EASL- and mRECIST-evaluated responses to combination therapy predict survival in patients with hepatocellular carcinoma

Running title: Radiographic response to therapy predicts survival

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; AEs, adverse events; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CT, computed tomography; CR, complete response; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; mRECIST, modified RECIST; OS, overall survival; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TACE, transarterial embolization; VEGF, vascular endothelial growth factor; PD, progressive disease; PR, partial response; and PVTT, portal vein tumor thrombus.
Statement of Translational Relevance

The combination therapy of sorafenib and TACE is considered an alternative for patients with unresectable HCC. The assessment of tumor response to this therapy is particularly crucial in determining treatment success, but the suitability of available criteria including Response Evaluation Criteria in Solid Tumors (RECIST), European Association for the Study of the Liver (EASL) criteria and modified RECIST (mRECIST) has not been investigated. Furthermore, the earliest time at which the response to combination therapy could be accurately assessed is also of great importance. We demonstrated that the earliest time to evaluate the response to combination therapy is 3-4 months post-therapy. EASL and mRECIST responses assessed after 3-4 months of therapy are more reliable for detecting the early changes in the tumor and can be considered valuable early indicators for making subsequent therapeutic decisions and predicting long-term survival.
Abstract

Purpose Published studies have not investigated the suitability of Response Evaluation Criteria in Solid Tumors (RECIST), European Association for the Study of the Liver (EASL) criteria and modified RECIST (mRECIST) for assessing the response of patients with hepatocellular carcinoma (HCC) to treatment with sorafenib combined with transarterial chemoembolization. Here, we aimed to define the earliest time at which the response to combination therapy could be accurately assessed and validate the prognostic value of these criteria at this early post-therapy time point.

Experimental Design A total of 114 consecutive HCC patients receiving combination therapy were retrospectively enrolled. The therapy response at different time points was assessed using RECIST, EASL, and mRECIST. Cox regression analysis and Kaplan-Meier curves were used to assess overall survival (OS) in the responders and nonresponders.

Results At the third follow-up (median: 94 days; range: 89-102 days) post-therapy, the response rates obtained using EASL (50.6%) and mRECIST (51.6%) were greater than that obtained using RECIST (16.5%). The agreement was strong between the mRECIST and EASL results (k=0.9) but weak between mRECIST and RECIST (k=0.3). The EASL and mRECIST responses significantly correlated with survival. Risk reductions of 52% and 50% were observed for EASL and mRECIST responders, respectively, compared with nonresponders. However, no significant association between the treatment response and survival was observed using RECIST.

Conclusions The earliest time to evaluate the response to combination therapy is 3
months (median: 94 days) post-therapy. EASL and mRECIST responses are independent predictors for OS at this early time point.
Introduction

The assessment of tumor response to therapy is of great importance in determining treatment success, identifying complications, and guiding future therapy. Until recently, tumor response to therapy has been measured using the standard Response Evaluation Criteria in Solid Tumors (RECIST), which relies on measurements of the greatest dimension of the target lesions (1). However, growing evidence has suggested that evaluation by RECIST may not be the best method for monitoring treatment response in hepatocellular carcinoma (HCC) (2-8); the goal of effective locoregional and targeted therapies in HCC is to cause tumor necrosis (2, 3, 7-9). As a result of this evidence, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have proposed the development of superior methods for assessing the response to therapy in HCC (3, 10-11). Both proposed response assessment systems focus on changes in the viable tumor burden, which is ascertained using dynamic imaging techniques to identify the contrast-enhanced areas. Several studies have shown that in patients treated with transarterial chemoembolization (TACE) or sorafenib monotherapy, survival correlates more closely with the tumor response defined by these new criteria than with the tumor response defined by RECIST (12-16). However, few studies have defined specific early time points at which the assessment of treatment response has potential prognostic value. Studies by Gillmore et al. have demonstrated that the EASL and modified RECIST (mRECIST) responses at the first follow-up assessment after TACE are
independently associated with survival (13). A new treatment modality of sorafenib combined with TACE (combination therapy) is considered an alternative for patients with unresectable HCC (17), and studies have demonstrated a favorable safety profile and a high disease control rate in HCC patients who have received this combination therapy (18-20). In agreement with these previously published reports, a recent multi-center study led by our team found impressive benefits of combination therapy in HCC patients, even among those with advanced disease (21). Unfortunately, progress in the treatment of HCC has not yet been accompanied by the application of simple and practical radiologic response criteria that allow reliable monitoring of the efficacy of the treatment approach in clinical practice.

To provide clinical evidence for the early application of radiologic assessment methods in combination therapy, we assessed response at multiple early time points using the RECIST, EASL, and mRECIST criteria in a group of 114 HCC patients with unresectable tumors who were treated at our center. We sought to define the earliest time at which response could be accurately evaluated, identify differences between the various assessment criteria, correlate early responses with survival, and identify the optimal criteria for the early evaluation of response to combination therapy.

Materials and Methods
Patient population

This retrospective study comprised 194 HCC patients who were treated with combined sorafenib and TACE therapy at our center between June 2008 and July 2011. The patients were eligible for combination therapy if they presented with unresectable HCC, an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq 2$, adequate hematological and renal function, and the absence of tumor thrombosis in the main portal trunk. In generating the study population for this analysis, we excluded patients who had a Child-Pugh score of greater than 8 (n=13). Patients who withdrew from the drug regimen due to personal reasons (such as economic difficulties), rather than the occurrence of adverse events (AEs) or disease progression (n=22), were also excluded because the best treatment effect could not be assessed under these confounding circumstances. Patients who had received previous treatment with other targeted agents or by transjugular intrahepatic portosystemic shunt (n=13) were also excluded. In addition, patients who had started sorafenib treatment more than 2 months after their last TACE session and did not undergo a subsequent TACE procedure during sorafenib treatment (n=10) were excluded. Finally, patients were required to have at least one index HCC lesion, defined as the target lesion, with a clear margin measuring 1 cm or larger in diameter at baseline diagnosis; this criterion excluded 22 patients. Therefore, our study population comprised 114 consecutive cases whose survival outcomes were analyzed with respect to their radiologic responses. Of the 114 patients, none had additional concurrent malignant diseases. The overall survival
was considered to be the period between the first TACE treatment and the last follow-up. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Xijing Hospital. Written informed consent was obtained from each patient before treatment with the combination therapy.

TACE protocol

TACE was performed by selective transarterial chemotherapy in the vessels feeding the tumor with a suspension of lipiodol (2-20 ml), doxorubicin (10-50 mg), and mitomycin (2-10 mg), followed by embolization with absorbable Gelfoam particles. The infusion continued until a stagnant flow was observed in the feeding vessels. The dosage of doxorubicin and lipiodol was determined based on the tumor size, extrahepatic collateral vessels, and underlying liver function. CT scans were performed 4-6 weeks after each TACE procedure. For patients with preserved liver function, repeated TACE sessions were implemented upon confirmation of viable tumor or local and/or distant intrahepatic recurrences.

Sorafenib treatment

Sorafenib was administered to the patients at a dosage of 400 mg twice daily, which was not interrupted during the TACE procedure. Dose reduction was allowed upon the occurrence of AEs or deterioration of liver function. In patients who stopped TACE treatment, sorafenib treatment was continued until the occurrence
of an unacceptable drug-related toxicity. AEs were monitored using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

**Pre- and post-procedural workup**

All patients underwent a pre-treatment assessment consisting of a medical history, laboratory evaluation, and imaging workup. The diagnosis of HCC was determined by either liver biopsy or radiological methods, as defined by published guidelines (22, 23). The baseline staging was performed using the Child-Pugh class and Barcelona Clinic Liver Cancer (BCLC) classification systems within 1 month before the first TACE procedure (3). In most cases, follow-up CT scans were performed every 4-6 weeks to monitor the treatment response and determine whether a repeated TACE procedure was needed.

**Measurement of treatment response**

Tumor burden was retrospectively assessed using the arterial-dominant phase of the CT scan at baseline and follow-up (10). RECIST, EASL, and mRECIST criteria were employed to assess response. Unlike the traditional size criteria (RECIST), which focuses on the change in the whole lesion, the enhancement criteria (EASL and mRECIST) emphasize the importance of changes in the viable tumor (defined as the enhanced area) during the arterial phase. Using the enhancement criteria, the presence of a dense, homogeneous lipiodol deposit in the liver-confined tumor
indicates a necrotic area. At baseline, measurable lesions with diameters of \( \geq 1 \) cm were qualified as target lesions. The target responses were classified into the following 4 categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (Fig. 1). When mRECIST was used, extra-abdominal target lesions, such as those in the lung, were assessed using RECIST criteria. These lesions could not be evaluated using the enhancement methods because chest CT scans do not include the arterial phase. To assess the overall response by RECIST or mRECIST, non-target lesions (including lesions that were initially considered target lesions but were ultimately not qualified based on the criteria, lesions that could not be measured or with a maximum diameter of \( < 1 \) cm), and new lesions were considered (10). EASL criterion defines target lesions as all measurable arterially-enhancing lesions with diameters 1 cm or greater in the liver. Target responses do not take into consideration changes in non-target lesions, and the appearance of new lesions. By contrast, overall responses assess all target lesions but also take into consideration non-target lesions (including measurable arterially-enhancing lesions with diameters smaller than 1 cm, non-measurable arterially-enhancing lesions in the liver, and extra-hepatic disease sites), as well as the appearance of new lesions (including arterially-enhancing lesions in the liver, and extra-hepatic disease sites). Supplementary Table 1 illustrates the final response categories according to various combinations of tumor responses in the target and non-target lesions and with and without the appearance of new lesions. Patients with CR or PR were categorized as responders. Those with SD or PD were
categorized as nonresponders.

To control for measurement bias, we selected easily measurable nodules as target lesions. The treatment responses were blindly assessed by 4 experienced clinicians (G.H., W.B., W.W., and Y.Z.). In cases of discrepancies, the images were jointly reviewed by all of the clinicians, and a consensus decision was reached.

Statistical analysis

Statistical analyses were performed using SPSS version 16.0 software. The k coefficient was used to measure the inter-method concordance of the 3 response criteria between similar categorical items (24). The differences in OS between responders and nonresponders were examined using Cox regression and Kaplan-Meier survival analyses. The survival time was calculated as the time between the date of initial treatment and the date of death from any cause. Survival was censored if a change in therapy occurred. Multivariate Cox models were created to estimate the enhancement criteria assessment of hazard increment independent of other explanatory covariates.

Results

Patient characteristics

Among the 114 eligible patients, the median follow-up duration was 11 months (range: 2-36 months), and 71 patients had died at the time of data closure on...
December 31, 2011. The detailed baseline clinical characteristics are provided in Table 1. Among the 88 patients who were classified as BCLC stage C, 65 had metastasis or a portal vein tumor thrombosis (PVTT) confined to the portal branches, rather than the trunk. In total, 41 patients had undergone previous local treatments, including resection, radiofrequency, ablation, and TACE. All previous treatments were implemented more than 1 month before the baseline CT scans, which were performed within 1 month of the first TACE treatment. The difference in median OS between the patients who received prior treatment and those who did not was not significant (14.0 months, [95% CI: 9.7, 18.3] versus 14.0 months, [95% CI: 10.7, 17.3], p=0.914). The lesions that had previously been treated were not considered target lesions.

In 85.1% of the patients, the interval between the initiation of TACE and sorafenib treatment was less than 7 days (median: 2 days; range: 3-12 days). Sorafenib was administered following TACE treatment in the 77 patients who started combination therapy before September 2010. However, based on the demonstration of the efficacy and safety of sorafenib in our work and the subsequent broad clinical implementation of sorafenib treatment, the remaining 37 cases began sorafenib treatment prior to TACE. The differences in median OS between the patients who received TACE before administration of sorafenib and those who received TACE after sorafenib was not significant (14.0 months [95% CI: 10.8, 17.2] versus 14.0 months [95% CI: 9.8, 18.2], p=0.973).
The median number of TACE sessions was 2 (range: 1-8), and 30.7, 34.2, and 21.9% of the patients received 1, 2, or 3 TACE treatments, respectively. Overall, the median duration of sorafenib treatment was 8.2 months (range: 0.6-29.6 months).

The incidence of treatment-related AEs for all grades was 82.5%. In total, 6 (5.3%) patients experienced dose reduction, and sorafenib was discontinued in 11 (9.6%) patients due to unacceptable drug-related toxicity.

**Treatment details at each time point**

For each patient, the treatment response was assessed and recorded at every follow-up. We correlated the patients’ response at different time points with their survival in chronological order and found a strong correlation between the treatment response defined by the enhancement criteria and survival as early as 3 months post-TACE. The treatment details are described below.

At the first follow-up (median: 33 days; range: 28-35 days) post-TACE response assessment, 23 cases were excluded due to a lack of imaging data at this time point. Thus, 91 patients who had undergone 1 TACE session prior to the imaging assessment were analyzed, and the median duration of sorafenib treatment for these patients was 31 days (range: 20-47 days). When the data were assessed at the second follow-up (median: 68 days; range: 62-73 days), 85 patients with imaging data were analyzed, and sorafenib had been administered in these
patients for a median of 64 days (range: 20-85 days). Prior to the assessment, 57.6% of the 85 patients had undergone 1 TACE session and 42.4% had undergone 2 sessions. At the third follow-up (median: 94 days; range: 89-102 days) assessment, 97 patients were analyzed after excluding patients who had died (n=3) and those who lacked imaging data (n=14). Prior to the assessment, 43.3, 50.5, and 6.2% of the 97 patients had received 1, 2, or 3 TACE sessions, respectively. The median duration of sorafenib treatment in these patients was 90 days (range: 30-114 days).

Comparison of the response criteria at multiple time points

Supplementary Fig.1, Supplementary Fig.2, and Fig. 2 shows the Kaplan-Meier survival curves of the HCC patients treated with combination therapy. The curves illustrate the survival probabilities for responders and nonresponders based on each set of criteria when assessed at first, second, and third follow-up post-TACE.

At the first follow-up assessment, none of the criteria identified a difference in OS between responders and nonresponders, as demonstrated by survival curve (Supplementary Fig.1) and log-rank test (p=0.145, 0.447, and 0.178 for RECIST, EASL, and mRECIST, respectively). A similar outcome was observed when OS was assessed at the second follow-up (log-rank test values of p=0.129, 0.189, and 0.265 for RECIST, EASL, and mRECIST, respectively) (Supplementary Fig.2). However, when analyzed at the third follow-up (median: 94 days; range: 89-102 days) after the first
TACE, both EASL and mRECIST responders displayed a significant, prolonged OS compared with nonresponders based on the log-rank test (p<0.001 for EASL and p=0.001 for mRECIST). In contrast, no difference was observed in the probability of survival between responders and nonresponders using the RECIST model (p=0.115) (Fig 2).

Based on these results, we considered the third follow-up (median: 94 days; range: 89-102 days) after treatment to be an appropriate early time point for assessing the response to combination treatment and chose to further analyze the treatment response at this stage.

Intercriterion agreement

At the third follow-up post-TACE, the RECIST assessment resulted in a much lower overall response rate compared with the EASL and mRECIST assessments (RECIST: 16.5%; EASL: 50.6%; and mRECIST: 51.6%). The patient evaluation in every response category was markedly different between the RECIST and mRECIST criteria, whereas an overwhelming majority of patients (with the exception of 6 patients) were classified into the same response categories when assessed using the EASL and mRECIST criteria (Table 2). The evident lack of a correlation between RECIST and mRECIST was reflected in the Cohen k statistic (k=0.3). An excellent agreement was observed between the EASL and mRECIST criteria, with a k value of 0.9.
OS according to response categories

Among the 97 patients assessed at the third follow-up, the median OS was 15.3 months with a 95% Confidence Interval [CI]: 12.5, 18.1. We identified 48 and 47 responders based on the EASL and mRECIST criteria, respectively. The HR for OS in responders compared with nonresponders was 0.39 (95% CI: 0.23, 0.68; p=0.001) for EASL and 0.42 (95% CI: 0.25, 0.71; p=0.001) for mRECIST. Importantly, the RECIST responders showed a 44.5% risk reduction compared to nonresponders, although this difference was not statistically significant (Table 3).

Re-categorization of patients with CR

In total, 18 patients were classified as having CR according to both EASL and mRECIST criteria. A reassessment of this subgroup of patients using the RECIST criteria classified 7 and 11 patients as PR and SD, respectively. However, after this re-categorization, no significant difference in OS was observed between patients with PR and SD (log rank p=0.7) (Supplementary Fig. 3).

Survival prediction based on the enhancement criteria

The association between survival and multiple clinical parameters was investigated (Table 4). The presence of ascites, tumor size, and the ECOG performance status were significantly associated with OS. Using the factors with statistical significance of p<0.1, we built 2 multivariate models to explore the prognostic factors for OS.
(Table 5). The HRs were adjusted for ascites, tumor size, ALB, ECOG, and EASL or mRECIST guidelines using the cut-off points shown in Table 4. After adjustment, a multivariate analysis revealed a significant ability of the mRECIST model to independently predict the OS in HCC patients treated with the combination therapy, with a 50% risk reduction for responders compared with nonresponders (adjusted HR, 0.50 [95% CI: 0.28, 0.89; p=0.019]). Similar results were obtained using the EASL model, which showed a 52% risk reduction for responders compared with nonresponders (adjusted HR, 0.48 [95% CI: 0.26, 0.87; p=0.015]).

Discussion

This retrospective study explored the feasibility of using early radiographic response to predict the survival of HCC patients treated with sorafenib in combination with TACE. To our knowledge, this is the first study to evaluate various time points for radiographic response assessment and analyze the suitability of different radiographic evaluation criteria to assess the response of HCC patients to this type of combination therapy.

Because treatment response is an indicator to consider in further treatment decisions and a surrogate marker for long-term survival in cancer therapy, response must be assessed as accurately and early as possible. However, previous studies of HCC have not determined the minimal interval of time after treatment required to accurately assess response (12, 14-16). In fact, most studies have indicated that the
best response to locoregional or sorafenib treatment is the patient’s final response.

Two difficulties arise from this observation. First, the best response cannot be ascertained prior to evaluating the series of CT scans acquired over the entire treatment and follow-up period, preventing the use of the best response as an early predictive marker. Secondly, as previous studies have shown the standard method of comparing responders with nonresponders without considering the time variable may lead to biased estimates of the survival distributions and misleading conclusions (25).

Memon et al. have recently used 3 methods (landmark, risk-of-death, and Mantel-Byar) to correct for analyses of responders and nonresponders (which are plagued by guarantee-time bias) and found that the EASL response at 6 and 12 months after locoregional therapy could predict survival times (12). We sought to determine the earliest time point at which the response to combination therapy is associated with a favorable prognostic value. Therefore, this exploratory analysis evaluated response at multiple early time points. We investigated the association between the response assessed at early time points and at the more clinically relevant end point (death), regardless of the guarantee-time bias.

Our study demonstrated that EASL- and mRECIST-based responses at 3-months (median: 94 days; range: 89-102 days) post-therapy can predict the efficacy of combination therapy with sorafenib and TACE. However, the treatment responses
at earlier time points did not correlate with survival in HCC patients. This result could be explained by the possibility that many patients had not completed their TACE treatments and had not received sorafenib for the proper duration at the earlier time points. Therefore, the response assessment was likely to underestimate the treatment effect. Georgiades et al. have also reported that the majority of HCC patients who do not respond to initial chemoembolization show a significant response to a second TACE procedure (26). Interestingly, the authors demonstrated that despite receiving additional treatments, patients who did not respond to the first and second chemoembolizations had shorter survival times than those who responded to the second chemoembolization. This finding is consistent with our observation that the majority of patients who required repeated TACE treatments after 3 months of therapy had already received a second procedure.

In the current study, we observed a robust agreement between the mRECIST and EASL assessments at 3 months after combination therapy, which is consistent with the results of previous studies that applied these criteria to either TACE or sorafenib monotherapy in patients with HCC (13,14). The considerably lower response rate assessed using RECIST may be partially due to the longer time for response required by RECIST (7-8 months) compared with EASL (1.6 months) (27). When the subset of patients who experienced CR according to the enhancement criteria were re-classified based on the size criteria, survival was similar between
those with PR and SD. This finding revealed that criteria based solely on tumor size are not completely accurate. The survival analysis showed a strong correlation between the EASL and mRECIST responses assessed after 3 months of therapy using the enhancement criteria and survival predictions, suggesting that the enhancement criteria are more reliable for detecting the early changes in the tumor that will have a clinically meaningful outcome for the patients.

The retrospective nature of our study resulted in several limitations. First, the population used in this study was heterogeneous with regard to the frequency of patients with Child-Pugh B, pretreated patients, number of TACE sessions, the order of TACE and sorafenib treatment, and patients with BCLC C disease. However, our population is similar to that of patients who are treated in routine clinical practice. Secondly, according to the enhancement criteria, necrosis was defined as a nonenhanced area, but nonenhancement may not accurately differentiate viable from necrotic tumor tissue (determined upon histopathologic analysis), resulting in an overestimation of the extent of the necrosis (28). However, pathologic explants were not available at the early time points post-treatment when our radiologic assessments were performed. Moreover, the explants cannot reveal the true effect of the treatment prior to explantation. Thus, the use of imaging-based enhancement criteria remains valuable for estimating treatment response. Finally, MRI is considered superior to CT for the detection of viable tumor tissue that remains after lipiodol-based TACE (29).
well-programed trial using MRI assessment of response will make our results much more convincing.

In summary, our study has demonstrated that 3 months (median: 94 days; range: 89-102 days) post-therapy is the earliest time point at which the response to sorafenib combined with TACE should be evaluated in HCC patients. Moreover, EASL and mRECIST responses are independent predictors for OS at this early time point and can be considered valuable early indicators for making subsequent therapeutic decisions and predicting long-term survival. To validate our conclusions, further studies that incorporate recommended MRI imaging systems are warranted.

Acknowledgments

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References


1786 – 92.


Figure Legends

Fig. 1: Illustration of the measurement methods of the 3 response criteria. The gray area within the nodules represents the enhanced viable lesions, and the white area represents nonenhanced or iodized oil-retaining lesions. A=the maximum diameter of the entire tumor before treatment (Pre-treatment); A′=the maximum diameter of the entire tumor after treatment (Post-treatment); A′′=the maximum diameter of the enhanced area of the tumor after treatment; B=the diameter perpendicular to A; and B′′=the diameter perpendicular to A′.

Fig. 2: Kaplan-Meier curves comparing survival between responders and non-responders according (G) RECIST, (H) EASL, and (I) mRECIST assessed at third follow-up after treatment. Abbreviations: EASL, European Association for the Study of the Liver; mRECIST, modified RECIST; RECIST, response evaluation criteria in solid tumors.
Table 1. Baseline characteristics of the 114 patients with unresectable HCC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female/Male)</td>
<td>18/96</td>
</tr>
<tr>
<td>Age (&lt;65 y/≥65 y)</td>
<td>94/20</td>
</tr>
<tr>
<td>Etiology (HBV/HCV/Alcohol/Other)</td>
<td>94/9/1/10</td>
</tr>
<tr>
<td>Prior treatment (No/Yes)</td>
<td>73/41</td>
</tr>
<tr>
<td>Ascites (Absent/Present)</td>
<td>93/21</td>
</tr>
<tr>
<td>PVTT (Absent/Present)</td>
<td>71/43</td>
</tr>
<tr>
<td>Metastases (Absent/Present)</td>
<td>84/30</td>
</tr>
<tr>
<td>Tumor distribution (Unifocal/Multifocal)</td>
<td>93/21</td>
</tr>
<tr>
<td>Maximum tumor diameter (≤10 cm/&gt;10 cm)</td>
<td>64/50</td>
</tr>
<tr>
<td>AFP (≤200 ng/ml/&gt;200 ng/ml)</td>
<td>49/65</td>
</tr>
<tr>
<td>ALB (≥35 ng/dl/&lt;35 ng/dl)</td>
<td>81/33</td>
</tr>
<tr>
<td>TBIL (≤17 mg/dl/&gt;17 mg/dl)</td>
<td>68/46</td>
</tr>
<tr>
<td>BCLC (B/C)</td>
<td>26/88</td>
</tr>
<tr>
<td>Child-Pugh (A/B)</td>
<td>98/16</td>
</tr>
<tr>
<td>ECOG† (0/1/2)</td>
<td>49/59/3</td>
</tr>
<tr>
<td>TACE order (Early/Late)</td>
<td>7/37</td>
</tr>
</tbody>
</table>

**Note:** †Baseline ECOG performance status was not available for 3 patients. **Abbreviations:** AFP, α-fetoprotein; ALB, albumin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; PVTT, portal vein tumor thrombosis; TBIL, total bilirubin.
Table 2. Intercriteria agreement between RECIST and mRECIST and between the EASL criteria and mRECIST.

<table>
<thead>
<tr>
<th>Response with RECIST</th>
<th>Response with mRECIST</th>
<th>No. (%)</th>
<th>K value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
<td>7 8</td>
<td>16 (16.5)</td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
<td>11 24</td>
<td>60 (61.9)</td>
</tr>
<tr>
<td>PD</td>
<td>PD</td>
<td>0 0</td>
<td>21 (21.6)</td>
</tr>
</tbody>
</table>

| Response with EASL  | CR            | 0       |
|---------------------|---------------|
| PR                  | 18 (18.6)     |
| SD                  | 0 3           |
| PD                  | 0 1           |

| No. (%)             | 18 (18.6) 32 (33) 22 (22.7) 25 (25.8) |

**Abbreviations:** CR, complete response; EASL, European Association for the Study of the Liver; mRECIST, modified RECIST; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease.
Table 3. Association between the response (as assessed by RECIST, EASL and mRECIST) and overall survival (as assessed by Cox regression analysis).

<table>
<thead>
<tr>
<th>Response</th>
<th>OS HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECIST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponder (n=81)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Responder (n=16)</td>
<td>0.555 (0.262-1.175)</td>
<td>0.124</td>
</tr>
<tr>
<td><strong>EASL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponder (n=48)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Responder (n=49)</td>
<td>0.394 (0.230-0.675)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>mRECIST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponder (n=47)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Responder (n=50)</td>
<td>0.417 (0.245-0.711)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EASL, European Association for the Study of the Liver; mRECIST, modified RECIST; OS, overall survival; RECIST, response evaluation criteria in solid tumors.
**Table 4. Univariate analysis of survival in 97 patients.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/Female)</td>
<td>1.09 (0.54-2.22)</td>
<td>0.81</td>
</tr>
<tr>
<td>Age (≥65/&lt;65)</td>
<td>0.95 (0.50-1.80)</td>
<td>0.88</td>
</tr>
<tr>
<td>HBV (Present/Absent)</td>
<td>1.83 (0.87-3.87)</td>
<td>0.11</td>
</tr>
<tr>
<td>HCV (Present/Absent)</td>
<td>0.68 (0.27-1.70)</td>
<td>0.41</td>
</tr>
<tr>
<td>Prior treatment (No/Yes)</td>
<td>0.95 (0.56-1.61)</td>
<td>0.86</td>
</tr>
<tr>
<td>Ascites (Present/Absent)</td>
<td>2.07 (1.11-3.85)</td>
<td>0.02</td>
</tr>
<tr>
<td>PVTT (Present/Absent)</td>
<td>1.54 (0.90-2.64)</td>
<td>0.12</td>
</tr>
<tr>
<td>Metastases (Present/Absent)</td>
<td>0.95 (0.53-1.69)</td>
<td>0.85</td>
</tr>
<tr>
<td>Tumor distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Multifocal/Unifocal)</td>
<td>0.92 (0.48-1.78)</td>
<td>0.81</td>
</tr>
<tr>
<td>Tumor size (&gt;10 cm/≤10 cm)</td>
<td>1.67 (0.99-2.81)</td>
<td>0.05</td>
</tr>
<tr>
<td>AFP (&gt;00 ng/ml/≤200 ng/ml)</td>
<td>1.18 (0.70-1.99)</td>
<td>0.54</td>
</tr>
<tr>
<td>ALB (&lt;5 ng/dl/≥35 ng/dl)</td>
<td>1.65 (0.96-2.85)</td>
<td>0.07</td>
</tr>
<tr>
<td>TBIL (&gt;17 mg/dl/≤17 mg/dl)</td>
<td>0.94 (0.55-1.61)</td>
<td>0.83</td>
</tr>
<tr>
<td>BCLC (C/B)</td>
<td>1.61 (0.85-3.05)</td>
<td>0.15</td>
</tr>
<tr>
<td>Child-Pugh (B/A)</td>
<td>1.03 (0.49-2.18)</td>
<td>0.93</td>
</tr>
<tr>
<td>ECOG (≥1/0)</td>
<td>2.11 (1.20-3.71)</td>
<td>0.01</td>
</tr>
<tr>
<td>TACE order (Late/Early)</td>
<td>0.89 (0.48-1.65)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**Abbreviations:** AFP, α-fetoprotein; ALB, albumin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; PVTT, portal vein tumor thrombus; TBIL, total bilirubin.
Table 5. Multivariate analysis of overall survival.

<table>
<thead>
<tr>
<th>Response</th>
<th>OS HR</th>
<th>(95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL</td>
<td>Nonresponder (n=48)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Responder (n=49)</td>
<td>0.48 (0.26-0.87)</td>
<td>0.015</td>
</tr>
<tr>
<td>mRECIST</td>
<td>Nonresponder (n=47)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Responder (n=50)</td>
<td>0.50 (0.28-0.89)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Note: Covariates with $p<0.1$ from the univariate analysis were included in the multivariate analysis. Abbreviations: EASL, European Association for the Study of the Liver; mRECIST, modified RECIST; OS, overall survival.
Fig. 1

Pre-treatment

Post-treatment

RECIST

PR

A'/A×100%≤70% 

SD

A'/A×100%≥70% and 
A'/A×100%-1≤20%

PD

A'/A×100%-1≥20%

mRECIST

B'=0

A''/A×100%≥70% and 
A''/A×100%-1≤20%

EASL

B'=0

(A''×B'')/(A×B)×100%≤50%

(A''×B')/(A×B)×100%≥50% and 
(A''×B')/(A×B)×100%-1≤25%

(A''×B')/(A×B)×100%-1≥25%
Fig. 2

A

log-rank p = 0.116

Non-Res

Res

Median survival:
Res: 19.2 months
Non-Res: 14.0 months

Overall survival

Time (months)

No. at risk
Res 16 11 7 5 0 0
Non-Res 81 65 37 10 5 0

B

log-rank p < 0.001

Non-Res

Res

Median survival:
Res: 18.0 months
Non-Res: 9.8 months

Overall survival

Time (months)

No. at risk
Res 49 32 16 8 1 0
Non-Res 45 33 16 9 1 0

C

log-rank p = 0.001

Non-Res

Res

Median survival:
Res: 18.0 months
Non-Res: 10.0 months

Overall survival

Time (months)

No. at risk
Res 50 45 33 16 9 1
Non-Res 49 45 33 16 9 1
Clinical Cancer Research

EASL- and mRECIST-evaluated responses to combination therapy predict survival in patients with hepatocellular carcinoma

Weijuan Wang, Lei Liu, Hui Chen, et al.

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