Intermediate and advanced hepatocellular carcinoma treated with the antiangiogenic agent sorafenib. Evaluation with unenhanced and contrast-enhanced ultrasonography

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Abstract

Aims: To evaluate the sonographic changes observed in hepatocellular carcinoma (HCC) post antiangiogenic treatment with sorafenib. Patients and methods: Twenty one intermediate or advanced HCC patients (19 men, 2 women; mean age: 66.8 years; 32 target tumors-TTs) received sorafenib as monotherapy and were studied with unenhanced ultrasonography (US) and contrast-enhanced ultrasonography (CEUS) with a second generation echo-enhancer (SonoVue) at bimonthly intervals. Changes in lesional size, echotexture and enhancement were evaluated. Response was classified according to RECIST (Response Evaluation Criteria In Solid Tumors) and modified (m) RECIST. Results: Cystic changes were detected on US in 4 patients (7 lesions); CEUS showed a significant (51-100%) decrease of viable, enhancing TTs in the aforementioned patients. Four additional patients (5 lesions) showed a 73-87% decrease of their viable TTs on CEUS, but no changes on US. 13/21 patients showed less than 30% decrease, no change, or increase of their viable TTs. Based on the last sonographic evaluation, response was as follows: RECIST- Complete Response, CR (n=0), Partial Response, PR (n=1), Stable Disease, SD (n=16), Progressive Disease, PD (n=4); mRECIST- CR (n=2), PR (n=6), SD (n=11), PD (n=2). The 8 responders (CR+PR) according to mRECIST had significantly longer mean overall survival (OS) compared to the 13 non-responders (21.5 vs 12.2 months, p=0.018, Kaplan-Meier method). However, statistical significance was reduced (p=0.065) after adjustment for BCLC and Child’s class. Conclusion: US may occasionally detect changes indicative of the effect of sorafenib on HCC, but CEUS is required to evaluate and grade post-therapeutic reduction of tumoral enhancement. The latter is likely to correlate with OS. Keywords: ultrasonography, contrast-enhanced ultrasonography, hepatocellular carcinoma, antiangiogenic treatment, sorafenib

Introduction

Sorafenib is an oral multikinase inhibitor which has been shown to inhibit angiogenesis, reduce tumor-cell proliferation and increase time to radiologic progression and overall survival in patients with advanced hepatocellular carcinoma (HCC) [1]. For patients with less advanced disease, the benefits of the combination of sorafenib with transarterial chemoembolization (TACE) are also under evaluation [2].

Radiologic imaging modalities have been applied for the follow-up of HCC-patients treated with sorafenib, in order to monitor the effect of this agent and to identify early non-responders, who are not likely to benefit from this treatment. Dynamic (contrast-enhanced) imaging with computed tomography (CT), magnetic resonance (MR) or ultrasonography (US) has been used for this pur-
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pose, the common criterion of response being a reduction (or rarely elimination) of tumor enhancement [3,4]. In particular, contrast-enhanced ultrasound (CEUS) has emerged as a versatile modality for monitoring antiangiogenic treatments of HCC; CEUS has been proven effective to detect early and to quantify post therapeutic changes in tumor perfusion [5-7]. On the other hand, many of the relevant studies are experimental [5,6], while clinical experience on this topic can still be considered as limited.

This study summarizes our initial experience with the clinical application of CEUS for the evaluation of a small series of HCC-patients treated with sorafenib. Gray-scale (unenhanced) sonographic changes associated with the therapeutic effect of sorafenib are also highlighted. Clearly, unenhanced US cannot depict tumor perfusion; however, it would be worth recognizing gray-scale sonographic patterns associated with tumor necrosis; these patterns, along with the respective CEUS findings, could serve as surrogate markers of tumor response.

Materials and methods

Patients and lesions

Twenty one patients (19 men; 2 women; mean age: 66.8; range: 53–81 years) with prior diagnosis of intermediate or advanced HCC were included in this prospective study. Demographic and clinical data of the study population are provided in table I.

Nine patients presented with solitary tumors. One of those lesions infiltrated diffusely the entire left lobe in one patient. The rest solitary tumors were encapsulated hepatomas. Twelve patients suffered from multifocal neoplastic involvement. In 4 of those patients, a dominant tumor could be detected, with a diameter at least 2 ½ times larger than the diameter of the daughter lesions, and this dominant tumor served as index lesion. In the rest of the patients with multifocal involvement, 2 or 3 lesions per patient were selected as index lesions, according to the following criteria: diameter >1 cm, baseline necrosis ≤ 70%, well defined borders and relatively superficial location, in order to facilitate sonographic imaging. A total of 32 index lesions were studied.

Sorafenib administration and prior treatments

Patients of this study were treated with sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals) per os, as a monotherapy. The standard dose of the drug was 400 mg (consisting of two 200 mg tablets) twice daily. Dose reductions (up to a total daily dose of 400mg) were permitted, if drug-related adverse effects were encountered. Treatment interruptions were also permitted, provided they lasted no more than 3 weeks. At the beginning of treatment, a dose escalation scheme was applied, by initiating sorafenib administration with 200 mg daily and by subsequently increasing the dose by 200 mg every 3 days, up to the standard dose.

In this study 8/21 subjects had undergone one or more sessions of trans arterial chemoembolization (TACE) with a protocol identical to that described in previous work [8]. The last session of TACE had been performed 3 or more months prior to initiation of sorafenib. Discontinuation of chemoembolizations was caused by: development of absolute contraindication to TACE (n=4), poor response to TACE (n=2) technical failure of TACE (n=1), patient’s refusal (n=1).

Sonographic imaging

Gray-scale (unenhanced) US of the liver was performed prior to CEUS, in order to identify target lesions, assess their size (longest diameter), and to evaluate the shape, borders and echotexture. Representative images of the lesions were stored in the hard disk of the ultrasonographic unit.

For CEUS, 4.8 ml of a second generation ultrasound contrast agent (microbubbles of sulphur hexafluoride, SonoVue, Bracco, Milan Italy) were injected as a bolus in a forearm vein, followed by a flush of 10 ml of normal saline. A dedicated, contrast specific, continuous scanning, low acoustic power technique was utilized (Mechanical Index = 0.08-0.09). Imaging parameters were individually adjusted to suppress background echoes and to optimize detection of the circulating microbubbles. The first step of the CEUS study included at least one complete sweep through the index tumor(s), when the contrast between the viable (enhancing) and necrotic (non-enhancing) parts of the tumor was greatest. This occurred in the arterial phase; however the portal phase was also evaluated, since the majority of the studied tumors exhibited delayed wash-out. In tumors with mul-

Table I. Demographic and clinical data of the patients of this study

<table>
<thead>
<tr>
<th>Age (yrs) mean+/−SD</th>
<th>66.8 ±8.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>19/2</td>
</tr>
<tr>
<td>Cirrhotic background</td>
<td>21</td>
</tr>
<tr>
<td>HBV</td>
<td>14</td>
</tr>
<tr>
<td>HCV</td>
<td>4</td>
</tr>
<tr>
<td>Alcohol</td>
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</tr>
<tr>
<td>HBV+Alcohol</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Child’s classification (A/B)</td>
<td>10/11</td>
</tr>
<tr>
<td>BCLC stage (B/C)</td>
<td>9/12</td>
</tr>
<tr>
<td>Tumor distribution (solitary/multifocal)</td>
<td>9/12</td>
</tr>
</tbody>
</table>
tiple and irregular necrotic areas, a special effort was made to locate and clearly depict the largest intratumoral viable component. As a second step, non-target lesions and the rest of the liver were scanned. The CEUS examination and the unenhanced US images were transferred and stored as digital archives in a personal computer for analysis.

Unenhanced US and CEUS was performed with a Philips HD11 XE (Philips Ultrasound, Andover, MA, USA) ultrasonographic unit. A convex, 2.5-5 MHz probe was used. The sonographic studies were transferred by 2 consultant radiologists (HM, MGP), experienced in both abdominal sonography and in CEUS.

A baseline examination was performed 1-5 days prior to the initiation of antiangiogenetic treatment; follow-up studies were performed approximately every 2 months (range: 7-10 weeks) after the first dose of the drug. At least 2 follow-up studies were performed in each patient. Follow-up period ranged from 4-24 months (mean: 12.1 months). All patients provided written informed consent prior to the beginning of the treatment. The study was approved by the institutional review board of our hospital.

Analysis of sonographic findings and evaluation of response

The aforementioned radiologists reviewed and compared in consensus the static images and the video acquisitions of each study. For the purposes of this study, assessment of tumor response was based on the results of the first (2 months) and of the last sonographic evaluation. Two systems were used to categorize tumor response: a) RECIST (Response Evaluation Criteria In Solid Tumors) [9], which relies exclusively on changes in tumor size to classify response, as follows: Complete Response (CR)-disappearance of all target lesions; Partial Response (PR)-at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; Progressive Disease (PD)-at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started, or appearance of new lesions; SD-all other cases.

Patients with CR or PR were classified as responders, while patients with SD or PD were non-responders. Differences in overall survival (OS) between responders and non-responders were evaluated. OS was defined as the time between the first day of treatment and the date of patient’s death, or the date at which the patient was last known to be alive.

Other imaging modalities

There was no standard protocol regarding the other imaging modalities that were applied for treatment monitoring. MR (performed every 2-3 months) was used as the primary imaging modality for the majority (18/21) of the patients. MR was performed with various types of scanners at 1.5 Tesla or 3 Tesla and included axial and coronal T1-weighted images, T2-weighted images, and dynamic, gadolinium-enhanced T1 sequences. CT was used in 3/21 patients, performed either on a 64-slice multi-detector scanner or on a single-slice helical CT scanner during a single breath-hold helical acquisition. CT studies included unenhanced and at least 2 enhanced (arterial and portal venous) phases. A detailed comparison between sonography and the other modalities in terms of diagnostic efficacy was not included in the aims of this study. However, an attempt was made to correlate changes in tumors’ echogenicity with changes in tumors’ signal intensity on MR.

Data analysis

Survival data were analyzed by using the Kaplan-Meier method with the log-rank test. To take into account confounders, cox regression was performed. The kappa test was used to evaluate the degree of concordance between RECIST and mRECIST. Statistical significance was defined as a p value of <0.05. Statistical analysis was performed with SPSS 19.0 (233 South Walker Drive Chicago, IL).

Results

At baseline, the size of the target tumors (longest diameter or sum of longest diameters) ranged from 27 to 156 mm (mean 75.1+/−36.8 mm). At the last follow up, the size of the target tumors ranged from 25 to 159 mm (mean 75.2+/−37.6mm). Tumor shrinkage was observed in 8 patients, with a reduction in the longest tumor diameter ranging from 1-50%. In 4/8 patients, the diameter reduction exceeded 10%. Tumor enlargement was observed in 12 patients, with an increase in the longest tumor diameter ranging from 1-44.7%. In 5/12 patients the increase in the longest diameter exceeded 10%. A solitary tumor in one patient showed no size changes (table II, 2nd-3rd column).
In 4 patients, cystic changes appeared within the 7 index lesions during sorafenib treatment (fig 1, fig 2).

In 3/4 patients (6/7 lesions) total or subtotal cystic transformation of the previously solid tumors was observed. These lesions exhibited thin, smooth walls, posterior enhancement and anechoic, as well as amorphous echogenic contents. In the fourth patient (1/7 lesions) partial cystic transformation was observed. In all tumors with cystic changes, the respective CEUS studies revealed significant necrosis post treatment, expressed by a decrease in the longest diameters of the viable target tumors ranging from 52-100%. In 3 out of 4 patients, cystic changes (along with the respective reduction in enhancement) were evident by the time of the first evaluation while in the fourth patient, the changes were detected on the second evaluation. Cystic transformation was accompanied by the enlargement of target tumors in 3 patients and by progressive coalescence of the liquefied

Table II. Size and degree of necrosis of the index tumors prior to, and post treatment with associated response and survival

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Lesion diam. (mm)</th>
<th>Lesion diam change % (baseline-last evaluation)</th>
<th>Enhancing component diam. (mm)</th>
<th>Enhancing component diam. change % (baseline-last evaluation)</th>
<th>Changes visible on US(^c)</th>
<th>Response (RECIST)(^d)</th>
<th>Response (mRECIST)</th>
<th>Survival (months)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>142</td>
<td>12(+)(^a)</td>
<td>118</td>
<td>21(+)(^a)</td>
<td>no</td>
<td>SD</td>
<td>PD</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>13(+)</td>
<td>68</td>
<td>1(-)</td>
<td>no</td>
<td>SD</td>
<td>SD</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>1(-)</td>
<td>53</td>
<td>100(-)</td>
<td>yes</td>
<td>SD</td>
<td>CR</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>6(+)</td>
<td>31</td>
<td>6(+)</td>
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<td>SD</td>
<td>SD</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>156</td>
<td>50(-)</td>
<td>109</td>
<td>87(-)</td>
<td>no</td>
<td>PR</td>
<td>PR</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>44,7(+)</td>
<td>81</td>
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<td>PD</td>
<td>CR</td>
<td>16</td>
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<tr>
<td>7</td>
<td>50</td>
<td>10(-)</td>
<td>45</td>
<td>75(-)</td>
<td>no</td>
<td>SD</td>
<td>PR</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>2(-)</td>
<td>29</td>
<td>3(+)</td>
<td>no</td>
<td>SD</td>
<td>SD</td>
<td>12</td>
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<tr>
<td>9</td>
<td>27</td>
<td>7(-)</td>
<td>26</td>
<td>4(-)</td>
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<td>SD</td>
<td>SD</td>
<td>10</td>
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<tr>
<td>10</td>
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<td>0</td>
<td>35</td>
<td>14(-)</td>
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<td>SD</td>
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<td>5</td>
</tr>
<tr>
<td>11</td>
<td>29</td>
<td>3(+)</td>
<td>25</td>
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<td>no</td>
<td>SD</td>
<td>SD</td>
<td>9</td>
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<tr>
<td>12</td>
<td>113</td>
<td>37(+)</td>
<td>68</td>
<td>1(+)</td>
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<td>PD</td>
<td>SD</td>
<td>4</td>
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<tr>
<td>13</td>
<td>118</td>
<td>15,2(-)</td>
<td>85</td>
<td>79(-)</td>
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<td>SD</td>
<td>PR</td>
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<tr>
<td>14</td>
<td>93</td>
<td>1(+)</td>
<td>87</td>
<td>3(+)</td>
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<td>SD</td>
<td>SD</td>
<td>4</td>
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<tr>
<td>15</td>
<td>42</td>
<td>7(+)</td>
<td>42</td>
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<td>SD</td>
<td>SD</td>
<td>8</td>
</tr>
<tr>
<td>16</td>
<td>109</td>
<td>20,1(-)</td>
<td>70</td>
<td>73(-)</td>
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<td>SD</td>
<td>PR</td>
<td>17</td>
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<tr>
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<td>56</td>
<td>28(+),</td>
<td>52</td>
<td>52(-)</td>
<td>yes</td>
<td>PD</td>
<td>PR</td>
<td>22</td>
</tr>
<tr>
<td>18</td>
<td>87</td>
<td>2(+)</td>
<td>87</td>
<td>25(-)</td>
<td>no</td>
<td>SD</td>
<td>SD</td>
<td>18</td>
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<tr>
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<td>1,5(+),</td>
<td>57</td>
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<td>SD</td>
<td>SD</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td>64</td>
<td>9(-)</td>
<td>64</td>
<td>19(-)</td>
<td>no</td>
<td>PD</td>
<td>PD</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td>88</td>
<td>2(+),</td>
<td>88</td>
<td>61(-)</td>
<td>yes</td>
<td>SD</td>
<td>PR</td>
<td>10</td>
</tr>
</tbody>
</table>

a. (+): tumor enlargement, (-): tumor shrinkage according to RECIST guidelines [9]
b. (+): increase, (-): decrease in the sum of diameters of viable target lesions according to mRECIST guidelines [10]
c. “yes”: cystic changes were detectable on unenhanced US, “no”: no changes on unenhanced US with the exception of size changes
d. RECIST diagnosed PD in 4 patients. In 3 of them the diagnosis was based on lesional enlargement exceeding 20% (patients#6,12,17); however, 2 of those patients (patients 6 and 17) had cystic lesions with significant necrosis. In the fourth patient (patient#20) new lesions appeared during follow-up. This patient was also diagnosed as PD with mRECIST. The latter detected 1 more case of PD (patient #1) on the basis of a more than 20% increase of viable (enhancing) tumor tissue
lesions in one of those patients. All cases with cystic lesions were also studied with MR. The cystic component of all treated HCCs was characterized by high signal on T2 weighted images and predominantly low signal on T1 weighted images, accompanied by varying extent of iso- and hyperintense components. In 4 other patients, unenhanced US demonstrated no obvious changes in the echotexture of the 5 index lesions. However, in these patients, CEUS revealed a remarkable decrease in the extent of the viable target tumors ranging from 73-87% (table II, 4th-6th column). Residual, viable tumor appeared as enhancing intratumoral septa, islets or ill-defined areas, as enhancement and thickening/nodularity of the lesional wall or as a combination of the aforementioned features (fig3).
Correlation of CEUS with MR was also feasible for these 4 patients with significant post therapeutic necrosis. In 1/4 patients, newly appearing, hyperintense foci were detected within treated lesions on T1 weighted images.

Regarding the 13 remaining patients, 5 showed lesser degrees of post-treatment necrosis (1-25% decrease in the diameter of viable tumors), 3 showed no changes and 5 showed an increase in enhancing tumor load, ranging from 1-21%. In these patients, no unenhanced US changes and no MR signal alterations were observed during follow-up.

On the basis of the results of the first follow-up and according to RECIST criteria, 19 patients were classified as SD, and 2 patients had PD; according to mRECIST, 7 patients showed PR, 13 patients had SD and one patient had PD. Regarding the results of the last follow-up, response was as follows: RECIST; CR (n=0), PR (n=1), SD (n=16), PD (n=4). mRECIST; CR (n=2), PR (n=6), SD (n=11), PD (n=2). 7 responders (mRECIST) were misclassified as SD or PD by RECIST (table II, 7th -8th column). The concordance between the two systems was poor (k=0.247, p=0.035). A striking example of discordance was patient#6, who was classified as PD according to RECIST and as CR according to mRECIST because complete necrosis was associated with cystic transformation and substantial swelling of the tumors. Responders had a mean OS of 21.5 months (median:21 months, 95% CI:18.6-24.3 months), while non-responders had a mean OS of 12.2 months (median:18 months, 95% CI:8.5-15.9 months, p=0.018) (fig 4).

However, after adjustment for BCLC and Child’s classification, the statistical significance of difference in survival between responders and non-responders was reduced (p=0.065).

After the establishment of CR or PR, responders were followed-up for 4-19 months. During this period, one of the responders experienced a temporary reactivation of his target tumor, most likely caused by the interruption of sorafenib.

**Discussion**

In this study we utilized unenhanced US and CEUS to study the effect of sorafenib treatment on HCC. Unenhanced US proved to be efficient for identifying the tumors with cystic transformation, as a result of sorafenib treatment. This was the case in half (4/8) of the responders, in whom treated tumors resembled hemorrhagic or other complex liver cysts [11]. To our knowledge, sorafenib-induced, gray-scale US changes in HCC have not been previously documented in detail. Our findings are probably equivalent to those of CT studies, which reported cystic changes within liver metastases from
GISTs and renal-cell carcinomas [12,13], after effective antiangiogenic therapy. Cystic transformation is probably caused by intratumoral hemorrhage and/or protein-rich necrosis, as indicated by our associated MR findings. In another (MR-based) study [14], hyperintense foci in T1 and T2 weighted images appeared within hepatomas in 15/21 of patients treated with sorafenib. In the same study, an enlargement of the treated lesions was noted in 38% of the patients and was attributed to an increased volume of liquid tumor contents. We could not detect other therapy-induced changes on unenhanced US. Tumor hypoechochogenicity has been reported elsewhere [4,15] as a gray-scale sonographic feature of post-therapeutic tumor necrosis, but the value of this sign seems to be limited.

Our small experience confirmed that the role of the echo-enhancer is indispensable, in order to sonographically assess changes in tumor perfusion post antiangiogenic treatment and to detect sites of residual or recurrent disease. In the 4 responders, who exhibited no changes on unenhanced US, CEUS clearly showed a reduction in tumoral enhancement. Moreover, CEUS accurately delineated foci of residual enhancement within largely necrotic tumors, thus differentiating subtotal from total necrosis. Finally, CEUS could detect disease reactivation by revealing reappearance of enhancement in a previously necrotic part of a treated tumor. A similar observation was made regarding tumor reactivation within treated hepatic GIST metastases [16].

In this study, mRECIST detected significantly more responders than RECIST (8 versus 1); of note, 7/8 of these responders were correctly classified by the time of the first follow up study. Although the statistical significance of the difference in OS between responders and non-responders could be challenged, our results support the potential prognostic value of mRECIST and the superiority of this system over RECIST. The latter criteria, originally designed to evaluate the efficacy of chemotherapeutic (cytotoxic) drugs, are often insensitive in detecting the effect of antiangiogenic or locoregional treatments [3]. These treatments may cause substantial devascularization, which is not accompanied by early tumor shrinkage; actually (as noted in our cases of cystic transformation), tumor swelling may accompany tumor response. The efficacy of mRECIST in detecting tumor response is of clinical relevance when evaluating novel targeted therapies, since it allows for the early selection of patients, who are likely to benefit from the treatment. For similar reasons, mRECIST is preferred instead of RECIST for the evaluation of HCC patients treated with TACE [17] or with a combination of TACE and sorafenib [18].

Our findings regarding the superiority of mRECIST over RECIST and the discordance between these two systems are in line with those of a larger study, in which contrast-enhanced CT was used to evaluate HCC patients under sorafenib [19]. Although mRECIST was originally designed for application with dynamic CT/MR [10], our work shows that application of mRECIST may, in selected cases, be feasible in combination with CEUS. However, CEUS cannot replace the aforementioned modalities, which are the primary methods for evaluation of tumor response.

Some authors have utilized dedicated software for quantitative analysis of tumor enhancement on CEUS and for calculation of perfusion parameters before and after antiangiogenic treatment [5-7]. Using this method, a reduction in tumor perfusion could be detected in HCCs treated with bevacizumab as early as 3 days after the start of treatment [7]. However, parametric CEUS requires optimal, standardized and fully reproducible imaging conditions and the analysis is limited at a selected slice of a single tumor. We initially tried to perform parametric analysis, but we experienced great difficulties in maintaining constant and favourable scanning parameters throughout the study. We thus relied on the unidimensional measurement of the viable tumors. This approach is simple and practical, although it may be inaccurate in tumors which exhibit multiple, irregular necroses. Advances in US equipment may contribute in overcoming such problems. For example, three-dimensional CEUS has shown promising results in peri-interventional imaging of liver tumors [20] and this technique could also be applied to provide a more global and objective evaluation of the dynamic changes after antiangiogenic treatment.

Several limitations are associated with the present study. Our study population was small and heterogeneous (a significant proportion of patients were BCLC B). These features decrease the statistical robustness of our observations; they may also account for the differences between our results and those of the large clinical trials [1,21], regarding the efficacy of sorafenib and OS. We did not scan our patients shortly (1-2 weeks) after the start of treatment; thus, contrary to other studies [7,14], we were not able to assess for very early indications of tumors’ response. Finally, as noted above, we did not perform a parametric or volumetric analysis of our CEUS findings.

In conclusion, this work provides evidence regarding, (a) the clinical use of CEUS, as a modality for monitoring antiangiogenic treatments of HCC (b) the potential application of mRECIST on CEUS findings and, (c) the value of cystic changes, as an easily detectable (albeit inconsistent) sign of tumor response on unenhanced US. Future work should probably focus on the development of practical and widely accepted systems for the calculation
of necrosis and for the classification of tumor response on the basis of CEUS findings; the correlation of potential sonographic “biomarkers” with standard clinical endpoints should also be further investigated.

Conflict of interest: none

References