values did not differ significantly between tumors having < 50% of fibrotic stroma and those having > 50% of fibrotic stroma ($P = 0.94$), or between tumors containing dense fibrosis and those containing loose fibrosis ($P = 0.81$). Regarding IVIM, Klauss *et al*[47] reported that the difference between the IVIM-derived D value between PDACs with moderate and severe fibrosis was significant, with a respective mean value of 1.02 ± 0.48 × 10^{-3} mm^2/s and 1.22 ± 0.76 × 10^{-3} mm^2/s, but the cellular complexes surrounded by fibrosis provided more structural limitations than did fibrosis alone.

Some authors have proposed a more practical role for DWI, testing correlations with clinical features or outcomes (*e.g.*, tumor stage, aggressiveness, or survival) rather than the histopathologic grade. Hayano *et al*[48] reported a significant negative correlation between ADC and tumor size ($r = -0.59$, $P = 0.004$) and the number of metastatic lymphnodes ($r = -0.56$, $P = 0.007$). Tumors with low ADC values had a significant higher tendency to show portal system and extra-pancreatic nerve plexus invasion ($P = 0.04$ and 0.01, respectively) than those with high ADC. On the contrary, Rosenkrantz *et al*[45] did not report significant difference in mean ADC between tumors with stage T3 *vs* stage T1/T2, or between tumors with and without metastatic peri-pancreatic lymph nodes. Fukukura *et al*[46] reported that the median ADC value of PDACs was not associated with significantly differences in survival ($P < 0.001$ for all phases).

It is therefore still unclear whether DWI could be helpful in PDAC prognostication; overall, ADC values tend to be low in less differentiated lesions. Moreover, it seems that PDACs with low ADC values tend to have a worse clinical course and prognosis than PDACs with high ADC values. Larger studies, particularly regarding IVIM-DWI, are needed to further evaluate these findings.

STAGING

About 80% of PDACs are unresectable at diagnosis, due to a locally advanced disease or to the presence of liver metastases: M+ stage precludes most treatments beyond chemotherapy. The detection of liver metastases is related to their size. The lower size threshold of conventional imaging techniques for the detection of metastases lays around 1 cm[49]; unfortunately, postmortem studies has shown that the ratio between metastases larger than 1 cm and those smaller than 1 cm is approximately 1:4[50]. These findings clearly indicate that imaging should have a capacity to detect and characterize metastases smaller than 1 cm. A meta-analysis by Niekel *et al*[51] reported sensitivity estimates of CT, MR, and FDG-PET on a per-lesion basis of 74.4%, 80.3%, and 81.4%, respectively, whereas on a per-patient basis, the sensitivities of CT, MR, and FDG-PET were 83.6%, 88.2%, and 94.1%, respectively. For lesions smaller than 10 mm, the sensitivity estimates for MR were higher than those for CT.

DWI is a reliable method to detect liver metastases, with a sensitivity and specificity higher than both CT and conventional MR sequences[51], even though most published studies comprised a small amount of patients with metastatic PDAC. DWI sensitivity and specificity in detecting liver metastases can reach respectively 90.8% and 97.5%[51-55]. Moreover, DW sequences are able to detect focal liver lesions even down to 3 mm, as reported in a study by Coenegrachts *et al*[56]. Some authors have pointed out that DWI alone should not be used for the diagnosis of liver metastases because of possible false positives; the overlap in ADC values among benign and malignant hepatic lesions strengthen this consideration. Whenever possible, MR findings obtained during the hepatobiliary phase after hepatocyte-specific contrast media administration, should be used in association with DW images to obtain a definite diagnosis[55-60].

Preoperative assessment of the N stage can be very difficult using MRI. The presence of diffusion restriction in multiple peri-pancreatic lymph nodes is not uncommon in patients with PDAC. Moreover, microscopic nodal metastases are frequently found in small peri-pancreatic lymphnodes at histopathological analysis[61,62]. A study by Imai *et al*[63] reported that, despite a low sensitivity, the specificity and accuracy for the detection of para-aortic lymph node metastases from PDAC were relatively high for MRI (96.8% and 88.4%, respectively); unfortunately, their protocol did not include DWI sequence. Literature data suggest that DWI is a good method for the detection of nodal metastases, at least when applied to pelvic, breast, and head/neck tumors[64-66]; these favorable results may be assumed to be applicable also to PDACs. Unfortunately, studies on diagnostic accuracy of DWI are difficult to perform, mainly because extended lymphadenectomy is not routinely performed during pancreatic resection[61,62]. Data regarding ADC measurement for the distinction

between inflammatory and metastatic lymphnodes are controversial[67-71]. Further studies should be therefore performed to assess the usefulness of DWI for the detection of nodal involvement by PDAC.

Several authors have reported the usefulness of DWI to diagnose peritoneal implants, but these studies included a small amount of patients with PDAC. Bozkurt[72] reported that the association of DW images and conventional MRI images had 83% sensitivity, 94% specificity, and 86% accuracy for the diagnosis of peritoneal implants. Low *et al*[73] reported high sensitivity and accuracy values when DWI was added to conventional MRI sequences for the detection of peritoneal implants.

DWI should be therefore ideally evaluated for first during the staging of patients with PDAC. In most cases, if no focal liver lesions are detected using DWI, then the presence of liver metastases is extremely unlikely, thanks to its high negative predictive value. Nevertheless, conventional sequences should be always taken into consideration, due to possible false positive results of DWI.

POST-TREATMENT FOLLOW-UP

DWI can depict microstructural changes during therapy. Niwa *et al*[74] reported differences in ADC values among patients with advanced pancreatic cancer treated with gemcitabine: ADC values were significantly different between the progressive and stable groups at 3 mo' and 6 mo' follow-up (P = 0.03 and P = 0.04, respectively). The rate of tumor progression was significantly higher in those with a low b-value (400 s/mm^2) ADC than in those with a high b-value ADC (median progression time, 140 d *vs* 182 d, P = 0.01).

Cuneo *et al*[75] reported a significant correlation between pre treatment mean ADC values of resectable PDACs and the amount of tumor cell destruction after chemoradiation evaluated on surgical specimens, with a Pearson correlation coefficient of 0.94 (P = 0.001). Mean pre-treatment ADC was 1.61 $\times$ 10^{-3} mm^2/s in responding patients (> 90% tumor cell destruction) compared to 1.25 $\times$ 10^{-3} mm^2/s in non-responding patients.

Overall, a very limited number of studies focused on the post-treatment DWI assessment of PDACs. This topic deserves further studies in order to establish the real usefulness of DWI for early assessment of chemotherapy outcome.

CONCLUSION

DWI is a robust imaging technique that should be performed during MRI evaluation of PDACs. The high contrast resolution of PDACs on DW images is useful for the identification of even very small lesions, thus allowing earlier diagnosis. IVIM, although not fully integrated into clinical practice, represent a promising DWI technique for characterization of PDACs, with particular interest on the differentiation between PDACs and MFPs. Considered its high negative prognostic values, DWI findings should be considered for the staging of patients with PDAC. Further studies are needed to evaluate the usefulness of DWI for treatment monitoring.

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