Nodule-in-Nodule Imaging Pattern in Hepatocellular Carcinoma Treated by Transarterial Chemoembolization – a Multiparametric Magnetic Resonance Imaging Study

Andreea E. Scheau¹, Cristian Scheau², Ioana G. Lupescu¹,²

ABSTRACT

Background & Aims: Emerging minimally invasive treatments for hepatocellular carcinoma (HCC) can significantly improve a patient's prognosis, but they may alter the imaging features of the treated nodules. This study focuses on a series of patients presenting with a rare pathology, the nodule-in-nodule imaging pattern of HCC, analyzes the imaging features and discusses possible approaches for the diagnosis of tumoral recurrence.

Method: Nine patients recruited over two years, having HCC with nodule-in-nodule imaging pattern on diagnosis, and treated by transarterial chemoembolization were monitored by magnetic resonance imaging (MRI). Nodule morphology, dynamic contrast behavior and size progression were followed in this study.

Results: All patients showed tumor recurrence. In 7 nodules, a T2 weighted-imaging hyperintense signal of the HCC foci was found, with isointensity of the background nodule. Restricted diffusion within the HCC foci was found in 6 cases but with no statistical significance. Dynamic contrast images evaluation showed a “classical” enhancement pattern in five patients. All nodules had hypointense HCC foci in the hepatobiliary phase. Four patients demonstrated progressive disease according to the mRECIST criteria.

Conclusions: Due to the particularly challenging nodule characteristics, the sensitivity in diagnosing HCC foci in these nodules is about 77% when using conventional imaging criteria related to nodule morphology. Contrast media uptake curves may be altered by changes in nodule hemodynamics caused by embolization. The diagnostic rate may be significantly increased by considering the tumoral size increase in follow-up studies and completing the study with a hepatobiliary phase using Acidum Gadoxeticum.

Key words: Nodule-in-nodule – transarterial chemoembolization – hepatocellular carcinoma – magnetic resonance imaging – image analysis – Acidum Gadoxeticum.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer worldwide, and the leading cause of death in patients with liver cirrhosis [1]. The most recent practice guidelines state that histological evidence is no longer necessary to confirm a HCC if the tumor is larger than 10 mm and shows typical imaging features on contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI)[2].

Transarterial chemoembolization (TACE) is the preferred method for treating intermediate stage HCC [3, 4], being widely used [5]. There is continued interest for its various procedures and chemotherapeutic agents used despite potential risks and complications [6]. After the successful occlusion of the arterial blood flow of the malignant nodule, the portal blood regurgitation into the adjacent sinusoid vessels may favor tumor remnants, thus reducing the efficacy of TACE [7, 8].

A relatively rare imaging pattern found in patients with TACE for HCC developed on a cirrhotic liver is the “nodule-in-nodule” appearance, which has an incidence of about 6%
in untreated patients [9]. This refers to HCC foci in a highly dysplastic nodule, and holds particular importance, since for a correct depiction one must surpass several diagnostic pitfalls. Furthermore, the availability of morphological and functional modalities for MRI, as well as hepatocyte-specific contrast media, allows a highly accurate diagnosis based on clear imaging criteria [10].

The goals of this paper are to describe the MRI profiles of patients treated with TACE for an HCC with "nodule-in-nodule" imaging features, and to identify the potential obstacles in the correct diagnosis of tumor recurrence.

**PATIENTS AND METHODS**

Nine patients (M/F: 4/5, aged 55 to 74 years old, mean age 64 years) with HCC on a cirrhotic liver treated with TACE recruited between January 2014 and December 2016 are evaluated in this study. Their baseline imaging scan, CT or MRI showed a “nodule-in-nodule” pattern. These patients underwent contrast enhanced MRI at four weeks after the embolization, as part of their follow-up management protocol. None of the patients were candidates for other minimally invasive procedures such as radiofrequency ablation or microwave ablation due to the presence of multinodular or intermediate stage HCC, which directs the treatment towards TACE, exclusively [11].

The follow-up MRI at four weeks used a Toshiba Vantage Titan 1.5 Tesla MRI platform with a dedicated Workstation. The protocol is shown in Table I. Dynamic contrast media administration was performed using Acudem Gadoxeteticum 0.1 ml/kg in five steps: unenhanced phase, arterial phase (30 seconds delay after the start of contrast media injection), portal venous phase (70 seconds delay), late (transitional) phase (180 seconds delay) and hepatobiliary phase (20 minutes delay), followed by a 20 ml serum bolus, both with a perfusion rate of 1 ml/second.

The images for all the 9 patients were evaluated using the dedicated certified imaging software Osirix 8.0.2 MD 64bit. The measurement of the signal intensity in the background nodule and in the HCC foci was performed using an elliptical region of interest (ROI) in the most homogeneous zone, with the largest possible area between 0.1 and 1 cm² according to the lesion size.

Arterial flash was defined as a vivid early arterial enhancement of the lesion compared to the remainder of the liver, while contrast wash-out as an early hypointensity of the lesion compared to the rest of the liver parenchyma [12]. Diffusion restriction is defined as an objective hyperintensity of the lesion in all b-values, including the highest, with corresponding hypointensity on the ADC map [13].

The nodule volume was estimated using the following formula for determining an ellipsoid volume based on three diameters: V = length * width * height * π/6.

Statistical data was analyzed using IBM SPSS Statistics 21 Premium x64bit. The data was tested for normality using Shapiro-Wilk Normality Test, and all data groups seemed normal for thresholds of p between 0.01 and 0.10 with accepted null hypothesis [14]. Chi-square test and Fisher’s exact test were used for testing contingency tables, the latter being used when the minimum value in a cell was zero. Mann-Whitney’s test for independent samples was used to determine if sets of data between sub-lots demonstrate significant differences. Due to the small sample size, Spearman’s correlation coefficient was chosen in favor of Pearson’s to test correlations between continuous variables.

All the patients enrolled in this study signed a written informed consent, and the study was approved by the local Ethics Committee.

**RESULTS**

The 9 patients included in the study presented background nodules with an average size of 41.1 ± 11.1 mm in the largest diameter, and an estimated volume of 27.4 ± 19.14 cc. The HCC foci measured in average 14.7 ± 3.16 mm and had a mean volume of 1.29 ± 0.95 cc.

Size comparison in the HCC foci between the baseline examination and the post-procedural MRI investigation was performed. The results were expressed in percentages of size increment (Table II). Four patients demonstrated progressive disease according to the mRECIST criteria [15].

### Table I. Parameters of the imaging protocol used in this study.

<table>
<thead>
<tr>
<th>Series no</th>
<th>Sequence name</th>
<th>Imaging plane</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Slice thickness (mm)</th>
<th>Gap (mm)</th>
<th>Voxel size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T1 IN-OPP PHASE</td>
<td>Transverse</td>
<td>133</td>
<td>2.38/4.76</td>
<td>4.0</td>
<td>0.8</td>
<td>0.8x0.8x4.0</td>
</tr>
<tr>
<td>2</td>
<td>T2 HASTE LONG TE</td>
<td>Coronal</td>
<td>3300</td>
<td>383</td>
<td>6.0</td>
<td>1.2</td>
<td>1.2x1.2x6.0</td>
</tr>
<tr>
<td>3</td>
<td>T2 HASTE SHORT TE</td>
<td>Coronal</td>
<td>1200</td>
<td>90</td>
<td>4.0</td>
<td>1.2</td>
<td>1.6x1.6x4.0</td>
</tr>
<tr>
<td>4</td>
<td>T2 TSE DIXON</td>
<td>Transverse</td>
<td>2000</td>
<td>90</td>
<td>6.0</td>
<td>1.2</td>
<td>1.3x1.3x6.0</td>
</tr>
<tr>
<td>5</td>
<td>T2 TSE</td>
<td>Transverse</td>
<td>2500</td>
<td>120</td>
<td>5.0</td>
<td>1.5</td>
<td>1.3x1.3x5.0</td>
</tr>
<tr>
<td>6</td>
<td>DWI (b=50,400,800)</td>
<td>Transverse</td>
<td>2000</td>
<td>56</td>
<td>5.0</td>
<td>1.5</td>
<td>1.5x1.5x5.0</td>
</tr>
<tr>
<td>7</td>
<td>GRADIENT ECHO (FA=12)</td>
<td>Transverse</td>
<td>250</td>
<td>12</td>
<td>6.0</td>
<td>1.8</td>
<td>0.8x0.8x6.0</td>
</tr>
<tr>
<td>8</td>
<td>DYNAMIC T1 FATSAT</td>
<td>Transverse</td>
<td>4.44</td>
<td>2.16</td>
<td>3.0</td>
<td>0.6</td>
<td>1.3x1.3x3.0</td>
</tr>
<tr>
<td>9</td>
<td>LATE ENHANCEMENT T1 FATSAT</td>
<td>Transverse</td>
<td>4.44</td>
<td>2.16</td>
<td>3.0</td>
<td>0.6</td>
<td>1.3x1.3x3.0</td>
</tr>
<tr>
<td>10</td>
<td>LATE ENHANCEMENT T1 FATSAT</td>
<td>Coronal</td>
<td>6.63</td>
<td>2.39</td>
<td>1.6</td>
<td>0.3</td>
<td>1.6x1.6x1.6</td>
</tr>
<tr>
<td>11</td>
<td>T1 FATSAT (FA=30)</td>
<td>Transverse</td>
<td>4.69</td>
<td>2.21</td>
<td>3.0</td>
<td>0.6</td>
<td>1.3x1.3x3.0</td>
</tr>
</tbody>
</table>

**TR:** time of repetition; **TE:** time of echo; **IN-OPP:** in-phase and out-of-phase; **TSE:** turbo spin echo; **FA:** flip angle; **FATSAT:** fat saturation.
Analyzing the nodule morphology in T2 WI, 7 out of the 9 nodules demonstrated a hyperintense signal of the HCC foci with an isointense aspect of the background nodule. Out of these 7, 6 demonstrated restricted diffusion within the HCC foci, with variable ADC values. No nodules showed hypointensity in T2 WI within the HCC foci.

Regarding the T1 WI signal in the HCC foci, 2 nodules showed isointensity in the unenhanced series. Restricted diffusion within the HCC foci was found in 6 cases, with ADC map values between 901 and 1632 *10^-3 mm^2/s (averaging 1280 ± 247 *10^-3 mm^2/s). The tumor nodules without restricted diffusion held ADC values between 1374 and 1783 *10^-3 mm^2/s (averaging 1579 ± 204 *10^-3 mm^2/s). There was no statistically significant difference between the two lots when compared with independent sample testing (p=0.1667). However, the presence of diffusion restriction marginally correlated positively with T2 hyperintensity in the HCC foci (p = 0.083).

Dynamic contrast images evaluation showed a “classical” pattern of enhancement in the arterial phase with subsequent wash-out in the late phase in 5 out of 9 patients. The other 4 showed either no contrast wash-out, or continual enhancement in the late phase. All nodules imaged in this study had hypointense HCC foci in the biliary phase.

No statistically significant correlation was found between the tumor nodule size and the degree of contrast enhancement (rho=0.0167, p=0.9661).

The overall patients’ characteristics and imaging findings are summarized in Table II.

**DISCUSSION**

A typical morphological imaging profile of a HCC nodule in the cirrhotic liver consists of hypointensity in T1 WI, hyperintensity in T2 WI, and restricted diffusion with ADC values ranging between 0.7 * 10^-3 mm^2/s and 1.3 * 10^-3 mm^2/s [16, 17]. The dynamic contrast profile of this type of tumor nodule demonstrates an intense contrast enhancement in the arterial phase, the so-called “arterial flash” with a decrease of signal intensity in the portal phase (tumoral “wash-out”) [18]. HCC nodules are commonly hypointense in the hepatobiliary phase [10, 19]. Using hepatocyte-specific contrast media, especially Acidum Gadoxeticum (Fig. 1), augments these findings and facilitates nodule detection [20].

### Table II. Imaging findings of the patients in the study at four weeks after TACE

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, gender/Cirrhosis etiology</th>
<th>Nodule-in-nodule area of interest</th>
<th>3-axis sizes (mm)</th>
<th>Volume (cc)</th>
<th>Size increase from baseline (mRECIST criteria)</th>
<th>Morphology</th>
<th>Dynamic contrast</th>
<th>Hepatobiliary phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60, female Background nodule</td>
<td>Background nodule</td>
<td>52</td>
<td>31</td>
<td>35</td>
<td>29.53</td>
<td>Hyper</td>
<td>Iso</td>
</tr>
<tr>
<td>2</td>
<td>65, female HVC</td>
<td>HCC foci</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>0.70</td>
<td>Iso</td>
<td>Iso</td>
</tr>
<tr>
<td>3</td>
<td>72, female HVC</td>
<td>Background nodule</td>
<td>56</td>
<td>37</td>
<td>64</td>
<td>69.40</td>
<td>Hyper</td>
<td>Hyper</td>
</tr>
<tr>
<td>4</td>
<td>58, male HVC</td>
<td>Background nodule</td>
<td>23</td>
<td>18</td>
<td>18</td>
<td>3.90</td>
<td>Hyper</td>
<td>Hyper</td>
</tr>
<tr>
<td>5</td>
<td>74, female HVB+D</td>
<td>HCC foci</td>
<td>14</td>
<td>9</td>
<td>11</td>
<td>0.73</td>
<td>Hyper</td>
<td>Hyper</td>
</tr>
<tr>
<td>6</td>
<td>65, male HVC</td>
<td>Background nodule</td>
<td>17</td>
<td>14</td>
<td>13</td>
<td>1.62</td>
<td>Hypo</td>
<td>Iso</td>
</tr>
<tr>
<td>7</td>
<td>55, male HVB+D</td>
<td>Background nodule</td>
<td>13</td>
<td>11</td>
<td>9</td>
<td>0.67</td>
<td>Hypo</td>
<td>Hyper</td>
</tr>
<tr>
<td>8</td>
<td>66, male HVC</td>
<td>Background nodule</td>
<td>42</td>
<td>40</td>
<td>37</td>
<td>32.53</td>
<td>Hyper</td>
<td>Iso</td>
</tr>
<tr>
<td>9</td>
<td>65, female HBV</td>
<td>Background nodule</td>
<td>16</td>
<td>12</td>
<td>13</td>
<td>1.31</td>
<td>Hypo</td>
<td>Hyper</td>
</tr>
</tbody>
</table>

However, these “classical” imaging findings of a HCC nodule may be substantially altered in patients previously submitted to TACE, due to several factors such as the alteration of the blood flow to- and possibly from the nodule, and the appearance of granulation tissue around the nodule [21]. Even more confounding variables may appear when imaging nodule-in-nodule patterns after TACE treated HCC foci (Fig. 2). Few literature data is available regarding the best diagnostic approach in these cases [22].

The nodule-in-nodule architecture is represented by a background nodule, which is usually highly dysplastic but better-differentiated, and a smaller inner-nodule, consisting of small HCC foci with less fat and iron, and poor tumoral cell differentiation [23].

The background nodule appears hyperintense in T1 WI, hypointense in T2 WI, with slight or moderate arterial enhancement, while the inner-nodule shows typical imaging features of a HCC nodule [24].
In our study, we recruited all patients with nodule-in-nodule imaging patterns on their baseline diagnostic scan. These patients were submitted to an MRI examination one month after the TACE procedure. Since no other diagnostic modality such as surgery or biopsy is indicated in these patients, dynamic contrast MRI holds the best sensitivity and specificity in this situation [2, 25]. All patients demonstrated progressive disease at four weeks after the procedure, albeit with various imaging patterns.

The image analysis of the selected patients demonstrated heterogeneous morphological and dynamic contrast patterns. Only 7 out of 9 patients showed T2 WI hyperintensity in the HCC foci, and among them, 6 demonstrated restricted diffusion. The other patient, with no restricted diffusion in the HCC foci, also presented an atypical contrast enhancement pattern, with just moderate and persistent contrast uptake, and without wash-out. In this case (patient 2), the diagnosis of tumor recurrence was made on a size increase of 23% from the baseline, which signified progressive disease according to mRECIST criteria [15]. The absence of diffusion restriction in the HCC foci in our case may be caused by respiration or magnetic susceptibility artifacts [26]. The two patients without T2 WI hyperintensity in the HCC foci demonstrated either a tumor viable tissue size increase (27% in patient 1) or typical arterial flash and portal washout in patient 4, diagnostic criteria for tumor recurrence in both patients.

The signal intensity in T2 WI correlates with the presence of restricted diffusion, and the marginal statistical significance most likely originates from the reduced number of cases and aforementioned artifacts, which may corrupt statistical interpretation. Higher p values in this case predispose the interpreter to a Type I error, since diffusion sequences use a T2 WI mask and new study models demonstrate the interconnectivity between the two sequence types [27].

T1 WI isointensity within the HCC foci was found in two cases, presumably due to liquefaction necrosis material [28] and partial signal summation of HCC foci and the background nodule due to the former's small size (largest diameter of 11 and 12 mm, respectively) and the latter's overall T1 hyperintensity.

The dynamic contrast analysis with hepatocyte-specific media demonstrated a typical pattern (arterial "flash" and portal "wash-out") in 5 cases (Fig. 3). Within the 4 remaining patients, the contrast intensity in the portal phase was similar to the arterial phase in 2 nodules and more intense in the other 2. In these situations, the presence of pseudolesions after TACE with the abnormally inner-nodule signal might have corresponded to granulation tissue. Nevertheless, the follow-up exam showed tumor viable tissue in all cases, albeit the atypical imaging features (Fig. 4). The shape of the contrast-enhanced lesion also holds an important significance when trying to rule out a pseudolesion. Previous studies have demonstrated that a nodular shape is more likely to harbor malignant tissue, when compared with crescent or rim enhancing lesions [29]. We assumed that the placement of the HCC foci inside a larger, predominantly hypovascular nodule, altered the arterial blood flow towards the residual tumor tissue, causing this atypical contrast uptake profile. Also, the average diameter of 14.7 mm of the HCC foci favors atypical imaging features [30].

In our patients we found no correlation between contrast enhancement measured in percentages over the unenhanced phase signal, and the HCC foci size or morphological appearance.

The correct detection of tumor recurrence in the selected patients using only the morphological criteria would be achieved in 7 out of 9 cases, and by using dynamic contrast analysis alone, it would be achieved in just 5 cases. These findings would be alarming when compared to the diagnostic efficiency of MRI for untreated HCC nodules in the cirrhotic liver, or even for TACE treated HCC nodules [31]. But when dealing with nodule-in-nodule baseline architecture with overlapped TACE treatment, more parameters that might influence the imaging aspects should be considered. For instance, the overall

Fig. 3. Nodule-in-nodule imaging pattern after TACE. Certain HCC foci within the larger background nodule, with typical tumoral features: T1 hypointensity/T2 hyperintensity, arterial flash with portal wash-out and late hypointensity, and demonstrating restricted diffusion. Arrow – background nodule, * – HCC foci; T1 FatSat images in unenhanced (a), arterial phase (b), portal venous phase (c), hepatobiliary phase (d); T2 FatSat images (e); DWI images (f) with ADC map correlation (g).
T1 WI hyperintensity of the background nodule, combined with the potential T1 hyperintensity of post interventional necrosis may obscure the arterial flash of the HCC foci, and may also impede the interpretation of tumor wash-out in the portal phase [32]. Another factor is the frequent appearance of pseudolesions, which mimic HCC foci; distinguishing the two is often challenging, and sometimes impossible by imaging alone.

When combining the diagnostic value of morphological and dynamic contrast images, the correct diagnosis of viable tumor tissue was set in 8 out of 9 cases. Adding the size evolution criteria, all patients were diagnosed with tumor viable tissue (100% sensitivity). When using the hepatobiliary phase as a criterion for the presence of HCC, all patients demonstrated marked hypointensity in the inner-nodule at 20 minutes after Acidum Gadoxeticum administration. Literature data demonstrates high sensitivity and specificity for the MRI hepatobiliary phase in detecting malignant hepatic lesions [19, 33]. In our study, the specificity could not be determined due to the lack of a control group.

Alongside morphological and functional MRI markers for the tumor detection, a correct and thorough patient follow-up protocol is essential in the early detection of tumor recurrence. The sequential follow-up imaging protocol may be the only criterion for tumor viable tissue depiction, as demonstrated in this study, when other imaging features may be inconspicuous or confusing. The relative controversy for the best timing and choice of imaging modality in the follow-up protocols should be surpassed by relying on the centers’ experience in practice and by a multidisciplinary approach in oncology boards [34, 35].

The study limits are the relatively low number of patients included for this particularly rare sub-type imaging pattern, and the lack of a gold standard test with absolute sensitivity and specificity to validate the MRI findings.

CONCLUSION

The nodule-in-nodule architecture of HCC treated by TACE may demonstrate atypical morphological and functional features of MRI for residual HCC foci. There was an expected correlation between T2 WI hyperintensity and restricted diffusion within the HCC foci.

The diagnostic accuracy for HCC recurrence in TACE-treated patients with nodule-in-nodule baseline imaging patterns was increased when combining T1 WI, T2 WI, DWI and dynamic contrast modalities. The diagnostic yield improved when adding the tumor size increase in follow-up studies, and was maximal when the hepatobiliary phase with Acidum Gadoxeticum was considered.

Conflicts of interest: None to declare. Funding: No financial support was received for this study.

Authors’ contribution: A.E.S.: study concept and design, data acquisition and interpretation; A.E.S. and C.S.: manuscript writing; C.S.: statistical analysis; I.G.L.: study supervision and coordination, critical revision of the manuscript for important intellectual content before submission. All authors approved the final version of the manuscript.

REFERENCES


