Diffusion weighted imaging: an additional value for the magnetic resonance study of pancreatic neoplasms

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Learning objectives

To describe the applications of diffusion-weighted imaging (DWI) in the study of pancreatic neoplasms and to discuss its usefulness in terms of detection, characterization, staging and evaluation of response to therapy both for solid and for cystic pancreatic lesions.
Background

Diffusion-weighted imaging (DWI) has become diffusely used for the evaluation of pancreatic diseases with MRI.

DWI allows the assessment of random molecular motion in tissues, providing apparent diffusion coefficient (ADC) values. Several studies have proved that diffusion varies with cellular density and organization, extracellular space morphology, and integrity of cellular membranes [1].

This poster focuses on the value of DWI for the evaluation of solid and cystic pancreatic neoplasms, particularly for detection and characterization, differentiation between benign and malignant masses, estimation of malignancy, evaluation of local extent, and intra-abdominal staging.
Findings and procedure details

Detection
Pancreatic adenocarcinoma is the most common pancreatic malignancy; it is an aggressive neoplasm, with very poor prognosis; the best way to improve survival in pancreatic adenocarcinoma is with early detection [2]. Small or well-differentiated ductal adenocarcinomas may lack classic features, as hypovascularization during arterial phase, and may not be detected. The use of DWI could simplify the detection of these lesions, since they show hyperintensity at high b values (> 500 mm²/s) and relatively low ADC values, because of the restricted diffusion associated with fibrosis [3] (Fig. 1 on page 8).

The detection of neuroendocrine tumors can sometimes be difficult [4]: some insulinomas and somatostatinomas containing abundant fibrosis may show hypointensity on both T1- and T2-weighted images, and lack of enhancement [5]. Again, DWI may represent a valuable tool to detect and localize these lesions, as previously reported by Bakir [6] and Caramella [7]; particularly, DWI could be useful for the pre-operative localization of small insulinomas, as reported by Anaye et al. [8]. Brenner et al. [9] reported the usefulness of post-processed fusion T2/b1000 images for the identification of small isointense pancreatic lesions: regarding DWI alone, 94% of the NETs included in this study had also lower ADC than normal adjacent parenchyma (Fig. 2 on page 8).

Characterization
It is still unclear if DWI could help in the characterization of pancreatic neoplasms. Koc et al. [10] reported promising results for the overall differentiation between malignant and benign lesions using a visual scoring, with the following sensitivities, specificities, and accuracies values: 100%, 93.8%, 92.5% (b=600); 84.7%, 82.6% and 80.4% (b=800); 94.4%, 89.7%, and 88.1% (b=1000). The mean ADC values of malignant lesions were significantly lower than those of benign lesions for all b-values, except b=0 and b=50.

Barral [11] reported significant differences in ADC values between malignant (1.150×10⁻³ mm²/s) and benign tumors (2.493 x10⁻³ mm²/s), also using a normalized ADC value (malignant tumors: 0.933x10⁻³ mm²/s; benign tumors: 1.807x10⁻³ mm²/s). It must be noted that patients’ selection in this study was unclear: within the 18 patients with malignant pancreatic tumors were included 5 non-secreting neuroendocrine tumors (not necessarily malignant), and within the 10 patients with benign tumors 1 mucinous cystadenoma (which must be considered at least pre-malignant) was included. Analyzing the main published studies, DWI seems capable to differentiate between neoplasms and normal pancreatic tissue and between benign and malignant lesions, but it does not seems to be able to differentiate between the two most frequent solid pancreatic neoplasms, i.e. adenocarcinomas and neuroendocrine tumors, due to a wide overlap in ADC values (Fig. 3 on page 9).

*Ductal adenocarcinoma*
In contrast to other neoplasms, ADC of ductal adenocarcinomas seems to be more correlate to fibrosis rather than to cellularity: Muraoka et al. [12] reported that the mean ADC value was significantly higher in tumors with loose fibrosis ($1.88\pm0.39\times10^{-3}$ mm$^2$/s) than in those with dense fibrosis ($1.01\pm0.29\times10^{-3}$ mm$^2$/s); in a quantitative analysis, ADC correlated well with the proportion of collagenous fibers. Moreover, as stated by Lemke et al. [13], the f value (perfusion) was the DWI-derived parameter with the highest sensitivity, specificity, negative predictive value, and positive predictive value (respectively 95.7%, 100%, 93.3%, and 100%) for the differentiation between healthy pancreas and pancreatic cancer. DWI seems able to identify different degrees of malignancy of pancreatic adenocarcinoma, thus providing the identification of potentially more aggressive lesions, but this is not universally accepted. Hayano et al. [14] reported a significant negative correlation between ADC values and tumor size and between ADC values and number of metastatic lymph nodes; moreover, tumors with low ADC value had a significant tendency to show portal/venous invasion and extra-pancreatic nerve plexus invasion. Wang [15] reported that poorly differentiated adenocarcinomas with histopathologic characteristics of limited glandular formation and dense fibrosis had significantly lower ADCs ($1.46\pm0.17\times10^{-3}$ mm$^2$/s) compared to those of well/moderately differentiated characterized by neoplastic tubular structures ($2.10\pm0.42\times10^{-3}$ mm$^2$/s). Well/moderately differentiated adenocarcinomas with dense fibrosis showed significantly lower ADC values ($1.49\pm0.19$) than those with loose fibrosis ($2.26\pm0.30$). Conversely, Rosenkrantz et al. [16] did not reported differences between poorly and well/moderately differentiated neoplasms; in addition, ADC was not significantly different between stage T3 neoplasms versus stage T1/T2, and between tumors with and without metastatic lymph nodes.

The radiological differentiation between mass forming pancreatitis and ductal adenocarcinoma could be challenging; DWI seems to be a valuable tool for this distinction. Wang et al. [15] stated that visual evaluation of DW images could be helpful for differentiation of malignant lesions from mass-forming focal pancreatitis: this latter has a similar signal intensity with remaining pancreas on b=600 images. Klauss et al. [17] reported that the perfusion fraction (f) was the superior DWI-derived parameter for differentiation of mass-forming pancreatitis and pancreatic adenocarcinoma, because it was significantly higher in pancreatitis compared with pancreatic carcinoma. Ma et al. [18] reported differences in ADC50 and ADC100 values in different lesion areas that helped the differential diagnosis between ductal adenocarcinoma and focal pancreatitis.

**Neuroendocrine tumors**

The possibility of characterizing NETs using DWI has been evaluated in different studies. Bakir [6] stated that, although all NETs included in his study showed high signal intensity on DW images, this criterion was not able to differentiate NETs from pancreatic adenocarcinomas, which present identical aspect. More interestingly, Wang [19] found that NETs with different grades of differentiation have varying ADC values: endocrine carcinomas had significantly lower mean ADC values ($1.00\pm0.19\times10^{-3}$ mm$^2$/s) compared to normal pancreatic tissue and to well-differentiated NETs. Moreover, ADCs values well correlated with Ki-67 labeling index and this may help predict growth of
endocrine tumors: the reason for this could be a difference in tumor cellularity, ratio of nuclei and cytoplasm, and extracellular fibrosis. Jang et al. [20] reported that mean ADC values were significantly different between benign and malignant NETs (1.48x10^-3 mm²/s versus 1.04x10^-3 mm²/s); using an ADC cut-off value of 1.09 x10^-3 mm²/s to dichotomize between benign and non-benign NETs, he reported an accuracy of 88.9%, sensitivity of 92.9%, specificity of 84.6%, positive predictive value of 86.7% and negative predictive value of 91.7%. When an ADC ratio of 1.03 was used as the cut-off value for discriminating between benign and non-benign NETs, a specificity of 100.0% was achieved for the diagnosis of benign NETs (Fig. 4 on page 9, Fig. 5 on page 10, Fig. 6 on page 10).

Cystic pancreatic neoplasms

DWI is sensitive to flow characteristics of water in tissues, which depend on viscosity and on the containment characteristics of the fluid [21]. Yamashita [22] first reported the possibility to differentiate mucin-producing tumors from other cystic lesions by means of DWI: mean ADCs of mucin-producing tumors (2.7±0.9x10^-3 mm²/s) were significantly lower than those of serous cysts (5.8±2.0x10^-3 mm²/s); at b=300, mucin-producing tumor had high signal intensity. It must be noted that this study did not distinguish MCNs from IPMNs, maybe because at those times these neoplasms were considered a single entity due to their similar appearance. Instead, Irie [23] stated that it was difficult to differentiate mucin-producing tumors from other cystic lesions by ADC measurements: the mean ADCs of mucin-producing tumors (2.8x10^-3 mm²/s), pseudocysts (2.9x10^-3 mm²/s) and serous cystadenomas (2.6x10^-3 mm²/s) were not statistically different. More encouraging results came from recent studies. In the study by Fatima et al. [24], all IPMNs demonstrated low- to iso-intensity compared to the pancreatic parenchyma on DWI, while most MCNs demonstrated high signal intensities. Mean ADC values of IPMNs (2.9±0.2x10^-3 mm²/s) were significantly higher than those of MCNs (2.1±0.3x10^-3 mm²/s). ROC analysis showed an optimal cut-off value of 2.4x10^-3 mm²/s for differentiating between IPMNs and MCNs, with a sensitivity of 98% and a specificity of 88%. The results of this study were explained with the lack of communication with the pancreatic ducts of MCNs, which produces a restricted water flow within these lesions; conversely, IPMNs have free flow due to their communication with the pancreatic ductal system, thus providing less restriction to water molecules diffusion and higher diffusion coefficient values. Inan et al. [25] reported that on visual evaluation on DWI with b=1000, all abscesses, hydatid and neoplastic cysts were hyperintense, whereas most of the simple cysts and pseudocysts were isointense. Quantitatively, with a b factor of 1000, the cyst-to-pancreas signal intensity ratios of the abscesses, hydatid cysts and neoplastic cysts were significantly higher than those of simple cysts and pseudocysts; with a signal intensity ratio cut-off of 1.9, the cyst-to-pancreas signal intensity ratio had a sensitivity of 70% and a specificity of 90% for differentiating abscesses, hydatid cysts, and neoplastic cysts from simple cysts and pseudocysts. The ADC and the ADC ratios of the abscesses, hydatid cysts, and neoplastic cysts were significantly lower than those of the simple cysts and pseudocysts. Because hydatid cysts, abscesses, and MCNs have a viscous content, they have decreased ADCs. On the contrary, simple cysts and pseudocysts
have a lower viscosity and thus a higher ADC. Kang et al [26] reported that mean ADC of malignant IPMNs (2.05±0.66x10-3 mm2/s) was significantly lower than that of benign IPMNs (2.95±0.32x10-3 mm2/s). Invasive intraductal papillary mucinous carcinomas showed significantly lower ADC than that of noninvasive IPMCs (1.51±0.32x10-3 mm2/s versus 2.67±0.23x10-3 mm2/s). Focal areas of diffusion restriction were more frequently seen in malignant IPMNs. These results could be explained with high cellularity and fibrosis of mural nodules or solid portions in invasive IPMC, which might restrict molecular diffusion in a manner similar to that seen in pancreas malignant tumors (Fig. 7 on page 11).

Staging
The detection of hepatic lesions with restricted diffusion in patients with pancreatic adenocarcinoma virtually eliminates cysts and hemangiomas from the differential diagnosis and suggests the presence of metastases [3]. Despite this, it is not possible to differentiate with DWI benign solid hepatic lesions from metastasis, because both will generally show restriction [27]. In a study aiming to evaluate the role of DWI in differentiation of hemangiomas from other hypervascular liver lesions, the mean ADC value of NETs metastasis was found to be 1.43±0.39 [28] slightly higher than that reported by Schmid-Tannwald (1.23±0.31) [29]. Moreover, DWI can also show small metastases not easily depictable with other sequences [3]. DWI could also help the identification of metastatic lymph nodes (Fig. 8 on page 11) and peritoneal implants (Fig. 9 on page 12). Bakir [6] reported that in his series peri-pancreatic lymph nodes were detected in 2 patients and liver metastasis was demonstrated in 1 patient: in DW images, both metastasis had high signal intensity.

Response to therapy
In patients with diffuse hepatic metastatization, transcatheter arterial chemoembolization can be used to control symptoms and improve prognosis; the assessment of the response to therapy is crucial in determining the success of therapy and to guide future treatments. DWI can provide functional informations by measuring water diffusion modifications, as stated by Liapi et al [30]: ADC of metastases increased from 1.51 before treatment to 1.79 after treatment. Li et al [31] found that mean ADC increased from a median of 1.31x10-3 mm2/s before treatment to a median of 1.59 x10-3 mm2/s at 1-month follow-up; they stated that an increase of ADC above a threshold of 0.16 x10-3 mm2/s could also be used to differentiate responders from non-responders.
Fig. 1: Small well-differentiated adenocarcinoma in the uncinate process, hypointense on T1-weighted image (arrow in a), isointense on T2-weighted fat-sat image (b), determining upstream dilation of the biliary tree (c); the lesion does not show hypovascularization during arterial phase (d-e; the asterisk represents the duodenum). On b=800 images (f) the lesion is markedly hyperintense.

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Fig. 2: Small pancreatic head insulinoma, isointense on T1-weighted fat-sat image (a), hyperintense on T2-weighted fat-sat image (arrow in b), without significant
hypervascularization (c); the lesion is hyperintense on b=800 image (d), hypointense on ADC map (e), with moderately low ADC mean value (9.73±2.28x10-3 mm2/s, f).

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<table>
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<tr>
<th>Study</th>
<th>N of patients</th>
<th>b-values</th>
<th>ADC (Mean±SD x10-3 mm²/s)</th>
<th>Histotype</th>
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<tr>
<td>Matsuki Abdom Imagin 2007</td>
<td>8</td>
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<td>Wang J Magen Reson Imaging 2011</td>
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<td>1.00 ± 0.19 (poorly differentiated)</td>
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<td></td>
<td></td>
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<td>1.150/0.933 (malignant)</td>
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**Fig. 3:** Mean ADC values of pancreatic lesions reported in the main published papers focusing on this issue.

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Fig. 4: G1 endocrine tumor. The lesion presents hyperintensity at b=800 images (1d). G1 tumors have high mean ADC value (1.49 ± 1.02 x10-3 mm/s2).

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Fig. 5: G2 endocrine tumor, hyperintense at b=800 image (2d). G2 tumors have high mean ADC value (1.32 ± 1.45 x10-3 mm/s2).

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**Fig. 6:** G3 endocrine tumor, which presents low ADC mean value (0.53 ± 1.00 x10^{-3} mm/s²).

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**Fig. 7:** Patient with mixed IPMN with malignant degeneration. A hypointense lesion can be seen on T1-weighted fat-sat image (arrow in a); at T2-weighted images (b and c), this lesion corresponds to some solid portions within a dilated pancreatic duct, confirmed by MRCP (d). No enhancement can be seen within the lesion (e). At b=800 image, the lesion is hyperintense.

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**Fig. 8:** Patient with pancreatic head adenocarcinoma. Below the uncinate process of the pancreas a small oval lymph node can be seen (arrow in a and b). On b=800 image (f), the lymph node shows hyperintensity. At histologic examination, the lymph node resulted positive for metastasis.

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**Fig. 9:** Patient with G3 endocrine tumor of the pancreatic tail (arrow in a). A small nodule can be seen in the ventral peritoneum (arrow in b). This nodule did not show significant enhancement (c), but showed restriction at DW images (d, e), with a low mean ADC value (f).

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Conclusion

DWI is a valuable tool for the evaluation of pancreatic neoplasms. It has a definite role in the improvement of detection of pancreatic solid lesions, especially small endocrine tumors, and in the detection of subtle metastasis. DWI could have a role in the distinction between malignant and benign lesions and in the grading of pancreatic neoplasms. It seems still difficult the use of DWI for the distinction between different solid histotypes.
References


