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The Impact of Antiangiogenic Therapy Combined With Transarterial Chemoembolization on Enhancement Based Quantitative Tumor Response Assessment in Patients With Hepatocellular Carcinoma

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Abstract

Purpose—To investigate whether Bevacizumab compromises early response assessment after Transarterial Chemoembolization (TACE) in patients with hepatocellular carcinoma by 3D quantitative European Association for the Study of the Liver (qEASL) criteria in comparison to other imaging-based criteria.

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Materials and Methods—Each of 14 patients receiving TACE and bevacizumab was matched with two patients receiving TACE alone. Baseline and Follow-up MRI was retrospectively analyzed regarding qEASL and other imaging-based criteria.

Results—Percentage-based qEASL achieved significant separation in both therapy arms ($p=0.046$ and $p=0.015$). Response and Overall Survival showed similar association among treatment groups ($p=0.749$).

Conclusions—Anti-angiogenic therapy with bevacizumab does not impede early response assessment by qEASL.

Graphical abstract

Keywords

Bevacizumab; qEASL; TACE; antiangiogenic agents; quantitative imaging; HCC

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death worldwide [1–3]. Most HCC patients present with intermediate or advanced stage disease, making curative treatments unattainable for most patients [4]. Trans-arterial chemoembolization (TACE) has meanwhile been established as the mainstay therapeutic option for many patients [4]. Recurrence following TACE is common, and a main cause is post-embolic tumor hypoxia leading to a surge of pro-angiogenic factors, such as the vascular endothelial growth factor (VEGF) [4–6]. Therefore, a strong rationale exists for investigating the use of bevacizumab, a humanized monoclonal antibody targeting VEGF, in combination with TACE, in order to contain tumor progression during and between TACE cycles [7].

Assessing tumor response is important for determining the course of patient treatment, and hence robust, precise, and reproducible criteria are essential for therapeutic success. Loco-regional embolization therapies like TACE cause tumor infarction, thus fundamentally changing the appearance of the targeted tissue on contrast-enhanced MRI by causing non-homogenous enhancement patterns [1, 8]. In addition, early follow-up imaging after TACE usually does not demonstrate tumor shrinkage, making conventional diameter-based measurements obsolete. A plethora of published data demonstrates that unidimensional

measurements such as Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST (mRECIST), as well as bidimensional measurements like the World Health Organization (WHO) and the European Association for the Study of the Liver (EASL) criteria, are unreliable in the setting of TACE at an early time point [1, 9]. New 3D imaging biomarkers, such as the quantitative EASL [qEASL], have meanwhile been established to address the previously unmet need for robust tumor assessment techniques after TACE [1, 8, 10, 11]. However, they have not yet been tested in the framework of TACE combined with systemic therapy using anti-angiogenic agents such as bevacizumab. All agents with similar molecular targets and comparable mechanism of action have been demonstrated to profoundly affect vascularity, pathologic vessel growth and tortuosity, as well as contrast agent permeability of the capillary bed of liver tumors. Little is known on the impact of bevacizumab on the role of tumor enhancement within the framework of imaging response.

Recently a number of studies have been done on bevacizumab in this context and while disagreeing on the safety and therapeutic success, they all struggled regarding appropriate early response assessment, with attempts ranging from subjective visual impression on MRI to diagnostic angiography [7, 12, 13]. Finding a not only early, but objective and reliable method could advance scientific knowledge on effective and safe bevacizumab application.

The purpose of our study is to investigate whether Bevacizumab compromises early response assessment after conventional TACE (cTACE) in patients with unresectable hepatocellular carcinoma (HCC) by 3D quantitative European Association for the Study of the Liver (qEASL) criteria in comparison to other imaging-based criteria.

Materials and Methods

Study design and patient selection

This is a retrospective single-institution Health Insurance Portability and Accountability Act-compliant and institutional review board-approved study. Informed consent was waived. Study design was in agreement with the Standards for Reporting of Diagnostic Accuracy guidelines. Enrolled were all 16 consecutive patients receiving cTACE and bevacizumab combination therapy between September 2006 and December 2008 during a Phase II clinical trial at one of the two institutions conducting the trial, which is described in detail in prior literature [12]. Patients without follow-up MR imaging (N=2) were excluded; the remaining 14 patients were analyzed.

The clinical study inclusion protocol required patients to demonstrate sufficient platelet count ($> 50,000/\text{nl}$), adequate liver and kidney function, Child-Pugh Class A or B, and Eastern Cooperative Oncology Group score (ECOG) 0 – 2 [12]. Exclusion criteria included risk factors for severe bleeding, major vessel or heart disease [12]. For each cycle the patients received 10 mg/kg bevacizumab intravenously 7 days prior to TACE, followed by subsequent biweekly administration. During the course of the study, the therapy regimen was adjusted to administer bevacizumab 14 days prior to TACE, due to prolonged recovery after the procedure which interfered with the next biweekly injection. Patients received up to

3 cycles of cTACE and bevacizumab therapy [12]. Further detail regarding the protocol used, is provided in the cited article addressing safety and efficacy [12].

To improve comparability, a control group was included consisting of patients who received TACE without bevacizumab. For this purpose, a prospectively acquired patient database was retrospectively used to randomly include TACE-naïve patients who received cTACE between May 2004 and April 2006 (before the enrolment period of the prospective trial) [14]. Inclusion and exclusion criteria for the control group were identical to those for the prospective trial group. For each patient receiving the combination therapy, two patients with matching Child-Pugh Class and Barcelona Clinic Liver Cancer stage (BCLC) as well as similar tumor size and number ($\pm 10\%$ in largest lesion diameter) were included into the control group (Fig. 1). An additional 1:1 control group matching was performed for basic consistency check.

TACE protocol

After decision by consensus agreement of a multidisciplinary tumor board for each patient, TACE was performed by an interventional radiologist (XX) with 19 years of experience. The Seldinger technique was used to gain access to the femoral artery and a catheter was advanced into the aorta under angiographic guidance. Following confirmation of the patient's vessel anatomy, access was gained to the hepatic artery through the coeliac trunk, or the replaced hepatic through the superior mesenteric respectively. Lobar or superselective embolization was performed with a solution containing 50 mg of doxorubicin and 10 mg of mitomycin C in a 1:1 mixture with iodized oil (Lipiodol; Laboratoire Guerbet, Aulnay-sous-Bois, France) under the guidance of intra-procedural imaging. This was followed by the application of microspheres with a diameter of 300–500 μm (Embospheres; Merit Medical Systems, South Jordan, Utah).

MR Imaging

For early assessment during treatment, contrast-enhanced multiphasic breath-hold MRI with T1-weighted sequences was acquired 2 ± 3 weeks prior to embolization (baseline MR), and 3 ± 3 weeks afterwards (follow-up MR) using a 1.5 Tesla MR scanner (Siemens Magnetom Avanto, Erlangen, Germany). Imaging was acquired prior to the intravenous administration of Gadolinium-base contrast agent (pre-contrast phase) and at multiple time points afterwards (arterial, portal venous, and delayed phases).

Image processing and analysis

With a semi-automatic 3D tumor segmentation software (Medisys, Philips Research, Suresnes, France) the largest targeted lesion on the arterial phase image was segmented. The inter-reader reliability and pathological validation for the 3D tumor segmentation was done in previous work [1, 15, 16].

qEASL validation to pathology and implications for patient care have been shown in previous work [1, 11]. To calculate qEASL, the pre-contrast phase images were registered to the corresponding arterial phase image (using Philips Fast Elastic Image Registration [FEIR] software) and subsequently subtracted from the arterial phase images to mitigate

contribution of background enhancement and to isolate the image intensity component corresponding to enhancement induced by contrast agent [10]. Thereafter a cubic (1 cm³) region of interest (ROI) was placed inside non-tumorous liver tissue proximal to the segmented lesion, while avoiding visible structures like blood vessels [17]. Finally, qEASL measures the volume of each lesion which displays enhancement greater than the mean plus two standard deviations of the distribution of voxel intensities within the ROI (Fig. 2). All segmentations and measurements were done by consensus agreement of two readers, ROI placement was performed by each reader independently. Inter-reader agreement was noted.

Response assessment and calculations

Two distinct qEASL measures were calculated: The volume-based qEASL which uses absolute volume measures of enhancing Volume V(e) before (old) and after (new) treatment

in cm³ (volume- based qEASL [%] = $\frac{V(e)_{\text{new}} - V(e)_{\text{old}}}{V(e)_{\text{old}}} * 100\%$) and the percentage-based

qEASL that uses the fraction $\frac{V(e)}{V(t)}$ of the volume of the tumor V(t) that is enhancing V(e) in

(percentage- based qEASL [%] = $\frac{\frac{V(e)_{\text{new}}}{V(t)_{\text{new}}} - \frac{V(e)_{\text{old}}}{V(t)_{\text{old}}}}{\frac{V(e)_{\text{old}}}{V(t)_{\text{old}}}} * 100\%$)
% before and after treatment

Hence, relevant differences would only be expected in cases of marked tumor growth or shrinkage between baseline and follow-up imaging.

The patient were classified into responders and non-responders for each of the response criteria based on the reduction of the corresponding parameter between baseline and follow-up MRI. The specific thresholds for response are: -30% reduction in overall/enhancing diameter for RECIST and mRECIST, respectively; -50% overall/enhancing area product reduction for WHO and EASL, respectively; and -65% enhancing volume reduction for qEASL, as established by previous studies [1]. All measurements were performed under the supervision of an interventional radiologist (XX) with 13 years of experience, who did not perform the TACE. In the case of disagreement, consensus was found by discussion.

Statistical Analysis

Patient characteristics (Table 1) were evaluated for significant differences between treatment groups using the chi-square test for categorical variables and t-test for continuous variables. The landmark analysis approach was chosen to compare the Overall Survival (OS) between responders and non-responders, with OS being calculated as the time between follow-up MR and the date of death [18]. Surviving patients or patients who were lost to follow up were censored at the last time point at which they were known to be alive. Kaplan-Meier curves were plotted for each of the response criteria. Univariate Cox proportional hazards models were applied to evaluate the impact of baseline characteristics and response criteria on OS. Multivariate Cox proportional hazards models were used with variables that were found to be significant on univariate analysis. The modification effect of the treatment groups was introduced through interaction between responder status and treatment group. P-values smaller than 0.05 were considered statistically significant. Response criteria showing statistically significant results in the 2:1 matched control group underwent consistency check

in the 1:1 matched control group. Inter-reader agreement was calculated by two way mixed intra-class correlation. Statistical analysis was done with SPSS (IBM SPSS Statistics 22.0.0.0 64 bit) and SAS (version 9.4, SAS Institute, Cary, NC, USA).

Results

Patient Data

Median OS was 16.7 (95%-Confidence Interval CI: 0 – 35.1) months for patients receiving cTACE and bevacizumab therapy, and 13.8 (95%-CI: 9.8 – 19.6) months for patients who received TACE without bevacizumab. Patients were censored as necessary in the combination therapy and control group (n=1 and n=3 respectively). Four of the bevacizumab patients had received one cycle of TACE prior to the trial and one patient received sorafenib after the trial.

Image Analysis and Survival

Criteria independent of enhancement (RECIST and WHO) failed to stratify responders and non-responders in both treatment groups. Specifically, RECIST showed no separation, and WHO classified one patient in the control group while reversing the risk between responders and non-responders and no patient in the combination therapy group (Fig. 3). Inter-reader agreement was low at 0.253 for RECIST and 0.416 for WHO, which could be attributed to the ill-defined tumor borders frequently seen in our patient cohort.

Enhancement-based response criteria and guidelines like mRECIST and EASL failed to classify all patients. mRECIST and EASL were non-measurable in the same 2 patients in the combination therapy group (14.3%) and the same 6 patients in the control group (21.4%), due to grossly inhomogeneous enhancement pattern, highly pathologic livers and ill-defined tumor growth pattern. For the patients that could be classified, neither mRECIST nor EASL showed statistically significant correlation with survival in univariate or multivariate analysis (Table 2). Moreover, a reversed hazard ratio (HR) was found e.g. EASL in the control group, meaning, patients classified as responders actually died sooner. The inter-reader agreement was 0.731 for mRECIST and 0.054 for EASL.

In contrast, both percentage-based and volume-based qEASL measurements were able to classify all patients in both groups. In the univariate analysis for the patients that received combination therapy, both qEASL measurements were statistically significant (p= 0.046 both measurements). For the control group, only the percentage-based measurement was significant (p= 0.014). The consistency check with the 1:1 matched control group performed regarding percentage-based qEASL showed a higher p-value than the 2:1 matched control group and reached significance at p=0.021. Inter-reader agreement was 0.984 for percentage-based qEASL and 0.992 for volume-based qEASL.

In addition to the response criteria, all patient characteristics were included in the univariate analysis; none showed statistical significance except presence of Hepatitis C infection, which was significant in the control group only. In the multivariate analysis, both qEASL measurements stayed statistically significant in the combination therapy group, no criteria

stayed significant in the control group. No other criteria reached significance in either treatment group.

Combination therapy versus TACE-only

The response rates as indicated by the qEASL measurements were comparable in both treatment groups (28.6% vs 32.1% for percentage-based qEASL and 28.6% vs 25.0% for volume-based qEASL). The HR of death for non-responders versus responders in the combination therapy group was 4.8 (1.0 – 22.8) and 3.3 (1.3 – 8.6) in the control group for percentage-based qEASL (Fig. 4). The association of responder status as defined by percentage-based qEASL and OS was not significantly different between treatment groups ($p=0.749$). For volume-based qEASL the HR of death for non-responders versus responders was 4.8 (1.0 – 22.8) in the combination therapy group and 2.2 (0.8 – 5.4) in the control group and again we did not find a significant interaction between responder status and treatment groups ($p=0.415$).

Discussion

The main finding of our study is that systemic anti-angiogenic therapy with bevacizumab does not impede response assessment after TACE by qEASL criteria at an early time point. It can therefore contribute to clinical decision making and to the assessment of therapeutic efficacy. The uni- and bi-dimensional methods considered were unable to predict patient survival in both treatment arms. Moreover, the current study demonstrates that no significant difference exists between the ability of qEASL to predict survival in patients with HCC receiving TACE without bevacizumab versus patients receiving combined TACE and bevacizumab therapy. Furthermore it is important to emphasize that our study is not an outcome study and therefore, did not investigate the effectiveness of the treatment, but investigated the aptitude of imaging and its evaluation for early response assessment after TACE combined with anti-angiogenic agents. Our study neither addressed safety, nor possible risks of the treatment, as these were subject of prior literature [12].

As a matter of therapeutic strategy, TACE treatment protocols usually require response assessment at a very early stage after therapy to determine the further therapeutic approach. In order to achieve this goal, response assessment during combination therapy faces a specific challenge: on the one hand, as shown in this and previous studies, enhancement-independent criteria based exclusively on tumor size or volume are not able to provide reliable response assessment early after treatment [1]. On the other hand, enhancement-based criteria that are generally better suited for an early response assessment depend on the contrast being distributed by the vasculature and its properties (e.g. morphology, perfusion and permeability). With those being the primary site of action for bevacizumab, the key question determining the feasibility of early response assessment in combination therapy was, whether the changes caused by bevacizumab inhibit response assessment by qEASL. Thus, it can be deduced by the result of this study, that changes induced by bevacizumab may, in fact, affect the vasculature and blood supply, but do not compromise the validity of qEASL. This study does not investigate what causes qEASL to remain a reliable biomarker for survival prediction.

Until now, bevacizumab studies have used RECIST, EASL, subjective enhancement estimation and diagnostic angiography for response assessment [7, 12, 13]. Previous studies on HCC and TACE have found that the uni-dimensional and bi-dimensional criteria are insufficient for response assessment this early after treatment [1]. Our study reflects this result, moreover, some of these criteria counter-intuitively show a reversed HR, which translates into patients classified as responders dying earlier than those classified as non-responders. This reversal of HR has been demonstrated for EASL in patients with HCC before [1].

Uni-dimensional and bi-dimensional criteria work best in continuously and homogeneously enhancing tumors with clearly defined borders and an approximately ellipsoid shape. The poor performance and inter-reader agreement of these methods in the present study, which exceed the variability in these criteria exhibited in other studies, are due to the early imaging time point as well as the characteristics of the patient group [1]. Specifically, they typically demonstrate highly pathologic livers and advanced stage tumors with irregular growth, vessel infiltration, ill-defined borders and non-homogeneous enhancement. Additionally, TACE therapy itself may compromise the effectiveness of these criteria by physiologically affecting tumors in a manner which reduces their morphological regularity and the homogeneity of their enhancement patterns with minimal change in tumor size [1].

In contrast, qEASL avoids arbitrariness by taking into account full 3D volumetric information, and precludes the difficulties posed by non-homogeneous enhancement patterns (through volumetric measurement of enhancement). It also increases robustness and reproducibility by subtracting the registered pre-contrast image from the arterial phase image and setting a lesion-specific threshold for tumor enhancement, hence removing background enhancement contribution, and mitigating variances introduced by segmentation [10]. This study (among others) demonstrates the high inter-reader agreement achieved by qEASL [19]. This criterion is also applicable in cases evading certain uni-dimensional and bi-dimensional measurements, like RECIST, mRECIST, WHO and EASL. The process of qEASL measurement has been streamlined in semi-automated software, which enables its time-efficient calculation [8].

The inclusion of a control group receiving TACE without bevacizumab, individually matched with patients from the combination of TACE and bevacizumab group according to parameters influencing response and survival, make this comparison more robust and conclusive. 2:1 matching was used to reduce statistic fluctuations due to small sample size, since the patient number for controls was not as restricted as for the bevacizumab and TACE group. The consistency check showed significance which is consistent with previous publications. Below the significance level, the p-value was higher than the one of the 2:1 matched control group, which is consistent with the lower patient number.

Selection bias that could have risen from ability or willingness to consent was avoided by the selection of control patients from a close time interval. This ensured all other factors remained constant, even up to the clinician treating both groups. In contrast to previous studies, the time from follow-up imaging to death was counted as OS instead of the time from TACE to death, since the prediction is based on the follow-up imaging and therefore

cannot predict a time interval that has already passed. There were no events during the interval.

There are some limitations for this study. Some bias could be introduced because our work was a retrospective study and not a randomized controlled prospective study. Four of the fourteen patients in the combination therapy group had received TACE prior to the study, whereas the patients in the control group were all TACE naïve. Also, selecting the patients for the control arm on the basis of the presence of follow-up imaging could induce some selection bias. The number of patients enrolled in this study was low (mostly due to the limited number of patients who receive bevacizumab in the first place), leaving it more open to bias based on statistical fluctuations. For example, the apparent difference in OS of the treatment groups that one could conclude from the median, in fact, is an artefact caused the median being one value in a discreet distribution of a small sample. Looking at the standard deviation, the confidence intervals and the entirety of the survival data, it is revealed that the OS is actually very similar.

In conclusion, the anti-angiogenic action of bevacizumab does not compromise the effectiveness of qEASL as a criterion for response measurement at an early time point during treatment. Although bevacizumab may have a major impact on vascular morphology and function, as well as perfusion and vascular permeability and may therefore even change imaging parameters, our study demonstrates that it neither prevents nor impedes response assessment by qEASL. Furthermore it does not reduce its accuracy. With new aspects of potential antiangiogenic therapy application coming up, future trials will need to rely on solid early assessment to find the most effective bevacizumab administration while minimizing undesirable effects [20]. qEASL can provide quick and reliable detection of therapeutic effects and therefore can contribute to delineate the subset of patients who benefit the most from combined TACE and antiangiogenic therapy.

Conclusions

Systemic anti-angiogenic therapy with bevacizumab does not impede response assessment after TACE by qEASL criteria at an early time point. qEASL can therefore contribute to clinical decision making and to assess therapeutic efficacy in clinical trials.

Abbreviations

TACE	Transarterial Chemoembolization
cTACE	conventional Transarterial Chemoembolization
HCC	hepatocellular carcinoma
EASL	European Association for the Study of the Liver Guidelines
qEASL	3D quantitative European Association for the Study of the Liver criteria
BCLC	Barcelona Clinic Liver Cancer staging classification
RECIST	Response Evaluation Criteria in Solid Tumors

mRECIST	modified Response Evaluation Criteria in Solid Tumors
WHO	World Health Organization
OS	Overall Survival
VEGF	vascular endothelial growth factor
ECOG	Eastern Cooperative Oncology Group score
ROI	region of interest
Bev	Bevacizumab
SD	Standard Deviation
HKLC	Hong Kong Liver Cancer Stage
NASH	Nonalcoholic Steatohepatitis
INR	International Normalized Ratio
HR	Hazard Ratio
CI	Confidence Interval

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Highlights

- Early Quantitative evaluation after TACE with bevacizumab is feasible and reliable.
- The induced vasculature changes do not compromise quantitative response assessment.
- Non 3D-based criteria failed to assess response at an early time point.

Fig 1.
Flowchart of inclusion and matching of the control group.

Fig 2.

Visualization of the qEASL method. The top row shows the arterial phase MRI before and after TACE. The middle Row shows the 3 D segmentation mask that contains the whole tumor volume and the bottom row shows the ROI which is used to determine the threshold for tumor enhancement next to the color map that represents tumor viability and is based on this threshold and the subtraction image (arterial – pre contrast T1). Blue represents enhancement below the threshold and is considered non-viable tumor, whereas green to red stand for different degrees of tumor enhancement (with red representing the highest degree

of enhancement). In this case we see a 79% decrease in percentage-based qEASL after TACE therapy.

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Fig 3.

Visualization of the measurements for the various response criteria and their survival prediction capability for the combination therapy group. Non-enhancement based criteria (RECIST and WHO) classifies none of the patients as responders and therefore shows no separation. Non 3 D enhancement based criteria (mRECIST and EASL) were not able to classify all patients due to very heterogeneous enhancement.

Fig 4.

Overall Survival in the combination therapy group and the control group stratified by the response indicated by percentage-based qEASL of the largest target lesion. There is no significant difference found in the capability of percentage-based qEASL to predict survival ($p=0.749$) between the treatment groups.

Table 1

Patient characteristics for each treatment group with p – Values reflecting potentially significant differences between the treatment groups.

Treatment group		Bev ¹ & TACE ²	TACE ² only	p-Value
Number of Patients		14	28	
Age	Mean in years $\pm$ SD ³	61.8 $\pm$ 13.7	63.7 $\pm$ 9.9	0,653
	Range	31.3 – 84.7	46.6 – 81.8	
Gender	male	11 (79)	22 (79)	1,000
	female	3 (21)	6 (21)	
Ethnicity	Caucasian	9 (64)	18 (64)	
	African American	3 (21)	4 (14)	0,423
	Asian/Pacific Islander	2 (14)	3 (11)	
	Other	1 (7)	3 (11)	
Number of Tumors	1	4 (29)	9 (32)	0,449
	2	2 (14)	2 (7)	
	3	3 (21)	2 (7)	
	>3	5 (36)	15 (54)	
Tumor Diameter	Mean $\pm$ SD ²	9.1 $\pm$ 5.5	9.1 $\pm$ 4.4	0,998
	< 5 cm	4 (29)	5 (18)	0,722
	5 cm	6 (43)	13 (46)	
	10 cm	4 (29)	10 (36)	
ECOG Score ⁴	0	8 (57)	17 (61)	0,824
	1	6 (43)	11 (39)	
Child-Pugh Score	A	9 (64)	18 (64)	1,000
	B	5 (36)	10 (36)	
	C	0 (0)	0 (0)	
BCLC Stage ⁵	A	1 (7)	2 (7)	0,627
	B	4 (29)	8 (29)	
	C	9 (64)	18 (64)	
HKLC Stage ⁶	I	2 (14)	4 (14)	0,851
	II	1 (7)	2 (7)	
	III	10 (71)	20 (71)	
	IV	2 (14)	4 (14)	
Cirrhosis		10 (71)	18 (64)	0,641
Portal Vein Thrombosis		5 (36)	8 (29)	0,639
Extrahepatic Disease		2 (14)	1 (4)	0,220
Alpha Fetoprotein	10 ng/mL	4 (29)	18 (64)	0,805
	> 10 ng/mL	10 (71)	10 (36)	
Disease Origin		5 (36)	5 (18)	0,209

Treatment group		Bev ¹ & TACE ²	TACE ² only	p-Value
	Hepatitis C	6 (43)	9 (32)	0,495
	Alcohol	2 (14)	11 (39)	0,085
	NASH ⁷	0 (0)	2 (7)	0,196
Serum Bilirubin	< 2 mg/dL	10 (71)	28 (100)	0.008*
	2.0 – 3.0 mg/dL	3 (21)	0 (0)	
	> 3.0 mg/dL	1 (7)	0 (0)	
Serum Albumin	> 3.5g/dL	8 (57)	13 (46)	0,267
	2.8 – 3.5 g/dL	6 (43)	12 (43)	
	< 2.8 g/dL	0 (0)	2 (7)	
INR ⁸	< 1.7	14 (100)	28 (1)	—
	1.7 – 2.2	0 (0)	0 (0)	
	> 2.2	0 (0)	0 (0)	
Ascites	negative	10 (71)	16 (57)	0,491
	mild	4 (29)	11 (39)	
	moderate	0 (0)	1 (4)	
Encephalopathy	negative	11 (79)	27 (96)	0,072
	Grade I – II	3 (21)	1 (4)	

* significant value

¹ Bevacizumab

² Transarterial Chemoembolization

³ Standard Deviation

⁴ Co-operative Oncology Group Score

⁵ Barcelona Clinic Liver Cancer Stage

⁶ Hong Kong Liver Cancer Stage

⁷ Nonalcoholic Steatohepatitis

⁸ International Normalized Ratio

Unless indicated, percentages in parenthesis and absolute numbers in front of parenthesis

Table 2

Patient classification by various response criteria with their corresponding survival predictive capabilities according to univariate and multivariate analysis.

Patients		Overall Survival (OS)			Univariate Analysis			Multivariate Analysis		
Bev ¹ & TA CE ²	TA CE ² only	Bev ¹ & TAC E ²	TACE ² only		Bev ¹ & TACE ²	TACE ² only		Bev ¹ & TACE ²	TACE ² only	
Number of Patients (%)				Median OS ³ ± SD ⁴ (95% CI ⁵)	P - Value	HR ⁶ (95% CI ⁵)	P - Value	HR ⁶ (95% CI ⁵)	P - Value	HR ⁶ (95% CI ⁵)
Responders	0 (0.0)	0 (0.0)	—	—	—	—	—	—	—	—
RECIST ⁷										
Non-Responders	14 (10.0)	28 (100.0)	16.7 ± 27.6 (0 – 35.1)	13.8 ± 29.0 (9.8 – 19.6)	—	—	—	—	—	—
Responders	5 (35.7)	8 (28.6)	23.5 ± 13.7 (0 – 65.1)	12.7 ± 28.3 (10.1 – 14.6)	0.472	1	0.423	1	0.132	1
mRECIST ⁸										
Non-Responders	7 (50.0)	14 (50.0)	23.1 ± 36.1 (0 – —)	15.4 ± 29.5 (2.7 – 28.3)	0.6 (0.2 – 2.2)	—	—	0.7 (0.3 – 1.7)	2.5 (0.3 – 24.6)	0.4 (0.1 – 1.4)
not measurable	2 (14.3)	6 (21.4)	8.2 ± 3.0 (0 – 35.3)	9.7 ± 33.8 (0 – 17.8)	—	—	—	—	—	—
Responders	0 (0.0)	1	—	15.5 no distribution	—	—	0.883	1	—	0.210
WHO ⁹										
Non-Responders	14 (10.0)	(3.6) 27 (96.4)	16.7 ± 27.6 (0 – 35.1)	13.0 ± 29.5 (9.9 – 19.5)	—	—	—	0.9 (0.1 – 6.5)	—	0.2 (0.0 – 2.5)
Responders	9 (64.3)	8 (28.6)	25.1 ± 31.8	12.7 ± 28.4 (10.1 – 14.6)	0.100	1	0.353	1	0.133	1
EASL ¹⁰										

Patients		Overall Survival (OS)		Univariate Analysis		Multivariate Analysis			
Bev ¹ & TA CE ²	TA CE ² only	Bev ¹ & TAC E ²	TACE ² only	Bev ¹ & TACE ²	TACE ² only	Bev ¹ & TACE ²	TACE ² only	TACE ² only	
Number of Patients (%)		Median OS ³ ± SD ⁴ (95% CI ⁵)		P -Value (95% CI ⁵)	HR ⁶ (95% CI ⁵)	P -Value (95% CI ⁵)	HR ⁶ (95% CI ⁵)	HR ⁶ (95% CI ⁵)	
qEASL ^{1/1} (%)									
Non-Responders		3 (21.4)	14 (50.0)	17.7 ± 29.3 (3.9 – 36.4)	3.9 (0.8 – 19.4)	0.6 (0.3 – 1.6)	6.8 (0.6 – 81.9)	0.4 (0.1 – 1.3)	
not measurable		2 (14.3)	6 (21.4)	8.2 ± 3.0 (0 – 35.3)	—	—	—	—	
Responders		4 (28.6)	9 (32.1)	53.5 ± 34.6 (0 – 82.4)	0.046 [*] 1	0.014 1	0.006 [*] 1	0.056 1	
Non-Responders		10 (71.4)	19 (67.9)	7.8 ± 11.1 (0 – 14.3)	4.8 (1.0 – 22.8)	3.4 (1.3 – 8.9)	81.0 (3.4 – 1916.4)	2.9 (1.0 – 8.4)	
Responders		4 (28.6)	7 (25.0)	53.5 ± 34.6 (0 – 82.4)	0.046 [*] 1	0.114 1	0.006 [*] 1	0.063 1	
Non-Responders		10 (71.4)	21 (75.0)	7.8 ± 11.1 (0 – 14.3)	4.8 (1.0 – 22.8)	2.1 (0.8 – 5.5)	81.0 (3.4 – 1916.4)	2.8 (0.9 – 8.2)	
qEASL ^{1/1} (Vol)									

* significant value

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- ¹ Bevacizumab
- ² Transarterial Chemoembolization
- ³ Overall Survival in months
- ⁴ Standard Deviation
- ⁵ Confidence Interval
- ⁶ Hazard Ratio
- ⁷ Evaluation Criteria in Solid Tumors
- ⁸ modified RECIST
- ⁹ World Health Organization criteria
- ¹⁰ European Association for the Study of the Liver criteria
- ¹¹ quantitative EASL