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Research Article

Diagnosis of hepatocellular carcinoma – usefulness of magnetic resonance T2-weighted images, diffusion weighted images, and T1 post-contrast injection sequences

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Abstract. Objectives: To comparatively assess the sensitivity of different magnetic resonance imaging sequences for the diagnosis of the hepatocellular carcinoma. Material and method: A total number of 60 hepatic nodules in 49 patients, with a final diagnosis of hepatocellular carcinoma have been included in the present study. All included lesions had a final histological diagnosis of hepatocellular carcinoma or they were considered as being hepatocellular carcinomas after a consensual reading made by two radiologists with experience in abdominal imaging . All nodules have been characterized through the following properties: the signal on T2-weighted images, the signal on diffusion weighted sequence, and the apparent diffusion coefficient obtained from the diffusion map. The vascular behavior in the arterial, portal and late interstitial phase has been also analyzed. Results: Of all assessed lesions, 75% were hyperintense on T2-weighted sequences and 68.3% were hypointense on the apparent diffusion coefficient map. The vascular criterion in favor of hepatocellular carcinoma (arterial hyper-vascularization accompanied by washing-out in the portal or the late phase) was met in 77.6% of the lesions, with arterial hyper-vascularization seen in 86.7% of the cases. Most of the arterial hyper-vascularized lesions with no washing-out, presented hyper-signal on the T2-weighted sequences or hypo-signal on the apparent diffusion coefficient map. Conclusions: The percentage of hepatocellular carcinoma nodules that follow the vascular criterion is under 80%. The hyper-signal on the T2 sequence and the hypo-signal on the apparent diffusion coefficient map are criteria with a reasonably good sensitivity for the diagnostic of HCC, and can be used as auxiliary diagnosis criteria.

Key Words: hepatocellular carcinoma, magnetic resonance imaging, sensitivity, diffusion, weighted sequence, vascular phases.

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Introduction

Hepatocellular carcinoma (HCC) is a malignant disease with an increasing incidence all over the world. The main risk factor for the development of HCC is liver cirrhosis, tumor's occurrence in case of non- cirrhotic liver being rare. In cases of patients with a documented diagnosis of hepatic cirrhosis, surveillance through ultrasonography every 6 months has reduced the mortality rate due to HCC by 37% (Llovet et al 2003). Once a nodule is diagnosed by sonographic screening, its nature has to be proved through contrast-enhanced imaging techniques: contrast enhanced ultrasound (CEUS), computed-tomography (CT) or magnetic resonance imaging (MRI). The additional advantages provided by cross-sectional imaging techniques, as compared to CEUS is that of whole liver scanning in the arterial phase, allowing the simultaneous characterization of multiple nodules, and also revealing the ones which were not sonographically detected in grey-scale (Zhang et al 2004).

In contrast-enhanced cross-sectional imaging techniques, the marker for the presence of a HCC lesion is the arterial phase hyper-enhancement followed by wash-out in the portal or late venous phases (the so called vascular diagnosis criterion for HCC). However, there are many studies showing that small HCC lesions (with a diameter of less than 2 cm) present in less than 50% of the cases the classical model of contrast-enhancement, presenting either hyper-enhancement during the arterial phase not accompanied by wash-out in portal/late phase, either without arterial enhancement at all, being iso- or even hypo-vascular to the hepatic parenchyma during the arterial phase (Bolondi et al 2005; Hammerstingl et al 2008; Huppertz et al 2004).

From a histological point of view, early HCC represents a distinct subtype of HCC, in general with a smaller size, with few internally neo-formation arteries, aspect which explains its hypo-vascular nature (Krinsky et al 2001).

Considering these, the strict application of the vascular criterion will lead to whether the increase of the biopsies number in cases of suspected HCC nodules, or to the sub-diagnosis/ delayed diagnosis of HCC nodules (Lorenz et al 2000). If we would try to improve the sensitivity of the technique by using hyper-enhancement during the arterial phase as the only

diagnosis criterion for HCC, then the specificity of the method would decrease very much. This can be explained by the arterial enhancement shown to be present also in cases of high grade dysplastic nodules. Moreover, in cirrhotic livers, small areas of transitory arterial hyper-enhancement due to portal microthromboses or some arteriovenous fistulas may be encountered (Sano et al 2011; Nakashima et al 2003).

Considering all these, additional criteria would be helpful for the diagnosis of HCC, especially in cases of small suspicious lesions. In general, larger lesions are following the vascular criterion thus, they can be diagnosed without problems. The goal of the present study was to analyze the usefulness of T2-weighted images and diffusion weighted imaging (DWI) sequences as additional tools for HCC's diagnosis, especially in cases of small hepatic lesions (Parente et al 2012).

Material and method

Patients

A total number of 60 HCC lesions, present in 49 patients have been included in the present study. All included lesions had either the histological confirmation of being HCCs, either they had typical MRI HCC appearance (image analysis has been made by two radiologists with experience in abdominal imaging).

From the patients included in the present study, 19 (38.8%) were women, and 30 (61.2%) men. The average age of the assessed sample was 63.06 years (standard deviation 10.28 years; age range [39-84]).

All MRI examinations were performed between 2012 and 2014 in the "Hiperdia" diagnostic center.

Inclusion criteria

Inclusion criteria were the presence of at least one focal hepatic lesion having histological diagnosis of HCC or a HCC aspect on MRI standard sequences, validated by a consensual reading made by two experimented radiologists.

Exclusion criteria

Nodules without typical MRI appearance of an HCC as considered by two radiologists and also lacking a histological diagnosis have been excluded from the present study. Cases of diffuse HCCs, as well as the already treated nodules have been also excluded.

MRI protocol

All MRI examinations have been performed using the same MRI machine (Siemens, 1,5T, Erlangen, Germany).

The routine protocol for superior abdomen MRI examinations has been used for all patients and it included the following sequences: T2-haste in coronal and axial planes, TIRM and T1-in and out of phase in axial plane, T2-Trufi in axial and coronal planes, DWI and ADC map, and the T1-vibe sequence, before and after injection of the contrast material. After contrast agent injection, the liver was scanned in arterial, portal, and late parenchymal phases. In cases when the hepatocyte-specific contrast product Gd-EOB-DTPA (Primovist, Bayer-Shering Pharma, Berlin, Germania) was applied, image acquisition has been performed also during the hepato-biliary phase (20 minutes after contrast agent injection).

Image analysis

The following data have been recorded for each patient: age, lesion size and

characteristics: aspect on T2 sequence, aspect on DWI sequence at b-800, aspect on the apparent diffusion coefficient (ADC) map, contrast-enhancement during the arterial phase, and the presence of wash-out phenomenon (regarded only for the hypo or isoenhancing lesions in regard to the hepatic parenchyma in the arterial phase of the examination). A 4 level scale has been used to asses the signal intensity on the T2- weighted image, A 4-level scale has been used to assess the signal at b-800 with 1 meaning hypointensity and 4 strong hyperintensity, a 3-level scale, to assess the ADC aspect with 1- hypointensity, 2- isointensity to the liver parenchyma and 3- hyperintensity. A 3-level scale was used for assessing enhancement in the arterial phase with 1-hyperenhanecment, 2-isoenhancement and 3-hypoenhancement. Presence or absence of wash-out in the portal or late phases of enhancement was also noted.

In the patients with multiple lesions, each lesion has been individually analyzed.

This working protocol was approved by Ethical Committee of University of Medicine and Pharmacy Cluj-Napoca and informed consent was obtained from every patient before any procedure.

Results

Focal hepatic lesions

From the included 49 patients, a total number of 60 focal hepatic lesions (average of 1.22 lesions/ patient) have been evaluated. The average size of the lesions was 34.83 mm with the smallest one being of 10 mm and the largest one, of 82 mm.

Image analysis - sequence T2

For the majority of the lesions (75%), a weak hyper-signal on the T2-weighted image has been registered. From the rest of the lesions 18.3% were in iso-signal on T2, and 5% showed hyposignal on the T2-weighted image. The distribution of different types of signal on the T2 sequence is shown in figure 1.

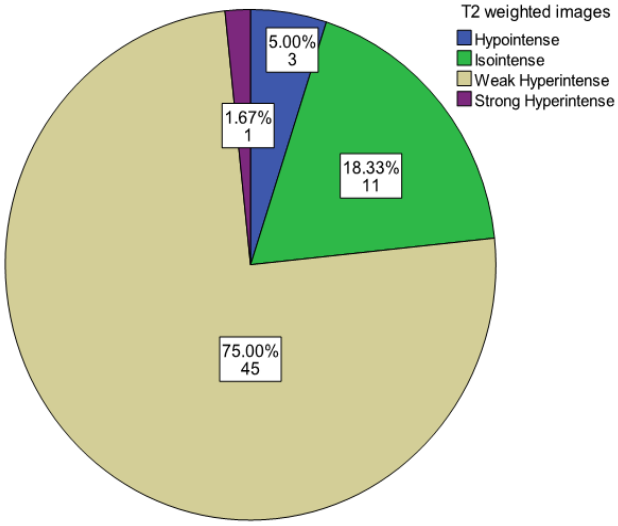

Figure 1. Distribution of HCC lesions according to the signal on T2 ponderation sequence

Image analysis – diffusion sequence and ADC map

Considering the diffusion measured at b800, strong hyper-signal has been registered for 43.3% of the lesions. The rest of the lesions presented with either weak hyper-signal (36.7%), or with iso-signal (16.7%). Only for 3.3% of the lesions a hypo-signal has been registered. These results are shown in figure 2.

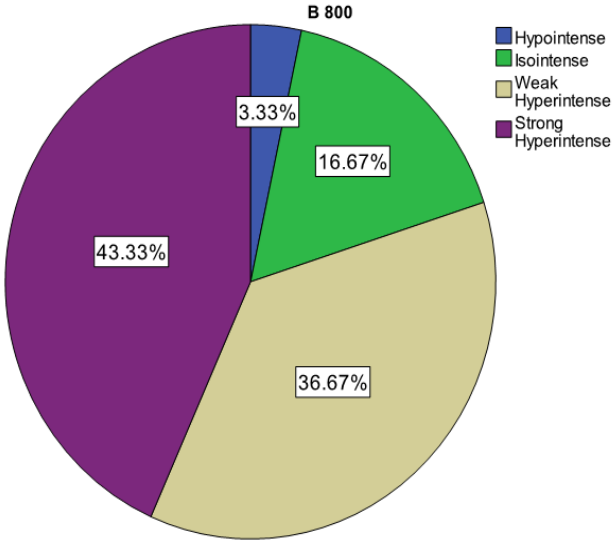

Figure 2. The distribution of HCC lesions according to their diffusion signal at b-800

Diffusion analysis on ADC map showed hypo-signal for an important majority of the assessed lesions (68%, i.e. 41 out of 60 lesions). A quarter of them (25%) presented iso-signal, whereas hyper-signal was shown only in 6.7% of the included sample. These results are shown in Table 1.

Table 1. The distribution of different types of signal on ADC map

ADC	Number	Percentage
Hypo-signal	41	68.3
Iso-signal	15	25
Hyper-signal	4	6.7
Total	60	100

Note that the pattern known as "restricted diffusion", representing hyper-signal on DWI b-800 sequence with hypo-signal on ADC map was present only in 34 lesions (56.6% of the sample).

Lesion vascularization analysis

From the assessed lesions, 86.7% of the lesions have shown hyper-enhancement in the arterial phase. From this group, 86% of the lesions presented the "wash-out" phenomenon. Thereby, the percentage of lesions presenting vascular behavior specific for HCC nodules (arterial hyper-vascularization followed by wash-out in the portal/late phase) was of 77.6%.

The lesions distribution based on their behavior during vascular phases is shown in figure 3.

Among the 8 lesions that have not presented wash-out but only arterial hyper-vascularization on MR contrast-enhanced examination, 6 (75%) have presented with hyper-signal on T2 sequence and all of them were in hypo-signal on the ADC map.

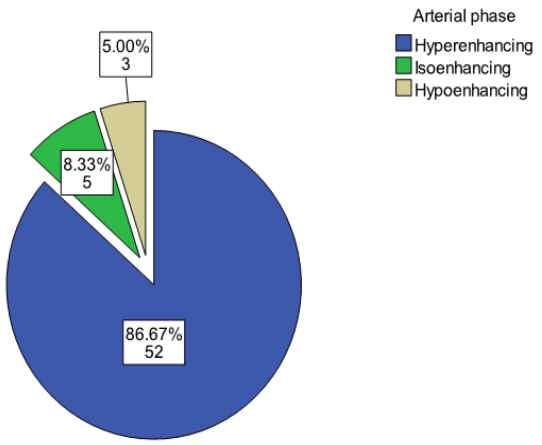

Figure 3. Behavior of HCC nodules after contrast material injection, in the arterial phase of the MR examination

From all the lesions taken into account, 9 had the size of early HCC (<2cm). Out of them, 8 have met the HCC vascular criterion. A number of 7 out of 9 (77.7%) lesions have presented hypo-signal on the ADC map and 8 out of 9 (88.8%) showed hyper-signal on T2-weighted images.

Discussion

HCC is a focal liver lesion easy to be diagnosed in its classical aspect of a hyperenhancing lesion in arterial phase followed by washing in venous phase. However, there are some practical limitations regarding the use of this vascular criterion. HCCs of small dimensions or those well differentiated may not present arterial hyper-enhancement due to the fact that the arterial vessels of neo-formation are not yet developed (Willatt et al 2008). On the other hand, more than half of the hypervascular areas not presenting portal or late wash-out are benign lesions, dysplastic nodules or areas of transitory arterial hyper-vascularization (Shimizu et al 2003; Freeman et al 2006).

In case of nodules smaller than 2 cm, there is a study proving that the application of the vascular criterion alone leads to a diagnostic specificity of 100% but with a low sensitivity of 30%. The results of strictly applying this criterion would be either an increase of the number of hepatic punctures, or missing many HCC nodules (Forner et al 2008).

The present study demonstrated a global sensitivity of 77.6% for the application of the vascular criterion. Applying only this criterion, as recommended by EASL (European Association for the Study of the Liver) and AASLD (American Association for the Study of Liver Diseases) guidelines, leads to a large number of hepatic punctures (McEvoy et al 2013).

On the T2 sequence, the lesions have variable aspect, generally showing moderate hyper-signal as compared to the surrounding hepatic parenchyma. The signal intensity on T2 sequence depends on the lesions' content in iron, copper, glycogen, proteins and fats (Itoh et al 1987). There are studies proving that hyperintensity on the T2 weighted images could accurately differentiate HCC from dysplastic nodules or areas of transitory arterial vascularization (isointense lesions with the hepatic parenchyma)

(Arif-Tiwari et al 2014). About 77% of the lesions considered in the present study presented signal hyper-intensity on the T2 weighted images (almost the same percentage with the lesions which met the vascular criterion). The analysis applied only on the lesions presenting arterial hyperenhancement, without wash-out on portal/late phase, proved that 7 out of 9 lesions present hyperintensity on the T2 weighted images. Thereby, if for the lesions not presenting with wash-out, we would consider the arterial hyper-vascularization associated to the hyper-intensity on the T2-weighted images as a diagnostic criterion of HCC, the sensitivity of the method will be much increased.

The interpretation of the DWI sequence is difficult in cases of a cirrhotic liver because the cirrhosis generates a global restriction of the hepatic diffusion (Vossen et al 2008, Goshima et al 2008). This difficulty would lead, according to the study realized by Taouli et al to a small sensitivity of about 43% in case of small lesions (1-2 cm). The presence of hyper-intensity on the DWI sequence with high b values does not help to differentiate the HCC nodules from benign hepatic lesions. Conversely, hypo-intensity compared to the surrounding liver on the ADC map could be considered a reliable indicator of malignity (when this aspect is found in a cirrhotic liver it shows, with a great probability, the presence of a HCC lesion) (Taouli et al 2003; Caraiani et al 2015).

In the present study, all the arterial hyper-enhancing nodules that didn't present subsequent wash-out in the portal or late phases were hypo-intense on the ADC map. Therefore, hypo-intensity on the ADC map could represent a useful diagnosis criterion for those patients with lesions showing only arterial hyper-enhancement, without wash-out in the portal/late phase. A percentage of 88.8% of the small sized nodules included in this study followed the vascular criterion. This value contradicts the literature data that cites values between 30 and 61% for the sensibility of vascular criteria used in the diagnosis of small HCC nodules (Bolondi et al 2005; Yoon et al 2009). The differences between the values registered by us and those in the literature are due to the inclusion criteria in the present study. Our study has been retrospective and, apart from the lesions having a histological confirmation (obtained by puncture-biopsy or intra-operatively) it included only lesions with typical imaging aspect considered by two experienced radiologists in consensus. This typical aspect consisted, in general, in meeting the vascular criterion. Thus, many HCC nodules, especially those of small size, including the ones not satisfying the vascular criterion and those without a histological diagnosis, were excluded from the present sample.

Conclusion

The vascular criterion, considered in the literature as being a criterion with very good specificity for HCC diagnosis, has, in return, a rather reduced sensitivity, thus being often necessary extra diagnosis work load, consisting in a puncture. The hyper-intensity on the T2 weighted sequences and the hypo-intensity on the ADC map could represent auxiliary diagnosis criteria which, associated with the arterial hyper-enhancement, could improve the sensitivity of the MRI HCC diagnosis.

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