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EDITORIAL

Prognostication and response assessment in liver and pancreatic tumors: The new imaging

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Abstract

Diffusion-weighted imaging (DWI), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and perfusion computed tomography (CT) are technical improvements of morphologic imaging that can evaluate functional properties of hepato-bilio-pancreatic tumors during conventional MRI or CT examinations. Nevertheless, the term "functional imaging" is commonly used to describe molecular imaging techniques, as positron emission tomography (PET) CT/MRI, which still represent the most widely used methods for the evaluation of functional properties of solid neoplasms; unlike PET or single photon emission computed tomography, functional imaging techniques applied to conventional MRI/CT examinations do not require the administration of radiolabeled drugs or specific equipments. Moreover, DWI and DCE-MRI can be performed during the same session, thus providing a comprehensive "one-step" morphological and functional evaluation of hepato-bilio-pancreatic tumors. Literature data reveal that functional imaging techniques could be proposed for the evaluation of these tumors before treatment, given that they may improve staging and predict prognosis or clinical outcome. Microscopic changes within neoplastic tissues induced by treatments can be detected and quantified with functional imaging, therefore these techniques could be used also for post-treatment assessment, even at an early stage. The aim of this editorial is to describe possible applications of new functional imaging techniques apart from

molecular imaging to hepatic and pancreatic tumors through a review of up-to-date literature data, with a particular emphasis on pathological correlations, prognostic stratification and post-treatment monitoring.

Key words: Diffusion magnetic resonance imaging; Perfusion imaging; Hepatocellular carcinoma; Liver neoplasms; Pancreatic neoplasms

Core tip: Diffusion-weighted imaging and perfusion imaging could add functional information to the morphological evaluation of hepatic and pancreatic tumors. Diffusion-weighted imaging findings seem to be correlated with pathological features and could predict the clinical outcome of hepatocellular carcinomas and pancreatic tumors, especially neuroendocrine neoplasms. Apparent diffusion coefficient quantification and perfusion techniques can be of value for the evaluation of response to ablative treatments, loco-regional therapies and anti-angiogenic therapies, even at an early stage.

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INTRODUCTION

Functional imaging techniques include different methods that can detect or measure changes in metabolism, blood flow, and chemical composition. This group included both molecular imaging methods, as positron emission tomography (PET)-computed tomography (CT)/magnetic resonance imaging (MRI) or single photon emission computed tomography (SPECT), and radiological techniques, as diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI) and perfusion CT (pCT). Functional imaging techniques are technical improvements of conventional morphological techniques that can provide both qualitative and quantitative information on hepato-bilio-pancreatic tumors[1-3], being therefore similar to molecular imaging techniques. Functional techniques can be performed during conventional imaging evaluations as CT or MRI, therefore they describe both morphological and functional features of solid tumors; moreover, they do not need radiolabeled agents as fluorodeoxyglucose (^{18}F-FDG) or specific equipments.

DWI evaluate the random diffusion of water molecules: biological tissues with high cellular density or altered cellular membranes will present diffusion restriction, which is depicted as signal hyperintensity areas on high *b*-value DW images and hypointensity on the apparent diffusion coefficient (ADC) maps; ADC measurement can also quantify water molecules' diffusion. As dedifferentiation or therapies may induce microscopic changes in neoplastic tissues that could modify water molecules' diffusion, DWI can distinguish between different degrees of malignancy and can be also proposed for post-treatment monitoring. Moreover, DWI can be performed in a single session with DCE-MRI, thus providing a comprehensive "one-step" morphological and functional evaluation of hepato-bilio-pancreatic tumors.

Perfusion imaging techniques evaluate changes in signal intensity (DCE-MRI) or density (pCT) after contrast medium injection, being therefore able to assess microvascularization through the evaluation of the dynamics of contrast medium distribution from vessels to the neoplastic tissue. Perfusion parameters are therefore theoretically good candidates for the evaluation of microscopic vascular differences between lesions with different pathological grade and for the assessment of treatment response, especially after chemoembolization or during treatments with anti-angiogenic drugs.

This editorial analyzes up-to-date literature data regarding the application of functional imaging techniques, apart from molecular imaging, to hepatic and pancreatic tumors, with particular emphasis on correlations to pathological features, prognostic stratification and therapeutic response assessment.

FUNCTIONAL IMAGING TECHNIQUES: TECHNICAL BASES

In 1965 Stejskal and Tanner[4] developed a modified T2-weighted MR sequence for the detection of water molecules' diffusion. DWI enables the visualization of Brownian random motions of water molecules in the extracellular, intracellular, and intravascular spaces[5]. DWI provides information on tissue cellularity and integrity of cell membranes, since the degree of restriction to water diffusion in biological tissues is inversely correlated to these features[6-9]. Restricted diffusion is present in tissues with narrowed extracellular spaces as a consequence of a high cellular density, which increases the number of hydrophobic cellular membranes, whereas in cystic or necrotic lesions water diffusion is relatively "free"[10]. The b value is a technical parameter that regulates the sensitivity of this sequence to water molecules' diffusion. Generally, both low and high *b* values are used for DWI examination; nevertheless, the choice of the b value may vary from institution to institution. The intravoxel incoherent motion (IVIM) model is an advanced DWI technique developed by Le Bihan[11,12] that enables a separate quantitative assessment of all the microscopic

translational motions that contribute to DWI signal. In biological tissues, these motions are represented by the molecular diffusion of water, expressed by diffusion (D) and pseudodiffusion (D*), and the perfusion effect caused by blood circulation in the capillary network (perfusion fraction - f). IVIM, therefore, can evaluate perfusion features without the need of contrast medium injection. Multiple *b* values must be used for IVIM evaluation.

DCE-MRI was developed to assess myocardial and pulmonary blood flow. This technique requires the intravenous injection of a gadolinium-based contrast agent, followed by rapid serial signal intensity measurements while the contrast agent enters tumor arterioles, passes through capillary beds and washes out of the tumor. Technical improvements have shortened the acquisition time and have led to the development of three-dimensional sequences, which replaced single-section examinations: as a consequence, DCE-MRI can be applied to abdominal imaging. The contrast kinetics features assessed by DCE-MRI reflect tissue perfusion, the concentration-time curve in the arterial input vessel, the capillary surface area, the permeability and the volume of the extracellular extravascular space. As a consequence, several metrics can be derived from DCE-MRI evaluation: the volume transfer constant (K^{trans}), the fractional volume of the extravascular-extracellular space (v_e), the rate constant (K_{ep}, where $K_{ep} = K^{trans}/v_e$), the fractional volume of the plasma space (v_p), the area under the contrast agent concentration-time curve (AUC)[13]. In 1999, a consensus opinion agreed to standardize the terminology of DCE-MRI studies[13] and selected AUC_{60} and K^{trans} as the preferred end points in clinical trials involving anti-angiogenic drugs[13,14]. Nevertheless, DCE-MRI end points can be tailored to the specific drug involved in the trial.

Perfusion CT has the same physical bases of DCE-MRI, as it is based on the evaluation of temporal changes in tissue density following intravenous administration of iodine contrast medium. By rapid sequential acquisitions during contrast medium passage, pCT allows the quantification of tissues' vascularity. Perfusion can be quantified using mathematical modeling techniques (mainly the compartmental and the deconvolution analysis) that use data derived both from the tissue and the vascular system[15-17]. The analytical methods and the acquisition protocols vary from institution to institution and between commercial vendors, leading to poor standardization. Many different metrics can be directly or indirectly derived from pCT studies: blood flow (BF), representing the flow rate through vasculature; blood volume (BV), representing the volume of flowing blood; mean transit time (MTT), representing the average time taken to travel from arteries to veins; perfusion, representing the flow rate through vasculature; permeability surface (PS), representing the total flux from plasma to interstitial space; peak enhancement image (PEI), representing the maximum enhancement in a tissue region of interest; and time to peak (TTP), defined as the time from the arrival of the contrast medium in major arterial vessels to the peak enhancement). Other than poor standardization, another important drawback of pCT is the high radiation dose, even though technical improvements have recently led to the development of low-dose pCT examination protocols[18].

CORRELATION WITH PATHOLOGICAL FINDINGS AND PROGNOSTIC STRATIFICATION

Primary liver tumors

The prognosis and management of hepatocellular carcinoma (HCC) depend on size, degree of dedifferentiation, presence of vascular invasion and intrahepatic metastases[19]. As advanced and poorly differentiated HCCs have a significantly worse prognosis than well and moderately differentiated lesions after surgical resection[20], preoperative staging and prognostic prediction play an important role, eventually suggesting wider surgical clearance margins and closer post-treatment surveillance.

As the pathological grade of HCC depends on cellular and structural atypia[21], increasing cellular density, nuclear-to-cytoplasmic ratio, and architectural complexity accompanying dedifferentiation may cause water diffusion restriction. DWI features can be assessed both with a visual (qualitative) and a quantitative analysis through ADC measurement. An *et al*[22] reported a linear correlation towards higher grades in HCCs showing diffusion restriction: the combination of absence of diffusion restriction (defined as no hyperintensity on high *b*-value DW images) and no arterial enhancement at conventional contrast-enhanced MRI in predicting well differentiated HCCs had a 100% positive predictive value. The multistep nature of HCC dedifferentiation probably necessitates a quantitative approach rather than a simple visual analysis. Details on the main published studies regarding ADC measurement and correlations with the pathological grade of HCCs are reported in Table 1. Overall, literature data show that HCC dedifferentiation tends to be associated with a decrease of the ADC value, despite differences between studies[23-29]. Apart from the direct correlation with the pathological grade, Nakanishi *et al*[29] found that ADC quantification might have a clinical prognostic value, being significantly lower in patients with early recurrence after surgery than in those without early recurrence. One important aspect dealing with ADC measurement is the choice of the region of interest (ROI), given that a "whole-tumor" ROI can be irrespective of lesion heterogeneity: as previously mentioned, necrotic areas have a relatively free diffusion and should be avoided during ROI placement because they may falsely increase the ADC value; ADC measurement should be therefore per-

Table 1 Data derived from the main published studies that have tested correlations between apparent diffusion coefficient values and pathological grade of hepatocellular carcinomas

Study	Number of patients	*b* values (s/mm^2)	mean ADC value ($\times 10^{-3}$ mm^2/s)
Nasu *et al*[23]	99	0, 500	1.45 (WD); 1.46 (MD); 1.36 (PD)
Piana *et al*[24]	99	0, 500	1.29 (WD); 1.22 (MD); 1.21 (PD)
Saito *et al*[25]	32	100, 800	1.25 (WD); 1.12 (MD); 1.13 (PD)
Muhi *et al*[26]	73	500, 800	0.91 (WD); 0.71 (MD); 0.68 (PD)
Nishie *et al*[27]	80	0, 500, 1000	1.21 (WD); 1.14 (MD); 0.76 (PD)
Heo *et al*[28]	27	0, 1000	1.20 (WD); 1.10 (MD); 0.90 (PD)
Nakanishi *et al*[29]	44	0, 50, 1000	1.29 (MD); 1.07 (PD)

ADC: Apparent diffusion coefficient; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated.

formed only on solid areas showing diffusion restriction.

Studies regarding IVIM imaging reported interesting results. Woo *et al*[30] found that the D value (diffusion) quantification had significantly higher AUC than ADC measurement for the differentiation between high-grade and low-grade HCCs. Moreover, the percentage of arterial enhancement depicted at conventional contrast-enhanced MRI, which is directly linked to the degree of dedifferentiation of HCCs, was correlated with IVIM-derived *f* value (perfusion fraction).

As previously mentioned, the prognosis of patients with HCC depends also on other pathological features: DWI has been tested for the detection of malignant features of HCC, as vascular involvement or intra-hepatic metastases. It has been reported that ADC measurement has a high sensitivity and specificity (reaching up to 93.5% and 78.6%, respectively) for the prediction of microvascular involvement[31,32]. Portal vein involvement precludes most curative options[33], but its diagnosis may be hampered by the presence of a non-neoplastic thrombus in a cirrhotic liver. Few and controversial papers have been published regarding the ability of DWI in distinguishing malignant from non-malignant thrombi: Catalano *et al*[34] reported that most neoplastic thrombi were isointense to the primary tumor on DWI, whereas all bland thrombi were hypointense; it must be noted that blood degradation products present variable T2 signal prolongation and water diffusivity, therefore false-positives may be encountered at DWI[35]. Satellite nodules are important determinants of patients' prognosis and influence the therapeutic approach. The high accuracy of DWI in detecting small HCCs, even smaller than 1 cm, may be assumed to be applicable to intrahepatic HCC metastases[36].

Arterial blood supply tends to increase during hepatocarcinogenesis. Perfusion imaging techniques would be ideal for the prediction of the pathological grade and clinical behavior of HCCs, but literature data at this regard are relatively poor. One single study[37] reported a significant negative correlation between the standardized uptake value (SUV) derived from ^{18}F-FDG PET/CT and K^{trans} in advanced HCCs. Some more studies have been conducted with pCT: while Ippolito *et al*[38] did not report any significant correlation between pCT-derived parameters and pathological grade, Sahani *et al*[39] found that well-differentiated HCCs had significantly higher perfusion values than less differentiated lesions. Yang *et al*[40] reported that pCT could quantitatively assess the blood supply and particularly its distribution during hepatocarcinogenesis, with statistically significant correlations between BF, hepatic arterial perfusion (HAP) and microvascular density (MVD).

Few experiences, mainly focused to a qualitative visual assessment of DW images, have been reported regarding cholangiocarcinoma (CCC). Cui *et al*[41] found an inverse correlation between the pathological grade and ADC values; Park *et al*[42] reported that the addition of DWI to conventional sequences might improve the pre-operative assessment of hilar CCC, increasing the sensitivity for the evaluation of tumor extent along the bile ducts and liver invasion, thus improving T stage, a parameter that is directly related to prognosis.

Pancreatic tumors

Although the prognosis of patients with pancreatic ductal adenocarcinomas (PDACs) is related to the pathological grade, treatment choice mainly relies on clinical stage. Surgical resection is the only curative treatment for this neoplasm, therefore the pre-operative prediction of the pathological grade may have a smaller importance for PDAC management as compared to other pancreatic tumors.

Some studies have tried to correlate DWI findings with the pathological grade, but results are controversial[43-45]. Details on the most relevant published studies are reported in Table 2. Overall, low-grade PDACs tend to present low ADC values[43-45], but it still not clear which histological feature mainly contributes to diffusion restriction. Wang *et al*[43] and Muraoka *et al*[46] reported that tumors with limited glandular formation and dense fibrosis (*i.e.*, paucicellular tumors) had lower ADC values as compared to well-differentiated lesions characterized by neoplastic tubular structures; moreover, PDACs with dense fibrosis showed significantly lower ADC values than those with loose fibrosis. Fibrosis may be therefore the key factor contributing to diffusion restriction in PDACs, but these findings have not been confirmed by other studies: particularly, Klauss *et al*[47] reported that the difference between the IVIM-derived D value (diffusion) of moderate and severe fibrosis PDACs was significant, but the cellular complexes surrounded by fibrosis

Table 2 Data derived from the main published studies that have correlated apparent diffusion coefficient quantification with the pathological grade of pancreatic ductal adenocarcinomas and neuroendocrine tumors

Study	*n*	*b* values (s/mm^2)	Histotype	mean ADC value ($\times 10^{-3}$ mm^2/s)
Wang *et al*[43]	21	0, 500	PDAC	2.10 (WD-MD); 1.46 (PD)
Legrand *et al*[44]	22	Multiple[1]	PDAC	1.43 (WD); 1.94 (MD-PD)
Rosenkrantz *et al*[45]	30	0, 500	PDAC	1.78/1.75 (WD-MD); 1.69/1.62 (PD)[2]
Wang *et al*[58]	18	0, 50, 500	PanNET	1.75 (G1); 1.00 (G3)
Jang *et al*[59]	20	0, 800	PanNET	1.48 (G1-G2); 1.04 (G3)
Hwang *et al*[60]	44	Multiple[3]	PanNET	1.31 (G1); 1.08 (G2-G3)

[1]50, 200, 400, 600, 800 s/mm^2; [2]Two readers; [3]0, 25, 50, 75, 100, 150, 200, 500, 800, 1000 s/mm^2. *n*: Number of patients; ADC: Apparent diffusion coefficient; PDAC: Pancreatic ductal adenocarcinoma; WD: Well differentiated; PanNET: Pancreatic neuroendocrine tumor; MD: Moderately differentiated; PD: Poorly differentiated.

might provide more structural limitations than fibrosis alone. Legrand *et al*[44] reported that mean ADC values did not significantly differ between tumors having < 50% and those having > 50% of fibrotic stroma, or between tumors containing dense fibrosis and those containing loose fibrosis. Similarly, Rosenkrantz *et al*[45] reported no associations between ADC values and "adverse" pathological features as poor differentiation. Some authors have proposed a more practical role for functional imaging, testing correlations with clinical features as tumor stage or survival. Hayano *et al*[48] reported a significant negative correlation between ADC values, size and number of metastatic lymphnodes; PDACs with low ADC values presented also a high tendency to show portal system and extra-pancreatic nerve plexus invasion. The comparison of CT and DWI performed by Fukukura *et al*[49], instead, reported that only CT findings might be associated with the clinical behavior of PDACs. Some studies focused on the application of DWI to the detection and characterization of liver metastases from PDAC and reported high sensitivity and specificity using DWI alone[50] or DWI plus other sequences[51-53]: imaging features derived from conventional MR sequences should be always taken into account because of the possible presence of DWI false-positives.

Well-differentiated PDACs have a higher microvascular density as compared to less differentiated tumors[54]; perfusion imaging should therefore theoretically be able to identify well-differentiated PDACs, which have better prognosis than poorly differentiated lesions. It has been reported that pCT-derived PEI and BV values could identify high grade PDACs with 100% specificity and 75% accuracy[55]. Ueno *et al*[56] reported that DCE-MRI might predict the survival of patients with advanced PDAC: all patients included in this study showed transient decreases in signal intensity [signal ratio (SR): 6.9%-55.7%]; high SR (cut-off 22%) significantly correlated with higher disease stage and presence of nodal metastases; patients with high SR had significantly short overall survival.

Pancreatic neuroendocrine tumors (PanNETs) can be divided into well/moderately differentiated and poorly differentiated lesions and their mitotic rate based on the quantification of the mitotic index (Ki67%) can distinguish three categories: G1, with a Ki67 $\leqslant$ 2%, G2 (Ki67 3%-20%), and G3 (Ki67 > 20%)[57]. Several treatment options, ranging from surgery to systemic therapy or loco-regional treatments, have been proposed for PanNETs according to their grade of differentiation. The histological grade plays therefore a key role in the clinical management of PanNETs; many studies have been conducted regarding the application of functional imaging techniques to PanNETs, apart from nuclear imaging techniques. Details regarding ADC measurements correlations with the grade of differentiation are reported in Table 2. Overall, it seems that ADC values are correlated with the Ki67 labeling index: G3 PanNETs tend to present lower mean ADC values compared to well-differentiated PanNETs[58-60]. As for PDACs, staging plays a fundamental for treatment planning and prognostication of PanNETs. In most cases, liver metastases from PanNETs are hypervascular; nevertheless, in some cases they can be iso- or hypovascular and therefore difficult to detect and correctly characterize using conventional imaging techniques. Moreover, heterogeneity of liver metastases has been reported[61]. DWI is a good functional technique for the detection of PanNET liver metastases, with 71% sensitivity and 85%-100% specificity, equal or even higher than T2-weighted and contrast-enhanced images[62,63]. In a study that evaluated the role of DWI in the differentiation of hemangiomas from other hypervascular liver lesions, the mean ADC value of NETs metastases was found to be $1.43 \times 10^{-3} \pm 0.39 \times 10^{-3}$ mm^2/s[64], slightly higher than that reported by Schmid-Tannwald ($1.23 \times 10^{-3} \pm 0.31 \times 10^{-3}$ mm^2/s)[65]. Nevertheless, MR features derived from conventional sequences should be always taken into account, due to a wide overlap in ADC values among different liver lesions. DWI can also obtain images from the entire body in one single acquisition (whole-body diffusion-weighted imaging - WBDWI). Cossetti *et al*[66] reported two cases of NETs with distant metastases (bone and mediastinal lymphnodes) discovered by WBDWI and confirmed by Octreoscan. Etchebehere *et al*[67] compared WBDWI with ^{68}Ga-DOTATATE PET-CT and 99mTc-HYNIC-Octreotide SPECT-CT: WBDWI had a similar accuracy when compared to molecular imaging techniques for lung and liver lesions, while showed a higher false-negative rate for bone lesions. Schraml *et al*[68] reported that PET-CT and WBDWI had comparable overall detection rates for NETs metastases but

significantly differed in organ-based detection rates with superiority of PET-CT for lymph node and pulmonary lesions and of WBDWI for liver and bone metastases.

Experimental applications of pCT to PanNETs reported interesting results. Rodallec *et al*[69] and D'Assignies *et al*[70] reported that pCT features were correlated with MVD; moreover, BF values of benign PanNETs were higher than those of uncertain behavior tumors and carcinomas, and significant correlations were reported between BF, MTT and proliferation index, microscopic vascular neoplastic involvement and presence of nodal or liver metastases. Regarding staging, Ng *et al*[71] reported that BF and hepatic arterial fraction were significantly higher in liver metastases from PanNETs than in healthy liver, thus reflecting an increased arterial blood supply to metastatic lesions; opposite relationships were found for MTT and PS. Guyennon *et al*[72] reported that pCT could provide additional information in respect to conventional CT; particularly, despite both hypervascular and hypovascular metastases presented higher hepatic arterial perfusion index as compared to the background liver, mean BF and BV values were higher in hyperdense metastases compared with hypodense lesions. All liver metastases showed higher BF, BV, PS and hepatic arterial perfusion index as compared to the background liver.

Functional parameters derived from pCT may therefore be useful for the characterization of suspect PanNET liver metastases when they present atypical morphological features, as hypovascularity.

Well- and poorly-differentiated PanNETs present different DCE-MRI features. Bali *et al*[73] reported that a signal intensity - time curve similar to that of the aorta was typical of well-differentiated PanNETs, while a curve characterized by a slow enhancement was present in non well-differentiated PanNETs, but also in PDACs. Moreover, a positive correlation was observed between the MVD and the distribution factor, which reflects the volume fraction of the tissue that is accessible to the contrast agent (*i.e.,* the plasma and the extravascular extracellular space). Kim *et al*[74] found a significant difference in the perfusion characteristics of well-differentiated PanNETs and neuroendocrine carcinomas: K^{trans} values, representing tissue blood flow, were significantly lower in G3 tumors. Interestingly, the mean K^{trans} of neuroendocrine carcinomas was higher than that of PDACs, thus reflecting the true histological features of PanNETs: even if poorly differentiated, they present higher MVD as compared to PDACs.

DCE-MRI has been tested for PanNETs staging. Koh *et al*[75] found three different patterns of contrast enhancement for neuroendocrine hepatic metastases, with specific perfusional parameters. DCE-MRI is therefore potentially able to categorize metastases on the basis of their vascular characteristics, with prognostic and therapeutic consequences. Armbruster *et al*[76] reported that arterial flow fraction and intracellular uptake fraction have a high diagnostic accuracy for the distinction between NET liver metastases and normal hepatic tissue. DCE-MRI parameters are also partially correlated to SUVs derived from ^{18}F-FDG- and ^{68}Ga-DOTA-Tyr(3)-octreotate (68Ga-DOTATATE-) PET/CT[77].

RESPONSE TO TREATMENTS

Primary liver tumors

Loco-regional therapies as percutaneous or intra-operative ablation techniques [radiofrequency ablation (RFA), microwaves, irreversible electroporation or transarterial chemoembolization (TACE) and radioembolization (TARE)], have significantly contributed to the control of unresectable localized HCCs[78]. As these therapies may be repeated and interchangeably applied, early assessment of treatment response is crucial. Response Evaluation Criteria In Solid Tumors (RECIST) criteria are not applicable to HCC, as both loco-regional treatments and systemic therapy generally result in tumor necrosis rather than shrinkage. The European Association for the Study of Liver Diseases has proposed to assess response to loco-regional treatments by assessing the decrease in viable tumor volume, seen as a decrease in contrast-enhancing areas at conventional contrast-enhanced CT/MRI[79]. However, the differentiation of viable tissue from treatment-induced changes as inflammation or granulation tissue can be difficult, as these non-tumoral changes can present contrast enhancement[80,81]. DWI and perfusion imaging techniques may have a potential role in the differentiation of viable tumor from treatment-induced necrosis. Viable neoplastic areas present high cellularity with intact cell membranes and show high vascularization; conversely, treatment-induced necrotic and inflammatory changes present a reduced cellular density, an increased membrane permeability and poor vascularization.

Radiofrequency ablation (RFA) induces coagulative necrosis in tumor tissues. Lu *et al*[82] reported that the ADC values of HCCs successfully treated with RFA showed a predictable evolution and might help radiologists to monitor tumor response, being significantly high starting from 1 mo after RFA. Ippolito *et al*[83] reported that pCT enabled the assessment of HCC vascularity after RFA, providing quantitative information about the presence of arterial vessels within viable residual neoplastic tissues: in this study, a significant difference in perfusion, arterial perfusion (AP), and hepatic perfusion index (HPI) values was found between treated lesions with residual tumor and those successfully treated. Eccles *et al*[84] reported statistically significant changes in ADC values of HCCs treated with radiotherapy (RT): in their study, the baseline median ADC of 1.56×10^{-3} mm^2/s increased to 1.89×10^{-3} mm^2/s at RT week one, to 1.91×10^{-3} mm^2/s during week two and to 2.01×10^{-3} mm^2/s one month following treatment; early increases of ADC values were correlated with sustained tumor response. Kim *et al*[85]

Table 3 Data derived from the main published studies that have evaluated apparent diffusion coefficient values before and after trans-arterial treatments of primary and metastatic liver tumors

Study	*n*	*b* values (s/mm^2)	ADC before treatment ($\times 10^{-3}$ mm^2/s)	ADC after treatment ($\times 10^{-3}$ mm^2/s)	Histotype	Treatment
Kamel *et al*[86]	38	0, 500	1.51	1.70	HCC	TACE
Sahin *et al*[87]	74	0, 50, 400, 800	1.10	1.27	HCC	TACE
Kamel *et al*[88]	24	0, 50, 750	1.86	2.13	HCC	TACE
Chen *et al*[89]	20	0, 500	1.56	2.09	HCC	TACE
Yuan *et al*[90]	41	0, 500	2.22	1.42	HCC	TACE
Deng *et al*[98]	6	0, 500	1.30	2.23	HCC	TARE
Kamel *et al*[99]	13	0, 500	1.65	1.95	HCC	TARE
Rhee *et al*[100]	20	0, 500	1.64	1.82	HCC	TARE
Mannelli *et al*[102]	36	0, 50, 500	1.64	1.92	HCC	TACE
Kubota *et al*[103]	25	0, 500	1.271	1.357[1]/1.222[2]	HCC	TACE
Liapi *et al*[120]	26	0, 500	1.51	1.79	Metastases (PanNET)	TACE
Li *et al*[121]	26	0, 750	1.31	1.59	Metastases (PanNET)	TACE

[1]No disease relapse; [2]Disease relapse. ADC values are presented as means. *n*: Number of patients; ADC: Apparent diffusion coefficient; HCC: Hepatocellular carcinoma; PanNET: Pancreatic neuroendocrine tumor; TACE: Trans-arterial chemoembolization; TARE: Trans-arterial radioembolization.

reported that ADC values and DCE-MRI parameters acquired before concurrent chemoradiotherapy correlated with progression-free survival (PFS) and were valuable in the prediction of the clinical outcome. The best cutoff values for response prediction of ADC, K^{trans}, K_{ep}, and extravascular extracellular volume fraction (v_e) were 1.008 × 10^{-3} mm^2/s, 0.108 /min, 0.570 min^{-1}, and 0.298%, respectively.

Many studies have been conducted on the application of functional imaging techniques for HCCs treated with TACE and TARE; the most significant results are reported in Table 3. Overall, ADC values tend to increase after TACE, even at an early evaluation[86-89]. DWI can reliably assess the efficacy of trans-arterial treatments: Yuan *et al*[90] reported differences in the mean ADC values of the necrotic and vital tumor tissues after TACE (2.22 × 10^{-3} ± 0.31 × 10^{-3} mm^2/s and 1.42 × 10^{-3} ± 0.25 × 10^{-3} mm^2/s, respectively); a significant linear correlation was identified between the ADC value of the entire area of the treated mass and the extent of tumor necrosis (r = 0.58; P < 0.001). Mannelli *et al*[91] did not report differences between conventional MRI sequences and DWI for the assessment of post-TACE necrosis, although enhancement decrease on MRI subtraction images was more significantly correlated with pathological findings than ADC increase. Although quantitative analysis of diffusion restriction appears to be of value in assessing response to TACE, visual analysis seems to be less accurate: Goshima *et al*[92] reported that DW images were significantly less sensitive than contrast-enhanced images in detecting residual/recurrent tumor after TACE, and Yu *et al*[93] reported that the addition of DW images to contrast-enhanced images reduced specificity and diagnostic accuracy in detecting perilesional recurrence. Probably, the presence of treatment-induced granulation tissue is the cause of DWI false positives.

Regarding pCT, Yang *et al*[94] reported a significant decrease of the HAP, total liver perfusion (TLP), and hepatic arterial perfusion index (HAPI) values 4 wk after TACE.

Braren *et al*[95] reported strong correlation between the extravascular extracellular volume fraction assessed with DCE-MRI and the percentage of residual tumor after TACE. Taouli *et al*[96] reported that untreated HCCs had higher arterial fraction and lower portal/venous hepatic blood flow values than chemo-embolized HCCs.

Trans-arterial yttrium-90 (^{90}Y) radioembolization (TARE) aims to deliver a high radiation dose to HCCs[97]. Although a small study reported a 60% increase in the mean ADC value after TARE[98], other studies reported less conspicuous ADC increases (approximately 10%-20%)[99]. Rhee *et al*[100] reported that 1-mo response to TARE assessed with DWI significantly preceded size changes: the mean baseline ADC value (1.64 × 10^{-3} ± 0.30 × 10^{-3} mm^2/s) increased to 1.81 × 10^{-3} ± 0.37 × 10^{-3} mm^2/s at 1 mo (P < 0.05), and to 1.82 × 10^{-3} ± 0.23 × 10^{-3} mm^2/s at 3 mo (P < 0.05), while the mean tumor size did not significantly modify at 1 or 3 mo. Functional imaging techniques may be helpful for response prediction to trans-arterial treatments. Park *et al*[101] reported that IVIM imaging could predict lipiodol uptake: the D* (pseudodiffusion) value was significantly higher in a "lipiodol-good uptake" HCC group than in a "lipiodol-poor uptake" group. Mannelli *et al*[102] reported that ADC quantification could predict response to TACE: HCCs with poor/incomplete response (< 50% necrosis) had significantly lower pre- and post-TACE ADC values than lesions with good/complete response. Kubota *et al*[103] reported that the percent ADC value modification after therapy was significantly higher in non-relapsed HCCs (85.2% ± 12.4%) as compared to lesions with disease relapse (8.0% ± 56.7%, P < 0.001). Konstantinidis *et al*[104] reported that DCE-MRI could predict treatment outcome after hepatic arterial infusion (HAI) of floxuridine and dexamethasone (with or without bevacizumab) in advanced intra-hepatic

Table 4 Data derived from the main published studies that have correlated functional radiological techniques with response to systemic therapies of hepatic and pancreatic tumors

Study	*n*	Technique	Imaging biomarker	Histotype	Treatment
Lewin *et al*[107]	12	IVIM	f increase	HCC	sorafenib
Vouche *et al*[108]	15	DWI	ADC increase	HCC	^{90}Y TARE ± sorafenib
Hsu *et al*[109]	31	DCE-MRI	Ktrans decrease	HCC	sorafenib+metronomic tegafur/uracil
Yopp *et al*[111]	17	DCE-MRI	AUC_{90}/AUC_{180}/K^{trans} decrease	HCC	bevacizumab
Jiang *et al*[112]	23	pCT	BF/BV/PS decrease MTT increase	HCC	bevacizumab + cytotoxic agents
Kim *et al*[113]	10	DCE-MRI/DWI	K^{trans}/K_{ep} decrease ADC increase	HCC	sunitinib
Sahani *et al*[114]	23	DCE-MRI/DWI	K^{trans}/K_{ep} decrease ADC increase	HCC	sunitinib
Kim *et al*[123]	35	pCT	BF decrease	CRC metastases	XELOX, FOLFOX, FOLFIRI
Schlemmer *et al*[124]	24	pCT	Perfusion decrease	PanNET metastases	Tyrosine-kinase inhibitors
Anzidei *et al*[125]	18	pCT, DWI	CP decrease ADC increase	CRC metastases	Oxaliplatinum, capecitabine, bevacizumab
De Bruyne *et al*[127]	19	DCE-MRI	AUC decrease	CRC metastases	Bevacizumab
Vriens *et al*[129]	23	DCE-MRI	K^{trans} decrease	CRC metastases	Cytotoxic therapy
Coenegrachts *et al*[130]	10	DCE-MRI	K_{ep} increase	CRC metastases	Bevacizumab + FOLFIRI
Deckers *et al*[126]	20	DWI	ADC decrease	CRC metastases	Chemotherapy
Niwa *et al*[133]	63	DWI	ADC decrease	PDAC	Gemcitabine
Cuneo *et al*[134]	12	DWI	ADC increase	PDAC	Chemoradiation
Yao *et al*[135]	39	pCT	BF decrease	PanNET	Bevacizumab ± everolimus
Miyazaki *et al*[132]	20	DCE-MRI	Distribution volume increase	PanNET metastases	^{90}Y-octretotide

n: Number of patients; IVIM: Intravoxel incoherent-motion diffusion-weighted imaging; f: Perfusion fraction; HCC: Hepatocellular carcinoma; ^{90}Y TARE: ^{90}Yttrium trans-arterial radioembolization; DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient; DCE-MRI: Dynamic contrast-enhanced MRI; K^{trans}: Volume transfer constant; AUC_{90}, AUC_{180}: Area under the curve at 90 and 180 s; pCT: Perfusion computed tomography; BF: Blood flow; BV: Blood volume; PS: Permeability surface; MTT: Mean transit time; K_{ep}: Rate constant; CP: Capillary permeability.

CCCs: AUC_{90} and AUC_{180} were significantly higher in ⩾ 3-year survivors than < 3-year survivors.

The advent of anti-angiogenic therapies, including sorafenib and bevacizumab, greatly expanded treatment options for HCCs. As anti-angiogenic drugs frequently do not induce tumor shrinkage but acts on tumor vascularization, functional imaging techniques may be suitable for the evaluation of patients treated with these agents. Details regarding the most relevant studies on treatment assessment by means of functional radiological techniques are reported in Table 4.

Sorafenib, an oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis, is so far the only drug that has shown overall survival benefit in patients with advanced HCC[105] and represents the standard systemic therapy for patients with advanced (unresectable and/or metastatic) HCCs with well-preserved liver function and for intermediate-stage HCCs with disease progression after local treatments[106]. As sorafenib inhibits neovascularization and decreases tumor vascularity, perfusion parameters should decrease in responding patients. Nevertheless, literature data are controversial. Lewin *et al*[107] reported a significant f (perfusion fraction) increase in responders at 2 wk and at 2 mo of sorafenib therapy, whereas a decrease was noted in non-responders at the same time intervals. Vouche *et al*[108] reported that ADC values did not change 1 and 3 mo after ^{90}Y TARE or ^{90}Y TARE plus sorafenib treatments. These results may be explained by the pleiotropic anti-angiogenic actions of sorafenib, which destroys tumor vessels and improves the integrity of basement membranes of the remaining microvessels, thus leading to less "water leakage" from the perfusion pool. Modifications during sorafenib treatment can be assessed also using perfusion-imaging techniques. Hsu *et al*[109] found good correlations between K^{trans} values and survival in patients who received sorafenib plus metronomic tegafur/uracil therapy: baseline K^{trans} was higher in patients with RECIST partial response (PR) or stable disease (SD) than in those with progressive disease (PD). Frampas *et al*[110] reported a non-significant decrease in all pCT-derived values between RECIST non-progressors and progressors treated with sorafenib.

Although not routinely used in clinical practice, other anti-angiogenic therapies are on study for HCCs, including bevacizumab (a monoclonal antibody directed against vascular endothelial growth factor - VEGF) and sunitinib (an oral multikinase inhibitor with VEGF-receptor as one of its targets). Yopp *et al*[111] reported a significant decrease of AUC_{90}, AUC_{180}, and K^{trans} in HCCs treated with bevacizumab; time to progression inversely correlated with AUC_{90} and AUC_{180} changes ($P < 0.05$ and $P < 0.001$). In one study focused on locally advanced HCCs receiving bevacizumab and cytotoxic therapy, high pretreatment K^{trans} identified patients with RECIST response to therapy[112]. Sunitinib seems to induce K^{trans} and K_{ep} decrease and ADC increase[113,114]; these modifications can be assessed even at a very early stage (after 2 wk of treatment).

Moreover, patients with larger K^{trans} and K_{ep} decrease might have a favorable clinical outcome; high baseline K^{trans} and large decreases of the extracellular volume fraction were correlated with longer PFS. No significant changes at DCE-MRI have been reported after vandetanib treatment[115,116].

Liver metastases

Lu *et al*[82] reported that metastatic liver lesions successfully treated by RFA showed a predictable evolution of ADC values, with an up-and-down variation during follow-up. Szurowska *et al*[117] reported that low pre-treatment ADC values could predict complete response of colorectal adenocarcinoma (CRC) liver metastases treated with RFA. Meijerink *et al*[118] reported that pCT-derived BF distribution fully paralleled PET/CT images in showing either the absence or presence of local recurrence after RFA: high hepatic arterial perfusion (> 50 mL/min per 100 g) and low portal venous perfusion (< 10 mL/min per 100 g) areas represented viable neoplastic tissue. Marugami *et al*[119] reported that ADC quantification might be helpful for the early detection of response in CRC liver metastases treated with HAI chemotherapy with 5-fluorouracil: ADC increase was significantly greater in responders than in non-responders.

Chemoembolization induces an increase of ADC values in PanNET liver metastases[120-122]; response to TACE can be assessed even at an early stage, starting from three weeks after treatment[122]. Details on the main published studies regarding functional imaging applications after trans-arterial treatments are reported in Table 3. Functional radiological techniques have been tested for follow-up evaluations during systemic treatment of liver metastases; details are reported in Table 4. Kim *et al*[123] reported that pCT-derived BF and flow extraction product (FEP) could be used as early response predictors in patients with liver metastases from CRC, being both significantly different between responders and non-responders to XELOX, FOLFOX or FOLFIRI chemotherapy regimens.

Schlemmer *et al*[124] reported that metastatic NETs with good response to tyrosine kinase inhibitors showed a significant tendency towards lower perfusion values assessed by pCT as compared to poor responders. Anzidei *et al*[125] reported that both pCT and DWI could detect therapy-induced (oxaliplatinum, capecitabine and bevacizumab) modifications in CRC liver metastases vascularization before significant size changes became evident: capillary permeability was significantly higher in lesions with complete and partial response; moreover, ADC values were significantly higher in partial response lesions than in patients with stable disease. Deckers *et al*[126] reported that the increase of ADC values in responding liver metastases could occur even within days after the start of chemotherapy; unfortunately, as these changes were of smaller magnitude than the variability of ADC measurement, ADC quantification was not reliable enough to predict final response at such an early time point in individual lesions.

Many studies have been conducted with DCE-MRI, probably as a consequence of the standardization of DCE-MRI-derived endpoints. De Bruyne *et al*[127] reported that bevacizumab therapy could decrease DCE-MRI-derived AUC in patients with CRC liver metastases. Vriens *et al*[128] reported a large reduction in DCE-MRI-derived perfusion parameters and glucose metabolic rate at ^{18}F-FDG PET/CT in CRC metastases treated with bevacizumab. The same author[129] reported also that cytotoxic chemotherapy did not alter DCE-MRI-derived properties of tumor vasculature. Coenegrachts *et al*[130] reported that a decrease of K_{ep} allowed early identification of response after 6 wk of FOLFIRI and bevacizumab treatment. O'Connor *et al*[131] reported that the variance of CRC liver metastases shrinkage after bevacizumab and FOLFOX-6 treatment was mainly explained by the median values of v_e, tumor enhancing fraction (EF), and microvascular uniformity. Miyazaki *et al*[132] reported that DCE-MRI-derived liver distribution volume and tumor distribution volume were significantly increased in liver metastases with good response to radiolabeled octreotide; low pretreatment values of liver distribution volume and high tumor arterial flow fraction were associated with better response.

Pancreatic tumors

DWI has been tested for treatment response evaluation of pancreatic tumors: therapy seems to increase ADC values. Niwa *et al*[133] reported ADC differences among patients with advanced pancreatic cancer treated with gemcitabine: in particular, significant differences between patients with progressive disease and those with stable disease were found at 3- and 6-mo follow-up. Tumor progression rate was significantly higher in patients with low ADC values than in those with higher values. Cuneo *et al*[134] reported a significant correlation between pre-treatment mean ADC values of surgically resected 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): the mean pre-treatment ADC value was 1.61 × 10^{-3} mm^2/s in responding patients (> 90% tumor cell destruction) compared to 1.25 × 10^{-3} mm^2/s in non-responding patients (> 10% viable tumor).

Regarding PanNETs, Yao *et al*[135] reported that bevacizumab was associated with a 44% decrease in BF in patients with low-to intermediate grade tumors; the addition of everolimus induced a further 29% BF decrease. Everolimus alone was associated with 13% increase in MTT. Pretreatment PS (P = 0.009), post-treatment MTT (P = 0.003), percent reduction in BF (P = 0.03), and percent reduction in BV (P = 0.002) were associated with high percent reduction in tumor diameters. Such perfusion changes occurred early

after treatment start and might be used as functional biomarkers of response to bevacizumab or everolimus treatment.

CONCLUSION

Literature data reveal that DWI can provide prognostic stratification of HCCs and PDACs, as DWI findings may reflect "adverse" pathological features associated with poor clinical outcome and prognosis. ADC values are generally low in poorly differentiated lesions, although different results have been reported regarding the direct correlation of ADC values and the pathological grade. Perfusion imaging techniques can theoretically depict microvascular changes related to dedifferentiation of HCCs and PDACs, but poor and controversial results have been reported.

Overall, it seems that functional radiological techniques find their most important applications in PanNETs: both DWI and perfusion imaging methods provide indirect information on their clinical behavior and improve their staging.

Functional imaging techniques can predict treatment outcome and assess response of primary and metastatic hepatic tumors to loco-regional therapies, particularly TACE: ADC increase seems to be associated with good clinical outcome.

Perfusion imaging can be of value in the post-treatment assessment of patients treated with tyrosine kinases inhibitors: DCE-MRI and pCT can distinguish responders from non-responders using DCE-imaging.

Functional radiological techniques are therefore reliable and useful to evaluate patients with hepatic and pancreatic tumors; these "new imaging" techniques could be therefore considered and -whenever possible- adopted as a part of CT/MRI examination protocols.

REFERENCES

1 **Lim KS**. Diffusion-weighted MRI of hepatocellular carcinoma in cirrhosis. *Clin Radiol* 2014; **69**: 1-10 [PMID: 24034549 DOI: 10.1016/j.crad.2013.07.022]

2 **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]

3 **Pandharipande PV**, Krinsky GA, Rusinek H, Lee VS. Perfusion imaging of the liver: current challenges and future goals. *Radiology* 2005; **234**: 661-673 [PMID: 15734925 DOI: 10.1148/radiol.2343031362]

4 **Stejskal EO**, Tanner JE. Spin Diffusion Measurements: Spin Echoes in the Presence of a Time Dependent Field Gradient. *J Chem Phys* 1965; **42**: 288 [DOI: 10.1063/1.1695690]

5 **Koh DM**, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am J Roentgenol* 2007; **188**: 1622-1635 [PMID: 17515386 DOI: 10.2214/AJR.06.1403]

6 **Guo Y**, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, Mahankali S, Gao JH. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *J Magn Reson Imaging* 2002; **16**: 172-178 [PMID: 12203765 DOI: 10.1002/jmri.10140]

7 **Gauvain KM**, McKinstry RC, Mukherjee P, Perry A, Neil JJ, Kaufman BA, Hayashi RJ. Evaluating pediatric brain tumor cellularity with diffusion-tensor imaging. *AJR Am J Roentgenol* 2001; **177**: 449-454 [PMID: 11461881 DOI: 10.2214/ajr.177.2.1770449]

8 **Sugahara T**, Korogi Y, Kochi M, Ikushima I, Shigematu Y, Hirai T, Okuda T, Liang L, Ge Y, Komohara Y, Ushio Y, Takahashi M. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging* 1999; **9**: 53-60 [PMID: 10030650]

9 **Lang P**, Wendland MF, Saeed M, Gindele A, Rosenau W, Mathur A, Gooding CA, Genant HK. Osteogenic sarcoma: noninvasive in vivo assessment of tumor necrosis with diffusion-weighted MR imaging. *Radiology* 1998; **206**: 227-235 [PMID: 9423677 DOI: 10.1148/radiology.206.1.9423677]

10 **Taouli B**, Koh DM. Diffusion-weighted MR imaging of the liver. *Radiology* 2010; **254**: 47-66 [PMID: 20032142 DOI: 10.1148/radiol.09090021]

11 **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]

12 **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 DOI: 10.1148/radiology.168.2.3393671]

13 **Tofts PS**, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999; **10**: 223-232 [PMID: 10508281 DOI: 10.1002/(SICI)1522-2586(199909)10:3]

14 **Leach MO**, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A, Jayson GC, Judson IR, Knopp MV, Maxwell RJ, McIntyre D, Padhani AR, Price P, Rathbone R, Rustin GJ, Tofts PS, Tozer GM, Vennart W, Waterton JC, Williams SR, Workman P. The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. *Br J Cancer* 2005; **92**: 1599-1610 [PMID: 15870830 DOI: 10.1038/sj.bjc.6602550]

15 **Miles KA**. Functional computed tomography in oncology. *Eur J Cancer* 2002; **38**: 2079-2084 [PMID: 12387833 DOI: 10.1016/S0959-8049(02)00386-6]

16 **Miles KA**. Perfusion CT for the assessment of tumour vascularity: which protocol? *Br J Radiol* 2003; **76** Spec No 1: S36-S42 [PMID: 15456712 DOI: 10.1259/bjr/18486642]

17 **Cao J**, Yang A, Long XY, Liu H, Cao JN, Li H. [CT hepatic volume measurement combined with CT perfusion imaging in evaluating the hepatic functional reserve]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2007; **32**: 422-426 [PMID: 17611318]

18 **Li HO**, Sun C, Xu ZD, Miao F, Zhang DJ, Chen JH, Li X, Wang XM, Liu C, Zhao B. Low-dose whole organ CT perfusion of the pancreas: preliminary study. *Abdom Imaging* 2014; **39**: 40-47 [PMID: 24258077 DOI: 10.1007/s00261-013-0045-1]

19 **Haratake J**, Takeda S, Kasai T, Nakano S, Tokui N. Predictable factors for estimating prognosis of patients after resection of hepatocellular carcinoma. *Cancer* 1993; **72**: 1178-1183 [PMID: 7687921 DOI: 10.1002/1097-0142(19930815)72:4<1178]

20 **Lauwers GY**, Terris B, Balis UJ, Batts KP, Regimbeau JM, Chang Y, Graeme-Cook F, Yamabe H, Ikai I, Cleary KR, Fujita S, Flejou JF, Zukerberg LR, Nagorney DM, Belghiti J, Yamaoka Y, Vauthey JN. Prognostic histologic indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. *Am J Surg Pathol* 2002; **26**: 25-34 [PMID: 11756766 DOI: 10.1097/00000478-200201000-00003]

21 **Coleman WB**. Mechanisms of human hepatocarcinogenesis. *Curr Mol Med* 2003; **3**: 573-588 [PMID: 14527088 DOI: 10.2174/1566524033479546]

22 **An C**, Park MS, Jeon HM, Kim YE, Chung WS, Chung YE,

Kim MJ, Kim KW. Prediction of the histopathological grade of hepatocellular carcinoma using qualitative diffusion-weighted, dynamic, and hepatobiliary phase MRI. *Eur Radiol* 2012; **22**: 1701-1708 [PMID: 22434421 DOI: 10.1007/s00330-012-2421-6]

23 **Nasu K**, Kuroki Y, Tsukamoto T, Nakajima H, Mori K, Minami M. Diffusion-weighted imaging of surgically resected hepatocellular carcinoma: imaging characteristics and relationship among signal intensity, apparent diffusion coefficient, and histopathologic grade. *AJR Am J Roentgenol* 2009; **193**: 438-444 [PMID: 19620441 DOI: 10.2214/AJR.08.1424]

24 **Piana G**, Trinquart L, Meskine N, Barrau V, Beers BV, Vilgrain V. New MR imaging criteria with a diffusion-weighted sequence for the diagnosis of hepatocellular carcinoma in chronic liver diseases. *J Hepatol* 2011; **55**: 126-132 [PMID: 21145857 DOI: 10.1016/j.jhep.2010.10.023]

25 **Saito K**, Moriyasu F, Sugimoto K, Nishio R, Saguchi T, Akata S, Tokuuye K. Histological grade of differentiation of hepatocellular carcinoma: comparison of the efficacy of diffusion-weighted MRI with T2-weighted imaging and angiography-assisted CT. *J Med Imaging Radiat Oncol* 2012; **56**: 261-269 [PMID: 22697322 DOI: 10.1111/j.1754-9485.2012.02374.x]

26 **Muhi A**, Ichikawa T, Motosugi U, Sano K, Matsuda M, Kitamura T, Nakazawa T, Araki T. High-b-value diffusion-weighted MR imaging of hepatocellular lesions: estimation of grade of malignancy of hepatocellular carcinoma. *J Magn Reson Imaging* 2009; **30**: 1005-1011 [PMID: 19856432 DOI: 10.1002/jmri.21931]

27 **Nishie A**, Tajima T, Asayama Y, Ishigami K, Kakihara D, Nakayama T, Takayama Y, Okamoto D, Fujita N, Taketomi A, Yoshimitsu K, Honda H. Diagnostic performance of apparent diffusion coefficient for predicting histological grade of hepatocellular carcinoma. *Eur J Radiol* 2011; **80**: e29-e33 [PMID: 20619566 DOI: 10.1016/j.ejrad.2010.06.019]

28 **Heo SH**, Jeong YY, Shin SS, Kim JW, Lim HS, Lee JH, Koh YS, Cho CK, Kang HK. Apparent diffusion coefficient value of diffusion-weighted imaging for hepatocellular carcinoma: correlation with the histologic differentiation and the expression of vascular endothelial growth factor. *Korean J Radiol* 2010; **11**: 295-303 [PMID: 20461183 DOI: 10.3348/kjr.2010.11.3.295]

29 **Nakanishi M**, Chuma M, Hige S, Omatsu T, Yokoo H, Nakanishi K, Kamiyama T, Kubota K, Haga H, Matsuno Y, Onodera Y, Kato M, Asaka M. Relationship between diffusion-weighted magnetic resonance imaging and histological tumor grading of hepatocellular carcinoma. *Ann Surg Oncol* 2012; **19**: 1302-1309 [PMID: 21927976 DOI: 10.1245/s10434-011-2066-8]

30 **Woo S**, Lee JM, Yoon JH, Joo I, Han JK, Choi BI. Intravoxel incoherent motion diffusion-weighted MR imaging of hepatocellular carcinoma: correlation with enhancement degree and histologic grade. *Radiology* 2014; **270**: 758-767 [PMID: 24475811 DOI: 10.1148/radiol.13130444]

31 **Suh YJ**, Kim MJ, Choi JY, Park MS, Kim KW. Preoperative prediction of the microvascular invasion of hepatocellular carcinoma with diffusion-weighted imaging. *Liver Transpl* 2012; **18**: 1171-1178 [PMID: 22767394 DOI: 10.1002/lt.23502]

32 **Xu P**, Zeng M, Liu K, Shan Y, Xu C, Lin J. Microvascular invasion in small hepatocellular carcinoma: is it predictable with preoperative diffusion-weighted imaging? *J Gastroenterol Hepatol* 2014; **29**: 330-336 [PMID: 24033853 DOI: 10.1111/jgh.12358]

33 **Salem R**, Lewandowski R, Roberts C, Goin J, Thurston K, Abouljoud M, Courtney A. Use of Yttrium-90 glass microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma in patients with portal vein thrombosis. *J Vasc Interv Radiol* 2004; **15**: 335-345 [PMID: 15064336 DOI: 10.1097/01.RVI.0000123319.20705.92]

34 **Catalano OA**, Choy G, Zhu A, Hahn PF, Sahani DV. Differentiation of malignant thrombus from bland thrombus of the portal vein in patients with hepatocellular carcinoma: application of diffusion-weighted MR imaging. *Radiology* 2010; **254**: 154-162 [PMID: 20032150 DOI: 10.1148/radiol.09090304]

35 **Yu JS**, Chung JJ, Kim JH, Kim KW. Limited value of diffusion-weighted MR imaging for differentiating bland from malignant portal venous thrombi. *Radiology* 2010; **256**: 673-674; author reply 674 [PMID: 20656851 DOI: 10.1148/radiol.100277]

36 **Yu JS**, Chung JJ, Kim JH, Cho ES, Kim DJ, Ahn JH, Kim KW. Detection of small intrahepatic metastases of hepatocellular carcinomas using diffusion-weighted imaging: comparison with conventional dynamic MRI. *Magn Reson Imaging* 2011; **29**: 985-992 [PMID: 21616624 DOI: 10.1016/j.mri.2011.04.010]

37 **Ahn SJ**, Park MS, Kim KA, Park JY, Kim I, Kang WJ, Lee SK, Kim MJ. ^{18}F-FDG PET metabolic parameters and MRI perfusion and diffusion parameters in hepatocellular carcinoma: a preliminary study. *PLoS One* 2013; **8**: e71571 [PMID: 23940769 DOI: 10.1371/journal.pone.0071571]

38 **Ippolito D**, Capraro C, Casiraghi A, Cestari C, Sironi S. Quantitative assessment of tumour associated neovascularisation in patients with liver cirrhosis and hepatocellular carcinoma: role of dynamic-CT perfusion imaging. *Eur Radiol* 2012; **22**: 803-811 [PMID: 22086560 DOI: 10.1007/s00330-011-2307-z]

39 **Sahani DV**, Holalkere NS, Mueller PR, Zhu AX. Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue--initial experience. *Radiology* 2007; **243**: 736-743 [PMID: 17517931 DOI: 10.1148/radiol.2433052020]

40 **Yang HF**, Du Y, Ni JX, Zhou XP, Li JD, Zhang Q, Xu XX, Li Y. Perfusion computed tomography evaluation of angiogenesis in liver cancer. *Eur Radiol* 2010; **20**: 1424-1430 [PMID: 20179942 DOI: 10.1007/s00330-009-1693-y]

41 **Cui XY**, Chen HW, Cai S, Bao J, Tang QF, Wu LY, Fang XM. Diffusion-weighted MR imaging for detection of extrahepatic cholangiocarcinoma. *Eur J Radiol* 2012; **81**: 2961-2965 [PMID: 22285604 DOI: 10.1016/j.ejrad.2011.12.040]

42 **Park MJ**, Kim YK, Lim S, Rhim H, Lee WJ. Hilar cholangiocarcinoma: value of adding DW imaging to gadoxetic acid-enhanced MR imaging with MR cholangiopancreatography for preoperative evaluation. *Radiology* 2014; **270**: 768-776 [PMID: 24475800 DOI: 10.1148/radiol.13130009]

43 **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 [DOI: 10.1002/jmri.22414]

44 **Legrand L**, Duchatelle V, Molinié V, Boulay-Coletta I, Sibileau E, Zins M. Pancreatic adenocarcinoma: MRI conspicuity and pathologic correlations. *Abdom Imaging* 2015; **40**: 85-94 [PMID: 25030776 DOI: 10.1007/s00261-014-0196-8]

45 **Rosenkrantz AB**, Matza BW, Sabach A, Hajdu CH, Hindman N. Pancreatic cancer: lack of association between apparent diffusion coefficient values and adverse pathological features. *Clin Radiol* 2013; **68**: e191-e197 [PMID: 23312674 DOI: 10.1016/j.crad.2012.11.006]

46 **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]

47 **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]

48 **Hayano K**, Miura F, Amano H, Toyota N, Wada K, Kato K, Sano K, Takeshita K, Aoyagi T, Shuto K, Matsubara H, Asano T, Takada T. Correlation of apparent diffusion coefficient measured by diffusion-weighted MRI and clinicopathologic features in pancreatic cancer patients. *J Hepatobiliary Pancreat Sci* 2013; **20**: 243-248 [PMID: 22311389 DOI: 10.1007/s00534-011-0491-5]

49 **Fukukura Y**, Takumi K, Higashi M, Shinchi H, Kamimura K, Yoneyama T, Tateyama A. Contrast-enhanced CT and diffusion-weighted MR imaging: performance as a prognostic factor in patients with pancreatic ductal adenocarcinoma. *Eur J Radiol* 2014; **83**: 612-619 [PMID: 24418286 DOI: 10.1016/j.ejrad.2013.12.016]

50 **Holzapfel K**, Reiser-Erkan C, Fingerle AA, Erkan M, Eiber MJ, Rummeny EJ, Friess H, Kleeff J, Gaa J. Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. *Abdom Imaging* 2011; **36**: 179-184 [PMID: 20563868 DOI: 10.1007/s00261-010-9633-5]

51 **Kim YK**, Kim CS, Han YM, Lee YH. Detection of liver malignancy with gadoxetic acid-enhanced MRI: is addition of diffusion-weighted MRI beneficial? *Clin Radiol* 2011; **66**: 489-496 [PMID: 21367403 DOI: 10.1016/j.crad.2010.09.007]

52 **Kenis C**, Deckers F, De Foer B, Van Mieghem F, Van Laere S, Pouillon M. Diagnosis of liver metastases: can diffusion-weighted imaging (DWI) be used as a stand alone sequence? *Eur J Radiol* 2012; **81**: 1016-1023 [PMID: 21377305 DOI: 10.1016/j.ejrad.2011.02.019]

53 **Miller FH**, Hammond N, Siddiqi AJ, Shroff S, Khatri G, Wang Y, Merrick LB, Nikolaidis P. Utility of diffusion-weighted MRI in distinguishing benign and malignant hepatic lesions. *J Magn Reson Imaging* 2010; **32**: 138-147 [PMID: 20578020 DOI: 10.1002/jmri.22235]

54 **Barău A**, Ruiz-Sauri A, Valencia G, Gómez-Mateo Mdel C, Sabater L, Ferrandez A, Llombart-Bosch A. High microvessel density in pancreatic ductal adenocarcinoma is associated with high grade. *Virchows Arch* 2013; **462**: 541-546 [PMID: 23579431 DOI: 10.1007/s00428-013-1409-1]

55 **D'Onofrio M**, Gallotti A, Mantovani W, Crosara S, Manfrin E, Falconi M, Ventriglia A, Zamboni GA, Manfredi R, Pozzi Mucelli R. Perfusion CT can predict tumoral grading of pancreatic adenocarcinoma. *Eur J Radiol* 2013; **82**: 227-233 [PMID: 23127804 DOI: 10.1016/j.ejrad.2012.09.023]

56 **Ueno M**, Niwa T, Ohkawa S, Amano A, Masaki T, Miyakawa K, Yoshida T. The usefulness of perfusion-weighted magnetic resonance imaging in advanced pancreatic cancer. *Pancreas* 2009; **38**: 644-648 [PMID: 19546836 DOI: 10.1097/MPA.0b013e3181ac1b27]

57 **Bosman FT**, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon, France: IARC press, 2010

58 **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]

59 **Jang KM**, Kim SH, Lee SJ, Choi D. The value of gadoxetic acid-enhanced and diffusion-weighted MRI for prediction of grading of pancreatic neuroendocrine tumors. *Acta Radiol* 2014; **55**: 140-148 [PMID: 23897307 DOI: 10.1177/0284185113494982]

60 **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]

61 **Couvelard A**, Deschamps L, Ravaud P, Baron G, Sauvanet A, Hentic O, Colnot N, Paradis V, Belghiti J, Bedossa P, Ruszniewski P. Heterogeneity of tumor prognostic markers: a reproducibility study applied to liver metastases of pancreatic endocrine tumors. *Mod Pathol* 2009; **22**: 273-281 [PMID: 18997736 DOI: 10.1038/modpathol.2008.177]

62 **d'Assignies G**, Fina P, Bruno O, Vullierme MP, Tubach F, Paradis V, Sauvanet A, Ruszniewski P, Vilgrain V. High sensitivity of diffusion-weighted MR imaging for the detection of liver metastases from neuroendocrine tumors: comparison with T2-weighted and dynamic gadolinium-enhanced MR imaging. *Radiology* 2013; **268**: 390-399 [PMID: 23533288 DOI: 10.1148/radiol.13121628]

63 **Singh N**, Telles S. High frequency yoga breathing can increase alveolar dead space. Comment to: Gastroesophageal reflux disease and pulmonary function: a potential role of the dead space extension, Damir Bonacin, Damir Fabijanić, Mislav Radić, Željko Puljiz, Gorana Trgo, Andre Bratanić, Izet Hozo, Jadranka Tocilj, Med Sci Monit, 2012; 18(5): CR271-275. *Med Sci Monit* 2012; **18**: LE5-L6; author reply LE5-L6; [PMID: 22739742 DOI: 10.12659/MSM.882719]

64 **Vossen JA**, Buijs M, Liapi E, Eng J, Bluemke DA, Kamel IR. Receiver operating characteristic analysis of diffusion-weighted magnetic resonance imaging in differentiating hepatic hemangioma from other hypervascular liver lesions. *J Comput Assist Tomogr* 2008; **32**: 750-756 [PMID: 18830105 DOI: 10.1097/RCT.0b013e31816a6823]

65 **Schmid-Tannwald C**, Thomas S, Ivancevic MK, Dahi F, Rist C, Sethi I, Oto A. Diffusion-weighted MRI of metastatic liver lesions: is there a difference between hypervascular and hypovascular metastases? *Acta Radiol* 2014; **55**: 515-523 [PMID: 23986455 DOI: 10.1177/0284185113501493]

66 **Cossetti RJ**, Bezerra RO, Gumz B, Telles A, Costa FP. Whole body diffusion for metastatic disease assessment in neuroendocrine carcinomas: comparison with OctreoScan® in two cases. *World J Surg Oncol* 2012; **10**: 82 [PMID: 22591909 DOI: 10.1186/1477-7819-10-82]

67 **Etchebehere EC**, de Oliveira Santos A, Gumz B, Vicente A, Hoff PG, Corradi G, Ichiki WA, de Almeida Filho JG, Cantoni S, Camargo EE, Costa FP. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. *J Nucl Med* 2014; **55**: 1598-1604 [PMID: 25168627 DOI: 10.2967/jnumed.114.144543]

68 **Schraml C**, Schwenzer NF, Sperling O, Aschoff P, Lichy MP, Müller M, Brendle C, Werner MK, Claussen CD, Pfannenberg C. Staging of neuroendocrine tumours: comparison of [^{68}Ga]DOTATOC multiphase PET/CT and whole-body MRI. *Cancer Imaging* 2013; **13**: 63-72 [PMID: 23466785 DOI: 10.1102/1470-7330.2013.0007]

69 **Rodallec M**, Vilgrain V, Couvelard A, Rufat P, O'Toole D, Barrau V, Sauvanet A, Ruszniewski P, Menu Y. Endocrine pancreatic tumours and helical CT: contrast enhancement is correlated with microvascular density, histoprognostic factors and survival. *Pancreatology* 2006; **6**: 77-85 [PMID: 16327283 DOI: 10.1159/000090026]

70 **d'Assignies G**, Couvelard A, Bahrami S, Vullierme MP, Hammel P, Hentic O, Sauvanet A, Bedossa P, Ruszniewski P, Vilgrain V. Pancreatic endocrine tumors: tumor blood flow assessed with perfusion CT reflects angiogenesis and correlates with prognostic factors. *Radiology* 2009; **250**: 407-416 [PMID: 19095784 DOI: 10.1148/radiol.2501080291]

71 **Ng CS**, Hobbs BP, Chandler AG, Anderson EF, Herron DH, Charnsangavej C, Yao J. Metastases to the liver from neuroendocrine tumors: effect of duration of scan acquisition on CT perfusion values. *Radiology* 2013; **269**: 758-767 [PMID: 23824990 DOI: 10.1148/radiol.13122708]

72 **Guyennon A**, Mihaila M, Palma J, Lombard-Bohas C, Chayvialle JA, Pilleul F. Perfusion characterization of liver metastases from endocrine tumors: Computed tomography perfusion. *World J Radiol* 2010; **2**: 449-454 [PMID: 21179313 DOI: 10.4329/wjr.v2.i11.449]

73 **Bali MA**, Metens T, Denolin V, Delhaye M, Demetter P, Closset J, Matos C. Tumoral and nontumoral pancreas: correlation between quantitative dynamic contrast-enhanced MR imaging and histopathologic parameters. *Radiology* 2011; **261**: 456-466 [PMID: 21852570 DOI: 10.1148/radiol.11103515]

74 **Kim JH**, Lee JM, Park JH, Kim SC, Joo I, Han JK, Choi BI. Solid pancreatic lesions: characterization by using timing bolus dynamic contrast-enhanced MR imaging assessment--a preliminary study. *Radiology* 2013; **266**: 185-196 [PMID: 23192779 DOI: 10.1148/radiol.12120111]

75 **Koh TS**, Thng CH, Hartono S, Kwek JW, Khoo JB, Miyazaki K, Collins DJ, Orton MR, Leach MO, Lewington V, Koh DM. Dynamic contrast-enhanced MRI of neuroendocrine hepatic metastases: A feasibility study using a dual-input two-compartment model. *Magn Reson Med* 2011; **65**: 250-260 [PMID: 20860001 DOI: 10.1002/mrm.22596]

76 **Armbruster M**, Zech CJ, Sourbron S, Ceelen F, Auernhammer CJ, Rist C, Haug A, Singnurkar A, Reiser MF, Sommer WH.

Diagnostic accuracy of dynamic gadoxetic-acid-enhanced MRI and PET/CT compared in patients with liver metastases from neuroendocrine neoplasms. *J Magn Reson Imaging* 2014; **40**: 457-466 [PMID: 24347148 DOI: 10.1002/jmri.24363]

77 **Armbruster M**, Sourbron S, Haug A, Zech CJ, Ingrisch M, Auernhammer CJ, Nikolaou K, Paprottka PM, Rist C, Reiser MF, Sommer WH. Evaluation of neuroendocrine liver metastases: a comparison of dynamic contrast-enhanced magnetic resonance imaging and positron emission tomography/computed tomography. *Invest Radiol* 2014; **49**: 7-14 [PMID: 24002080 DOI: 10.1097/RLI.0b013e3182a4eb4a]

78 **Ramsey DE**, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002; **13**: S211-S221 [PMID: 12354839 DOI: 10.1016/S1051-0443(07)61789-8]

79 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430 [PMID: 11592607 DOI: 10.1016/S0168-8278(01)00130-1]

80 **Vossen JA**, Buijs M, Kamel IR. Assessment of tumor response on MR imaging after locoregional therapy. *Tech Vasc Interv Radiol* 2006; **9**: 125-132 [PMID: 17561215 DOI: 10.1053/j.tvir.2007.02.004]

81 **Hwang SH**, Yu JS, Chung J, Chung JJ, Kim JH, Kim KW. Transient hepatic attenuation difference (THAD) following transcatheter arterial chemoembolization for hepatic malignancy: changes on serial CT examinations. *Eur Radiol* 2008; **18**: 1596-1603 [PMID: 18351345 DOI: 10.1007/s00330-008-0916-y]

82 **Lu TL**, Becce F, Bize P, Denys A, Meuli R, Schmidt S. Assessment of liver tumor response by high-field (3 T) MRI after radiofrequency ablation: short- and mid-term evolution of diffusion parameters within the ablation zone. *Eur J Radiol* 2012; **81**: e944-e950 [PMID: 22817977 DOI: 10.1016/j.ejrad.2012.06.011]

83 **Ippolito D**, Bonaffini PA, Capraro C, Leni D, Corso R, Sironi S. Viable residual tumor tissue after radiofrequency ablation treatment in hepatocellular carcinoma: evaluation with CT perfusion. *Abdom Imaging* 2013; **38**: 502-510 [PMID: 22743839 DOI: 10.1007/s00261-012-9924-0]

84 **Eccles CL**, Haider EA, Haider MA, Fung S, Lockwood G, Dawson LA. Change in diffusion weighted MRI during liver cancer radiotherapy: preliminary observations. *Acta Oncol* 2009; **48**: 1034-1043 [PMID: 19634060 DOI: 10.1080/02841860903099972]

85 **Kim KA**, Park MS, Ji HJ, Park JY, Han KH, Kim MJ, Kim KW. Diffusion and perfusion MRI prediction of progression-free survival in patients with hepatocellular carcinoma treated with concurrent chemoradiotherapy. *J Magn Reson Imaging* 2014; **39**: 286-292 [PMID: 24302545 DOI: 10.1002/jmri.24161]

86 **Kamel IR**, Bluemke DA, Eng J, Liapi E, Messersmith W, Reyes DK, Geschwind JF. The role of functional MR imaging in the assessment of tumor response after chemoembolization in patients with hepatocellular carcinoma. *J Vasc Interv Radiol* 2006; **17**: 505-512 [PMID: 16567675 DOI: 10.1097/01.RVI.00002000-52.02183.92]

87 **Sahin H**, Harman M, Cinar C, Bozkaya H, Parildar M, Elmas N. Evaluation of treatment response of chemoembolization in hepatocellular carcinoma with diffusion-weighted imaging on 3.0-T MR imaging. *J Vasc Interv Radiol* 2012; **23**: 241-247 [PMID: 22019180 DOI: 10.1016/j.jvir.2011.08.030]

88 **Kamel IR**, Liapi E, Reyes DK, Zahurak M, Bluemke DA, Geschwind JF. Unresectable hepatocellular carcinoma: serial early vascular and cellular changes after transarterial chemoembolization as detected with MR imaging. *Radiology* 2009; **250**: 466-473 [PMID: 19188315 DOI: 10.1148/radiol.2502072222]

89 **Chen CY**, Li CW, Kuo YT, Jaw TS, Wu DK, Jao JC, Hsu JS, Liu GC. Early response of hepatocellular carcinoma to transcatheter arterial chemoembolization: choline levels and MR diffusion constants--initial experience. *Radiology* 2006; **239**: 448-456 [PMID: 16569781 DOI: 10.1148/radiol.2392042202]

90 **Yuan Z**, Li WT, Ye XD, Peng WJ, Xiao XS. Utility of diffusion-weighted imaging to assess hepatocellular carcinoma viability following transarterial chemoembolization. *Oncol Lett* 2014; **8**: 831-836 [PMID: 25013505 DOI: 10.3892/ol.2014.2228]

91 **Mannelli L**, Kim S, Hajdu CH, Babb JS, Clark TW, Taouli B. Assessment of tumor necrosis of hepatocellular carcinoma after chemoembolization: diffusion-weighted and contrast-enhanced MRI with histopathologic correlation of the explanted liver. *AJR Am J Roentgenol* 2009; **193**: 1044-1052 [PMID: 19770328 DOI: 10.2214/AJR.08.1461]

92 **Goshima S**, Kanematsu M, Kondo H, Yokoyama R, Kajita K, Tsuge Y, Watanabe H, Shiratori Y, Onozuka M, Moriyama N. Diffusion-weighted imaging of the liver: optimizing b value for the detection and characterization of benign and malignant hepatic lesions. *J Magn Reson Imaging* 2008; **28**: 691-697 [PMID: 18777553 DOI: 10.1002/jmri.21467]

93 **Yu JS**, Kim JH, Chung JJ, Kim KW. Added value of diffusion-weighted imaging in the MRI assessment of perilesional tumor recurrence after chemoembolization of hepatocellular carcinomas. *J Magn Reson Imaging* 2009; **30**: 153-160 [PMID: 19557734 DOI: 10.1002/jmri.21818]

94 **Yang L**, Zhang XM, Tan BX, Liu M, Dong GL, Zhai ZH. Computed tomographic perfusion imaging for the therapeutic response of chemoembolization for hepatocellular carcinoma. *J Comput Assist Tomogr* 2012; **36**: 226-230 [PMID: 22446364 DOI: 10.1097/RCT.0b013e318245c23c]

95 **Braren R**, Altomonte J, Settles M, Neff F, Esposito I, Ebert O, Schwaiger M, Rummeny E, Steingoetter A. Validation of preclinical multiparametric imaging for prediction of necrosis in hepatocellular carcinoma after embolization. *J Hepatol* 2011; **55**: 1034-1040 [PMID: 21354233 DOI: 10.1016/j.jhep.2011.01.049]

96 **Taouli B**, Johnson RS, Hajdu CH, Oei MT, Merad M, Yee H, Rusinek H. Hepatocellular carcinoma: perfusion quantification with dynamic contrast-enhanced MRI. *AJR Am J Roentgenol* 2013; **201**: 795-800 [PMID: 24059368 DOI: 10.2214/AJR.12.9798]

97 **Goin JE**, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, Goin K, Van Buskirk M, Thurston K. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities. *J Vasc Interv Radiol* 2005; **16**: 205-213 [PMID: 15713921 DOI: 10.1097/01.RVI.00001142592.89564.F9]

98 **Deng J**, Miller FH, Rhee TK, Sato KT, Mulcahy MF, Kulik LM, Salem R, Omary RA, Larson AC. Diffusion-weighted MR imaging for determination of hepatocellular carcinoma response to yttrium-90 radioembolization. *J Vasc Interv Radiol* 2006; **17**: 1195-1200 [PMID: 16868174 DOI: 10.1097/01.RVI.0000227234.81718.EB]

99 **Kamel IR**, Reyes DK, Liapi E, Bluemke DA, Geschwind JF. Functional MR imaging assessment of tumor response after 90Y microsphere treatment in patients with unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2007; **18**: 49-56 [PMID: 17296704 DOI: 10.1016/j.jvir.2006.10.005]

100 **Rhee TK**, Naik NK, Deng J, Atassi B, Mulcahy MF, Kulik LM, Ryu RK, Miller FH, Larson AC, Salem R, Omary RA. Tumor response after yttrium-90 radioembolization for hepatocellular carcinoma: comparison of diffusion-weighted functional MR imaging with anatomic MR imaging. *J Vasc Interv Radiol* 2008; **19**: 1180-1186 [PMID: 18656011 DOI: 10.1016/j.jvir.2008.05.002]

101 **Park YS**, Lee CH, Kim JH, Kim IS, Kiefer B, Seo TS, Kim KA, Park CM. Using intravoxel incoherent motion (IVIM) MR imaging to predict lipiodol uptake in patients with hepatocellular carcinoma following transcatheter arterial chemoembolization: a preliminary result. *Magn Reson Imaging* 2014; **32**: 638-646 [PMID: 24703575 DOI: 10.1016/j.mri.2014.03.003]

102 **Mannelli L**, Kim S, Hajdu CH, Babb JS, Taouli B. Serial diffusion-weighted MRI in patients with hepatocellular carcinoma: Prediction and assessment of response to transarterial chemoembolization. Preliminary experience. *Eur J Radiol* 2013; **82**: 577-582 [PMID: 23246330 DOI: 10.1016/j.ejrad.2012.11.026]

103 **Kubota K**, Yamanishi T, Itoh S, Murata Y, Miyatake K,

Yasunami H, Morio K, Hamada N, Nishioka A, Ogawa Y. Role of diffusion-weighted imaging in evaluating therapeutic efficacy after transcatheter arterial chemoembolization for hepatocellular carcinoma. *Oncol Rep* 2010; **24**: 727-732 [PMID: 20664980 DOI: 10.3892/or_00000914]

104 **Konstantinidis IT**, Do RK, Gultekin DH, Gönen M, Schwartz LH, Fong Y, Allen PJ, D'Angelica MI, DeMatteo RP, Klimstra DS, Kemeny NE, Jarnagin WR. Regional chemotherapy for unresectable intrahepatic cholangiocarcinoma: a potential role for dynamic magnetic resonance imaging as an imaging biomarker and a survival update from two prospective clinical trials. *Ann Surg Oncol* 2014; **21**: 2675-2683 [PMID: 24664624 DOI: 10.1245/s10434-014-3649-y]

105 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

106 **Verslype C**, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23** Suppl 7: vii41-vii48 [PMID: 22997453 DOI: 10.1093/annonc/mds225]

107 **Lewin M**, Fartoux L, Vignaud A, Arrivé L, Menu Y, Rosmorduc O. The diffusion-weighted imaging perfusion fraction f is a potential marker of sorafenib treatment in advanced hepatocellular carcinoma: a pilot study. *Eur Radiol* 2011; **21**: 281-290 [PMID: 20683597 DOI: 10.1007/s00330-010-1914-4]

108 **Vouche M**, Kulik L, Atassi R, Memon K, Hickey R, Ganger D, Miller FH, Yaghmai V, Abecassis M, Baker T, Mulcahy M, Nayar R, Lewandowski RJ, Salem R. Radiological-pathological analysis of WHO, RECIST, EASL, mRECIST and DWI: Imaging analysis from a prospective randomized trial of Y90 ± sorafenib. *Hepatology* 2013; **58**: 1655-1666 [PMID: 23703789 DOI: 10.1002/hep.26487]

109 **Hsu CY**, Shen YC, Yu CW, Hsu C, Hu FC, Hsu CH, Chen BB, Wei SY, Cheng AL, Shih TT. Dynamic contrast-enhanced magnetic resonance imaging biomarkers predict survival and response in hepatocellular carcinoma patients treated with sorafenib and metronomic tegafur/uracil. *J Hepatol* 2011; **55**: 858-865 [PMID: 21338641 DOI: 10.1016/j.jhep.2011.01.032]

110 **Frampas E**, Lassau N, Zappa M, Vullierme MP, Koscielny S, Vilgrain V. Advanced Hepatocellular Carcinoma: early evaluation of response to targeted therapy and prognostic value of Perfusion CT and Dynamic Contrast Enhanced-Ultrasound. Preliminary results. *Eur J Radiol* 2013; **82**: e205-e211 [PMID: 23273822 DOI: 10.1016/j.ejrad.2012.12.004]

111 **Yopp AC**, Schwartz LH, Kemeny N, Gultekin DH, Gönen M, Bamboat Z, Shia J, Haviland D, D'Angelica MI, Fong Y, DeMatteo RP, Allen PJ, Jarnagin WR. Antiangiogenic therapy for primary liver cancer: correlation of changes in dynamic contrast-enhanced magnetic resonance imaging with tissue hypoxia markers and clinical response. *Ann Surg Oncol* 2011; **18**: 2192-2199 [PMID: 21286939 DOI: 10.1245/s10434-011-1570-1]

112 **Jiang T**, Kambadakone A, Kulkarni NM, Zhu AX, Sahani DV. Monitoring response to antiangiogenic treatment and predicting outcomes in advanced hepatocellular carcinoma using image biomarkers, CT perfusion, tumor density, and tumor size (RECIST). *Invest Radiol* 2012; **47**: 11-17 [PMID: 21512396 DOI: 10.1097/RLI.0b013e3182199bb5]

113 **Kim H**, Keene KS, Sarver DB, Lee SK, Beasley TM, Morgan DE, Posey JA. Quantitative perfusion- and diffusion-weighted magnetic resonance imaging of gastrointestinal cancers treated with multikinase inhibitors: a pilot study. *Gastrointest Cancer Res* 2014; **7**: 75-81 [PMID: 25276260]

114 **Sahani DV**, Jiang T, Hayano K, Duda DG, Catalano OA, Ancukiewicz M, Jain RK, Zhu AX. Magnetic resonance imaging biomarkers in hepatocellular carcinoma: association with response and circulating biomarkers after sunitinib therapy. *J Hematol Oncol* 2013; **6**: 51 [PMID: 23842041 DOI: 10.1186/1756-8722-6-51]

115 **Hsu C**, Yang TS, Huo TI, Hsieh RK, Yu CW, Hwang WS, Hsieh TY, Huang WT, Chao Y, Meng R, Cheng AL. Vandetanib in patients with inoperable hepatocellular carcinoma: a phase II, randomized, double-blind, placebo-controlled study. *J Hepatol* 2012; **56**: 1097-1103 [PMID: 22245891 DOI: 10.1016/j.jhep.2011.12.013]

116 **Mross K**, Fasol U, Frost A, Benkelmann R, Kuhlmann J, Büchert M, Unger C, Blum H, Hennig J, Milenkova TP, Tessier J, Krebs AD, Ryan AJ, Fischer R. DCE-MRI assessment of the effect of vandetanib on tumor vasculature in patients with advanced colorectal cancer and liver metastases: a randomized phase I study. *J Angiogenes Res* 2009; **1**: 5 [PMID: 19946413 DOI: 10.1186/2040-2384-1-5]

117 **Szurowska E**, Nowicki TK, Izycka-Swieszewska E, Zadrozny D, Markiet K, Studniarek M. Predictive value of apparent diffusion coefficient in evaluation of colorectal carcinoma hepatic metastases' response to radiofrequency ablation. *J Magn Reson Imaging* 2013; **38**: 1027-1032 [PMID: 23526807 DOI: 10.1002/jmri.24089]

118 **Meijerink MR**, van Waesberghe JH, van der Weide L, van den Tol P, Meijer S, Comans EF, Golding RP, van Kuijk C. Early detection of local RFA site recurrence using total liver volume perfusion CT initial experience. *Acad Radiol* 2009; **16**: 1215-1222 [PMID: 19524457 DOI: 10.1016/j.acra.2009.03.023]

119 **Marugami N**, Tanaka T, Kitano S, Hirohashi S, Nishiofuku H, Takahashi A, Sakaguchi H, Matsuoka M, Otsuji T, Takahama J, Higashiura W, Kichikawa K. Early detection of therapeutic response to hepatic arterial infusion chemotherapy of liver metastases from colorectal cancer using diffusion-weighted MR imaging. *Cardiovasc Intervent Radiol* 2009; **32**: 638-646 [PMID: 19238482 DOI: 10.1007/s00270-009-9532-8]

120 **Liapi E**, Geschwind JF, Vossen JA, Buijs M, Georgiades CS, Bluemke DA, Kamel IR. Functional MRI evaluation of tumor response in patients with neuroendocrine hepatic metastasis treated with transcatheter arterial chemoembolization. *AJR Am J Roentgenol* 2008; **190**: 67-73 [PMID: 18094295 DOI: 10.2214/AJR.07.2550]

121 **Li Z**, Bonekamp S, Halappa VG, Corona-Villalobos CP, Pawlik T, Bhagat N, Reyes D, Lai H, Geschwind JF, Kamel IR. Islet cell liver metastases: assessment of volumetric early response with functional MR imaging after transarterial chemoembolization. *Radiology* 2012; **264**: 97-109 [PMID: 22627602 DOI: 10.1148/radiol.12112161]

122 **Gowdra Halappa V**, Corona-Villalobos CP, Bonekamp S, Li Z, Reyes D, Cosgrove D, Pawlik TM, Diaz LA, Bhagat N, Eng J, Geschwind JF, Kamel IR. Neuroendocrine liver metastasis treated by using intraarterial therapy: volumetric functional imaging biomarkers of early tumor response and survival. *Radiology* 2013; **266**: 502-513 [PMID: 23192780 DOI: 10.1148/radiol.12120495]

123 **Kim DH**, Kim SH, Im SA, Han SW, Goo JM, Willmann JK, Lee ES, Eo JS, Paeng JC, Han JK, Choi BI. Intermodality comparison between 3D perfusion CT and ^{18}F-FDG PET/CT imaging for predicting early tumor response in patients with liver metastasis after chemotherapy: preliminary results of a prospective study. *Eur J Radiol* 2012; **81**: 3542-3550 [PMID: 22459347 DOI: 10.1016/j.ejrad.2012.02.012]

124 **Schlemmer M**, Sourbron SP, Schinwald N, Nikolaou K, Becker CR, Reiser MF, Berger F. Perfusion patterns of metastatic gastrointestinal stromal tumor lesions under specific molecular therapy. *Eur J Radiol* 2011; **77**: 312-318 [PMID: 19720488 DOI: 10.1016/j.ejrad.2009.07.031]

125 **Anzidei M**, Napoli A, Zaccagna F, Cartocci G, Saba L, Menichini G, Cavallo Marincola B, Marotta E, Di Mare L, Catalano C, Passariello R. Liver metastases from colorectal cancer treated with conventional and antiangiogenetic chemotherapy: evaluation with liver computed tomography perfusion and magnetic resonance diffusion-weighted imaging. *J Comput Assist Tomogr* 2011; **35**: 690-696 [PMID: 22082538 DOI: 10.1097/RCT.0b013e318230d905]

126 **Deckers F**, De Foer B, Van Mieghem F, Botelberge T, Weytjens R, Padhani A, Pouillon M. Apparent diffusion coefficient

measurements as very early predictive markers of response to chemotherapy in hepatic metastasis: a preliminary investigation of reproducibility and diagnostic value. *J Magn Reson Imaging* 2014; **40**: 448-456 [PMID: 24924334 DOI: 10.1002/jmri.24359]

127 **De Bruyne S**, Van Damme N, Smeets P, Ferdinande L, Ceelen W, Mertens J, Van de Wiele C, Troisi R, Libbrecht L, Laurent S, Geboes K, Peeters M. Value of DCE-MRI and FDG-PET/CT in the prediction of response to preoperative chemotherapy with bevacizumab for colorectal liver metastases. *Br J Cancer* 2012; **106**: 1926-1933 [PMID: 22596235 DOI: 10.1038/bjc.2012.184]

128 **Vriens D**, de Geus-Oei LF, Heerschap A, van Laarhoven HW, Oyen WJ. Vascular and metabolic response to bevacizumab-containing regimens in two patients with colorectal liver metastases measured by dynamic contrast-enhanced MRI and dynamic 18F-FDG-PET. *Clin Colorectal Cancer* 2011; **10**: E1-E5 [PMID: 21609927 DOI: 10.3816/CCC.2011.n.010]

129 **Vriens D**, van Laarhoven HW, van Asten JJ, Krabbe PF, Visser EP, Heerschap A, Punt CJ, de Geus-Oei LF, Oyen WJ. Chemotherapy response monitoring of colorectal liver metastases by dynamic Gd-DTPA-enhanced MRI perfusion parameters and 18F-FDG PET metabolic rate. *J Nucl Med* 2009; **50**: 1777-1784 [PMID: 19837750 DOI: 10.2967/jnumed.109.064790]

130 **Coenegrachts K**, Bols A, Haspeslagh M, Rigauts H. Prediction and monitoring of treatment effect using T1-weighted dynamic contrast-enhanced magnetic resonance imaging in colorectal liver metastases: potential of whole tumour ROI and selective ROI analysis. *Eur J Radiol* 2012; **81**: 3870-3876 [PMID: 22944331 DOI: 10.1016/j.ejrad.2012.07.022]

131 **O'Connor JP**, Rose CJ, Jackson A, Watson Y, Cheung S, Maders F, Whitcher BJ, Roberts C, Buonaccorsi GA, Thompson G, Clamp AR, Jayson GC, Parker GJ. DCE-MRI biomarkers of tumour heterogeneity predict CRC liver metastasis shrinkage following bevacizumab and FOLFOX-6. *Br J Cancer* 2011; **105**: 139-145 [PMID: 21673686 DOI: 10.1038/bjc.2011.191]

132 **Miyazaki K**, Orton MR, Davidson RL, d'Arcy JA, Lewington V, Koh TS, Thng CH, Leach MO, Collins DJ, Koh DM. Neuroendocrine tumor liver metastases: use of dynamic contrast-enhanced MR imaging to monitor and predict radiolabeled octreotide therapy response. *Radiology* 2012; **263**: 139-148 [PMID: 22344403 DOI: 10.1148/radiol.12110770]

133 **Niwa T**, Ueno M, Ohkawa S, Yoshida T, Doiuchi T, Ito K, Inoue T. Advanced pancreatic cancer: the use of the apparent diffusion coefficient to predict response to chemotherapy. *Br J Radiol* 2009; **82**: 28-34 [PMID: 19095814 DOI: 10.1259/bjr/43911400]

134 **Cuneo KC**, Chenevert TL, Ben-Josef E, Feng MU, Greenson JK, Hussain HK, Simeone DM, Schipper MJ, Anderson MA, Zalupski MM, Al-Hawary M, Galban CJ, Rehemtulla A, Feng FY, Lawrence TS, Ross BD. A pilot study of diffusion-weighted MRI in patients undergoing neoadjuvant chemoradiation for pancreatic cancer. *Transl Oncol* 2014; **7**: 644-649 [PMID: 25389460 DOI: 10.1016/j.tranon.2014.07.005]

135 **Yao JC**, Phan AT, Hess K, Fogelman D, Jacobs C, Dagohoy C, Leary C, Xie K, Ng CS. Perfusion computed tomography as functional biomarker in randomized run-in study of bevacizumab and everolimus in well-differentiated neuroendocrine tumors. *Pancreas* 2015; **44**: 190-197 [PMID: 25426617]

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