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Comparison of Existing Response Criteria in Patients with Hepatocellular Carcinoma Treated with Transarterial Chemoembolization Using a 3D Quantitative Approach[1]

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Purpose: To compare currently available non–three-dimensional methods (Response Evaluation Criteria in Solid Tumors [RECIST], European Association for Study of the Liver [EASL], modified RECIST [mRECIST]) with three-dimensional (3D) quantitative methods of the index tumor as early response markers in predicting patient survival after initial transcatheter arterial chemoembolization (TACE).

Materials and Methods: This was a retrospective single-institution HIPAA-compliant and institutional review board–approved study. From November 2001 to November 2008, 491 consecutive patients underwent intraarterial therapy for liver cancer with either conventional TACE or TACE with drug-eluting beads. A diagnosis of hepatocellular carcinoma (HCC) was made in 290 of these patients. The response of the index tumor on pre- and post-TACE magnetic resonance images was assessed retrospectively in 78 treatment-naïve patients with HCC (63 male; mean age, 63 years ± 11 [standard deviation]). Each response assessment method (RECIST, mRECIST, EASL, and 3D methods of volumetric RECIST [vRECIST] and quantitative EASL [qEASL]) was used to classify patients as responders or nonresponders by following standard guidelines for the uni- and bidimensional measurements and by using the formula for a sphere for the 3D measurements. The Kaplan-Meier method with the log-rank test was performed for each method to evaluate its ability to help predict survival of responders and nonresponders. Uni- and multivariate Cox proportional hazard ratio models were used to identify covariates that had significant association with survival.

Results: The uni- and bidimensional measurements of RECIST (hazard ratio, 0.6; 95% confidence interval [CI]: 0.3, 1.0; $P = .09$), mRECIST (hazard ratio, 0.6; 95% CI: 0.6, 1.0; $P = .05$), and EASL (hazard ratio, 1.1; 95% CI: 0.6, 2.2; $P = .75$) did not show a significant difference in survival between responders and nonresponders, whereas vRECIST (hazard ratio, 0.6; 95% CI: 0.3, 1.0; $P = .04$), qEASL (Vol) (hazard ratio, 0.5; 95% CI: 0.3, 0.9; $P = .02$), and qEASL (%) (hazard ratio, 0.3; 95% CI: 0.15, 0.60; $P < .001$) did show a significant difference between these groups.

Conclusion: The 3D-based imaging biomarkers qEASL and vRECIST were tumor response criteria that could be used to predict patient survival early after initial TACE and enabled clear identification of nonresponders.

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V.T. and M.L. contributed equally to this work.

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and it is the second most common cause of cancer-related death (1,2). Most patients in whom a diagnosis of HCC is made have intermediate- or advanced-stage disease. In these patients, local-regional therapies, such as transarterial chemoembolization (TACE), often represent the only therapeutic option according to the official treatment guidelines in both Europe and the United States (3–5). The use of early radiologic biomarkers to assess tumor response after TACE plays a fundamental role in therapeutic decisions, and although anatomic biomarker imaging methods routinely are used to evaluate tumor response, no universally accepted standard exists (6,7).

The Response Evaluation Criteria in Solid Tumors (RECIST) system has been widely accepted in the evaluation of tumor response to systemic chemotherapy (8,9). However, most intraarterial therapies involve embolization to induce tumor infarction, which leads to tissue necrosis without immediate effects on tumor size (10). The deficiencies of RECIST criteria in assessing tumor response after intraarterial therapy prompted the development of a more suitable approach (3,11–14). As a consequence, the European Association for Study of the Liver (EASL) guidelines were introduced and included the component of tumor enhancement as an independent imaging biomarker. EASL expresses the relative change in the bidimensional amount of enhancing tumor tissue after treatment, thus reflecting the extent of necrosis caused by the treatment (15). More recently, modified RECIST (mRECIST) criteria were proposed, with the goal of improving EASL guidelines (11,12). This method adopted a single long-axis measurement of enhancing tumor tissue. However, in practice, only a minority of tumors fit the morphologic preconditions required by the technical mRECIST guidelines, thus hampering the practical value of this approach. Nevertheless, both EASL and mRECIST methods have demonstrated superior efficacy in the assessment of treatment responses and in the prediction of survival outcomes compared with RECIST guidelines in patients with HCC (11–14). However, the ability to predict patient survival with EASL and mRECIST methods is reliable only 2 months after TACE and only 3 months after TACE with sorafenib, thereby preventing treatment decisions from being made sooner in the course of treatment (14,16).

By their nature, current one- and two-dimensional measurement methods are limited by high inter- and intraobserver variability (17–21). Furthermore, they are surrogates of the overall tumor volume and do not reflect its actual extent (22,23). The advent of new automated and semiautomated tumor segmentation methods has contributed to the shift away from one- and two-dimensional methods toward three-dimensional (3D) quantitative image analysis (24–26). Initial works established the feasibility and accuracy of 3D quantitative enhancement-based analysis to assess liver tumors after local-regional therapy (27,28).

The purpose of our study was to compare currently available non-3D methods (RECIST, EASL, mRECIST) with 3D quantitative methods of the index tumor as early response markers in the prediction of patient survival after initial TACE.

Advances in Knowledge

- Three-dimensional (3D) quantitative tumor response methods (volumetric Response Evaluation Criteria in Solid Tumors [RECIST] and quantitative European Association for Study of the Liver [EASL] guidelines) were early response markers that could be used to predict survival after initial transarterial chemoembolization (TACE) and enabled clear identification of responders and nonresponders in terms of median overall survival.
- The non–3D-based imaging biomarkers of RECIST, modified RECIST, and EASL guidelines did not enable prediction of patient survival at an early time point.

Implication for Patient Care

- The 3D quantitative methods enable early identification of nonresponders to TACE; thus, treatment decisions can be made sooner.

Materials and Methods

One author (M.L.) is a Philips Research North America employee. Another author (J.F.G.) received a grant from Philips Healthcare. The data and information submitted for publication were controlled by the remaining authors (V.T., R.D., H.Y., H.L., J.C., M.C., Z.W., C.F., J.S., M.M., and T.P.), who had no conflicts of interest.

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Abbreviations:
CE = contrast material enhanced
EASL = European Association for Study of the Liver
HCC = hepatocellular carcinoma
mRECIST = modified RECIST
OS = overall survival
qEASL = quantitative EASL
qEASL (%) = enhancing tumor percentage
qEASL (Vol) = enhancing tumor volume
RECIST = Response Evaluation Criteria in Solid Tumors
TACE = transarterial chemoembolization
3D = three-dimensional
vRECIST = volumetric RECIST

Author contributions:
Guarantor of integrity of entire study, J.F.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, V.T., M.L., R.D., H.Y., J.C., M.C., J.F.G.; clinical studies, V.T., M.L., R.D., H.L., J.C., M.C., Z.W., J.F.G.; statistical analysis, V.T., M.L., M.C., C.F., J.H.S., M.G.M., T.P., J.F.G.; and manuscript editing, V.T., M.L., R.D., H.Y., J.C., M.C., C.F., J.H.S., T.P., J.F.G.

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Conflicts of interest are listed at the end of this article.

Patient Selection and Data Collection

This was a retrospective single-institution Health Insurance Portability and Accountability Act–compliant and institutional review board–approved study. The design of the study was in agreement with the Standards for Reporting of Diagnostic Accuracy guidelines. From November 2001 to November 2008, 491 consecutive patients underwent intraarterial therapy for liver cancer. A diagnosis of HCC was made in 290 of these patients with cross-sectional dynamic imaging (multidetector computed tomography [CT]/contrast material–enhanced [CE] magnetic resonance [MR] imaging) or biopsy according to EASL or American Association for the Study of Liver Diseases guidelines (3,5,15). From this group, 78 treatment-naïve patients who were undergoing first TACE (conventional TACE or TACE with drug-eluting beads) and who had readily available CE MR images obtained 4–6 weeks before and 4–6 weeks after therapy were included in the study. A patient flowchart with exclusion criteria is shown in Figure 1. Baseline laboratory values, demographics, and pre- and posttreatment clinical and imaging data were analyzed. The observation time ended on February 1, 2013. The study endpoint was overall survival (OS).

Figure 1

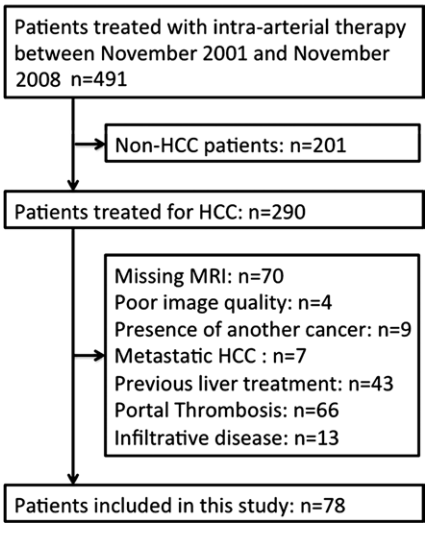


Figure 1: Flowchart shows patient selection criteria.

TACE

A multidisciplinary liver tumor board determined indications for TACE treatment. One interventional radiologist (J.F.G., 18 years of experience) performed all TACE procedures for the entire cohort of patients by using a consistent approach reported elsewhere (29). Briefly, for conventional TACE, a mixture of ethiodized oil (Lipiodol; Guerbet, Aulney-sous-Bois, France), doxorubicin (Adriamycin; Pharmacia & Upjohn, Kalamazoo, Mich), mitomycin-C (Bedford Laboratories, Bedford, Ohio), and cisplatin (Bristol-Myers Squibb, Princeton, NJ) was injected in the hepatic arterial vasculature through a selectively to superselectively advanced microcatheter. This was followed by injection of up to 4 mL of 100–300-μm microsphere particles (Embosphere; Biosphere Medical, Boston, Mass). For TACE with drug-eluting beads, patients received 2 mL of 100–300-μm-diameter microsphere particles (LC Beads; BioCompatibles, Surrey, England) loaded with 50 mg of doxorubicin hydrochloride (25 mg/mL) and mixed with nonionic contrast material (300 mg of iodine per milliliter, Oxilan; Guerbet, Bloomington, Ind). Repeat TACE was performed on demand every 6–8 weeks if enhancing tumor tissue was evident on sequential CE MR images.

MR Imaging Technique

All patients underwent a standardized liver imaging protocol. MR imaging was performed with a 1.5-T MR imager (Magnetom Avanto; Siemens, Erlangen, Germany) by using a phased-array torso coil. The protocol included breath-hold unenhanced and contrast-enhanced (0.1 mmol of intravenous gadopentetate per kilogram of body weight, Magnevist; Bayer, Wayne, NJ) T1-weighted 3D fat-suppressed spoiled gradient-echo imaging (repetition time msec/echo time msec, 5.77/2.77; field of view, 320–400 mm; matrix, 192 × 160; section thickness, 2.5 mm; receiver bandwidth, 64 kHz; flip angle, 10°) in the hepatic arterial (20 seconds), portal venous (70 seconds), and delayed (180 seconds) phases.

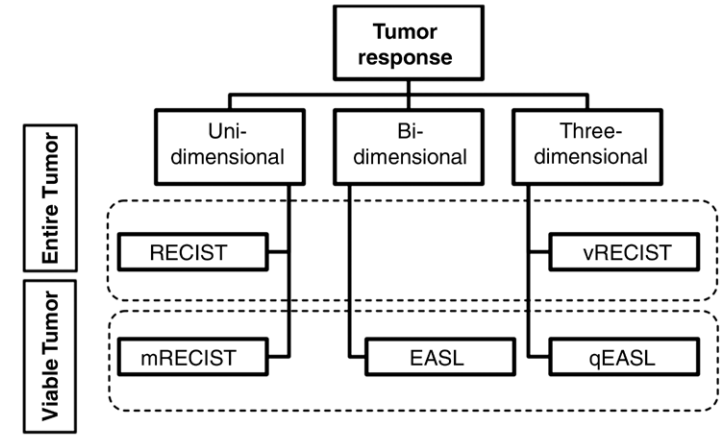
Tumor Response Assessment

Tumor response assessment was performed independently by two radiologists (R.D., H.Y.; 7 and 13 years of experience, respectively) who did not perform the TACE procedures and who were blinded to patient records and outcomes. Their results were averaged. Assessment was performed by comparing pre- and post-TACE CE MR images. Treatment response was assessed on arterial phase CE MR images by using RECIST, mRECIST, EASL, volumetric RECIST [vRECIST], and quantitative EASL (qEASL) (assessing both volume and percentage) methods. The primary index tumor was evaluated, and this was defined as the largest target tumor that was considered to be the most appropriate target for the first TACE session (30,31). The percentage of tumor change (TC) was calculated for all assessment methods with the following equation:

$$\mathrm{TC} = \frac{(M_{\mathrm{post}} - M_{\mathrm{pre}})}{M_{\mathrm{pre}}} \times 100\,,$$

where M_{pre} was the baseline tumor measurement at pre-TACE CE MR imaging, and M_{post} was the tumor measurement at follow-up CE MR imaging. Patients were classified as responders or nonresponders on the basis of the degree of tumor change (Fig 2). For the RECIST and mRECIST methods, patients with a decrease of 30% or more were considered responders; for the EASL method, those with a decrease of 50% or more were considered responders (32,33). Because of the absence of guidelines for volumetric tumor response criteria, we selected the same cutoff values that are currently used with RECIST and mRECIST methods for the vRECIST and qEASL methods to unify and simplify response assessment in the clinical setting. Thus, by using the formula $V = 4/3\pi r^3$, where V is the volume, r is the radius, and π is the mathematical constant representing the ratio of a

Figure 2



Tumor Assessment Methods	Calculation of Objective Tumor Response
RECIST	R: ≥ 30% decrease NR: R criteria not met or new lesion(s)
mRECIST	R: ≥ 30% decrease NR: R criteria not met or new lesion(s)
EASL	R: ≥ 50% decrease NR: R criteria not met or new lesion(s)
vRECIST	R: ≥ 65% decrease NR: R criteria not met or new lesion(s)
qEASL	R: ≥ 65% decrease NR: R criteria not met or new lesion(s)

Figure 2: Flowchart shows radiologic response methods used to assess the effects of HCC treatment with TACE.

circle's circumference to its diameter, a decrease of 30% defining responders with the unidimensional RECIST and mRECIST guidelines corresponds to a decrease of approximately 65% of tumor volume (32,33).

vRECIST and qEASL Calculation

Like the one- and two-dimensional measurements described previously, the two observers (R.D., H.Y.) independently performed (results averaged) 3D quantitative tumor assessments using an in-house software prototype (Medisys; Philips Research, Suresnes, France) as described in previous works (27). Briefly, the 3D tumor assessment software is based on non-Euclidean geometry and theory of radial basis functions for a semiautomated segmentation of objects with straight edges and corners. It is a fully interactive process that allows the user to define an initial control point and to expand the volume in 3D by clicking the mouse and dragging the cursor towards the tumor boundary. This system permits user input and corrections at all steps of the process (34,35). Semiautomatic 3D tumor segmentation was used to directly measure the entire tumor volume (vRECIST) and the percentage and volume of the enhancing tumor (qEASL) in about 20–80 seconds per patient. To calculate 3D tumor enhancement (qEASL), the difference between unenhanced and CE MR images acquired 20 seconds after injection of contrast material was used (32). Viable tumor was defined as voxels in the 3D tumor segmentation in which enhancement was greater than 2 standard deviations of healthy liver parenchyma as defined in a 10 × 10 × 10 voxel region of interest (28,36). Enhancing tumor volume (qEASL [Vol] [in cubic centimeters]) and percentage (qEASL [%]) were obtained with the following equation:

$$\mathrm{qEASL(Vol)} = \mathrm{qEASL(\%)} \times \mathrm{vRECIST(Vol)}.$$

Subsequently, enhancing tumor volume was represented as a 3D color map on the arterial phase CE MR image (Fig 3).

Statistical Analysis

The Kolmogorov-Smirnov test was used to determine whether the measurements were normally distributed. Since all variables were not normally distributed, the Wilcoxon rank test was used to determine whether differences between pre- and post-TACE tumor measurements were significant. All tumor assessment measurements made by the two observers were averaged for the survival analysis. OS was defined as the time between the first TACE session and death (regardless of the cause of death), the last known follow-up, or the end of the observation period. Patients who crossed over to other intraarterial modalities, such as yttrium 90 radioembolization, or who underwent liver resection, liver transplantation, or radiofrequency ablation were censored at the time of the therapy change. Survival curves between responders and nonresponders were estimated with the Kaplan-Meier curve and were analyzed with the log-rank test. The Cox proportional hazards model was used to identify predictors that have a significant influence on the survival of patients and to check which methods can be used to differentiate between the survival of responders and the survival of nonresponders.

The predictive value of each response criterion was evaluated on its own (univariate analysis) and then in a multivariate analysis. In the first step, univariate Cox regression was used to assess the association of survival to each of nine clinical baseline factors: sex, age, Eastern Cooperative

Figure 3

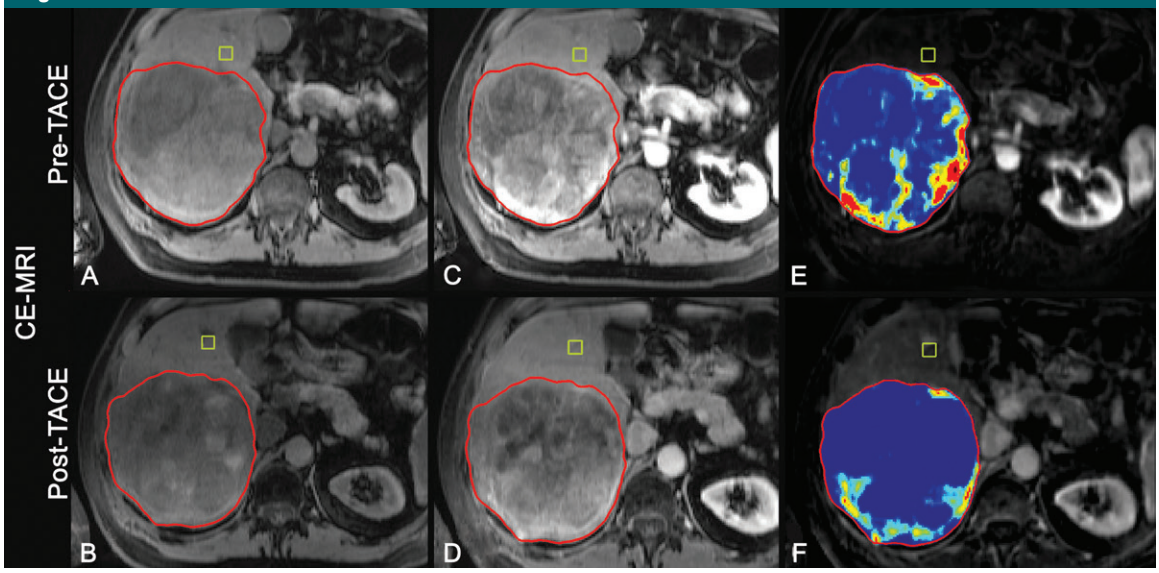


Figure 3: Images in a 66-year-old man with one HCC tumor. Before first TACE, the primary index tumor volume was 1874 cm^3, with an enhancing volume of 555 cm^3 (29.6% of the tumor volume). After treatment, the tumor volume was 1370 cm^3 (vRECIST), with an enhancing volume of 162 cm^3 (qEASL [Vol]), or 11.8% of the tumor volume (qEASL [%]). Unenhanced T1-weighted MR images obtained, *A*, before and, *B*, after TACE show background signal intensity. CE T1-weighted MR images obtained, *C*, before and, *D*, after TACE in the arterial phase. The images in *A* and *B* were subtracted from *C* and *D*, respectively, to remove background signal intensity as shown in, *E*, and, *F*, with the qEASL color map overlay before and after TACE. Red outline shows tumor segmentation, and green box represents location of the 3D region of interest used as the reference background for qEASL enhancement calculation. Note the heterogeneity of tumor enhancement, as seen in *E* and *F* and the substantial changes after TACE.

Oncology Group score, disease origin, α-fetoprotein level, Child-Pugh stage, Barcelona Clinic for Liver Cancer stage, presence of cirrhosis, tumor number, and tumor size. Most patients in the cohort had Child-Pugh class A disease. To have an adequate number of patients to discriminate for tumor size, a 5-cm cutoff (borrowed from the Milan criteria) was chosen. In the second step, the adjusted hazard ratio for a radiologic measurement was estimated via Cox regression, which simultaneously included the radiologic measurement and each clinical factor that was found to be a significant predictor of survival in the first step (37).

Median OS and the 95% confidence interval between responders and nonresponders according to the primary index tumor response were reported based on all tumor assessment methods. The assumption of proportionality was tested with the log minus log plot and was found to be satisfactory. All statistical analysis was performed with the SPSS statistical software program (SPSS, version 20.0; SPSS Chicago, Ill). A two-sided *P* value of less than .05 indicated a significant difference.

Results

Patient Characteristics

Baseline patient characteristics are shown in Table 1. Within the entire group, the mean age was 63 years ± 11 [standard deviation]. The majority of patients were male (n = 63 [81%]). Multifocal tumors were present in 47 (60%) patients. Prior to first TACE, 53 (68%) patients were classified as having Child-Pugh class A disease. The majority of patients (n = 40 [51%]) had Barcelona Clinic for Liver Cancer stage C or D disease. The majority of primary index tumors (n = 56 [72%]) were larger than 5 cm. Most patients underwent conventional TACE (n = 71 [91%]). The mean number of TACE interventions per patient was three (standard deviation, 2).

MR Imaging Analysis

The observers (R.D., H.Y.) independently evaluated 78 tumors and then calculated the average. All selected tumors were treated during the first TACE session. After TACE, mean tumor diameter (RECIST) decreased significantly from 6.3 cm ± 3.7 to 6.0 cm ± 3.5 (P = .001) and the mean tumor enhancing lengths (mRECIST) decreased from 5.6 cm ± 3.4 to 4.6 cm ± 3.3 (P < .001). The mean area of tumor enhancement (EASL) decreased from 30.6 cm^2 ± 37.7 to 20.4 cm^2 ± 32.8 (P < .001). The mean tumor volume (vRECIST) decreased from 235 cm^3 ± 477 to 224 cm^3± 412 (P = .344). The mean percentage of enhancing tumor (qEASL [%]) decreased from 63% ± 28 to 44% ± 31 (P < .001), and the mean volume of enhancing tumor (qEASL [Vol]) decreased from 119 cm^3 ± 250 to 95 cm^3± 200 (P < .001).

Table 1

Baseline Patient Characteristics

Patient Characteristic ($n = 78$)	Finding
Age	
Mean (y)*	63 ± 11
≤60 y	33 (42)
>60 y	45 (58)
Sex	
Male	63 (81)
Female	15 (19)
ECOG score	
0	38 (49)
1	31 (40)
2	9 (11)
Method of diagnosis	
Biopsy	34 (44)
Imaging	44 (56)
Disease origin	
Alcohol abuse	16 (20)
HBV	17 (22)
HCV	32 (41)
NASH	3 (4)
Unknown	9 (12)
Cirrhosis	
Present	75 (96)
Absent	3 (4)
No. of tumors	
1	31 (40)
2	9 (11)
3	10 (13)
>3	28 (36)
α-Fetoprotein level	
Mean (ng/mL)*	6343 ± 34 835.2
≤200 ng/mL	50 (64)
>200 ng/mL	38 (36)
Child-Pugh stage	
A	53 (68)
B	22 (28)
C	3 (4)
BCLC stage	
A	15 (19)
B	23 (30)
C or D	40 (51)
Tumor diameter	
Mean (cm)*	6.3 ± 3.7
≤5 cm	22 (28)
>5 cm	56 (72)
TACE type	
TACE with drug-eluting beads	7 (9)
Conventional TACE	71 (91)
No. of TACE treatments*	3 ± 2

Table 1 (continues)

Table 1 (continued)

Baseline Patient Characteristics

Note.—Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. BCLC = Barcelona Clinic Liver Cancer, ECOG = Eastern Cooperative Oncology Group, HBV = hepatitis B virus infection, HCV = hepatitis C virus infection, NASH = nonalcoholic steatohepatitis.

* Data are mean ± standard deviation.

Survival Analysis

During the observational period, 65 (83%) patients died, five (6%) were still alive, and eight (10%) were lost to follow-up. Twelve (15%) of the patients were censored because of surgical resection ($n = 3$), orthotopic liver transplantation ($n = 7$), cryoablation ($n = 1$), or radioembolization ($n = 1$). The median OS of the entire patient population was 23 months (range, 1–90 months).

Results of uni- and multivariate analyses are shown in Table 2. Univariate analysis revealed that tumor number (specifically, more than three tumors; $P = .049$) was associated with a significant reduction in OS. The uni- and bidimensional measurements obtained with the RECIST and EASL methods did not show a significant difference in survival between responders and nonresponders for either uni- or multivariate analyses. The EASL method not only did not enable prediction of survival but also inverted nonresponders and responders (Table 2, Fig 4). The mRECIST method revealed a significant difference at univariate analysis and a clear trend at multivariate analysis; however, the latter failed to reach statistical significance (Table 2, Fig 4). On the other hand, in uni- and multivariate analyses, vRECIST, qEASL (%), and qEASL (Vol) were identified as predictors of patient survival (Table 2, Fig 5). Most notable is the strong separation of responders and nonresponders in terms of median OS for qEASL (%) (47.7 months vs 15.0 months) and qEASL (Vol) (29.7 months vs 15.5 months).

Discussion

The main finding of our study is that 3D tumor assessment methods (vRECIST and qEASL) were response criteria that could be used to predict patient survival early after the first TACE.

The goal of imaging biomarkers used to asses tumor response is to reliably identify nonresponders and, ideally, to do so early in the course of treatment to allow for potential changes in therapy. Numerous approaches, among them the Assessment for Retreatment with TACE (or ART) score, were proposed with the aim of selecting suitable candidates for follow-up treatment (6). In particular, the early identification of nonresponders has been shown to prolong OS because it provides feedback for early consideration of additional or earlier retreatments or alternative therapies (38). In this context, the role of 3D quantitative MR imaging has been explored and has shown promising results. Indeed, several works have shown the predictive value of tumor segmentation–based quantitative analysis in patients with HCC (24,25). This was also done for metastatic disease in the liver, where it was shown that the same 3D methods used in our work had improved survival prediction when compared with the one- and two-dimensional methods (32,33,39).

Conventional nonvolumetric methods used in current guidelines assume that tumor growth is symmetrical. However, liver tumors are prone to asymmetry and frequently demonstrate inhomogeneous patterns of tumor enhancement. This is especially true after local-regional therapy, when changes in tumor viability may not be uniform due to multiple tumor feeding vessels that are treated unequally. This challenges tumor assessment made by the radiologist, which is additionally limited to the selection of one representative section of the CE MR image (7). RECIST, mRECIST, and EASL methods measure only a representative portion of the tumor tissue, while vRECIST and qEASL methods include the entire tumor volume in the analysis

Table 2

Survival Analysis Based on All Tumor Assessment Methods

Predictive Response	No. of Patients*	Median Overall Survival (mo)	Univariate Analysis (responders/nonresponders only)		Multivariate Analysis (responders/nonresponders with >3 tumors)	
			Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
RECIST						
Nonresponders	54 (69)	16.4 (12.0, 28.7)	1	.362	1	.088
Responders	24 (31)	25.9 (14.8, 48.3)	0.77 (0.44, 1.35)	…	0.59 (0.33, 1.08)	…
mRECIST						
Nonresponders	43 (55)	15.5 (11.3, 26.6)	1	.030†	1	.050
Responders	35 (45)	25.9 (15.0, 47.7)	0.56 (0.33, 0.95)	…	0.59 (0.35, 1.00)	…
EASL						
Nonresponders	11 (14)	20.2 (13.2, NA)	1	.707	1	.753
Responders	67 (86)	15.8 (12.0, 29.7)	1.13 (0.58, 2.24)	…	1.12 (0.57, 2.20)	…
vRECIST						
Nonresponders	42 (54)	15.5 (11.3, 22.1)	1	.045†	1	.035†
Responders	36 (46)	26.7 (14.8, 47.7)	0.58 (0.35, 0.99)	…	0.57 (0.34, 0.96)	…
qEASL (%)						
Nonresponders	57 (73)	15.0 (11.3, 20.2)	1	<.001†	1	<.001†
Responders	21 (27)	47.7 (28.7, NA)	0.28 (0.14, 0.54)	…	0.30 (0.15, 0.60)	…
qEASL (Vol)						
Nonresponders	46 (59)	15.5 (12.2, 22.1)	1	.022†	1	.018†
Responders	32 (41)	29.7 (11.3, 52.0)	0.53 (0.30, 0.91)	…	0.51 (0.29, 0.89)	…

Note.—Unless otherwise indicated, data in parentheses are 95% confidence intervals.

* Data in parentheses are percentages.

† Significant *P* value.

and thus reflect the true extent and distribution of the tumor tissue. Indeed, the volumetric quantification of tumor volume provides a particular advantage of whole-tumor analysis regardless of the tumor morphology or enhancement pattern and is a closer approach from the standpoint of tumor biology, especially for larger tumors that often manifest with inhomogeneous enhancement patterns and hypovascular necrotic areas that would otherwise confound non-3D measurements (27). For example, the available data on the mRECIST method show a great variety of survival estimates and offer no uniform applicability (14,31,40). Our study results validate a reliable universally applicable 3D cutoff value (65% of enhancing volume reduction) for a broad morphologic variety of tumors and successfully establish 3D quantitative response criteria as a reproducible method with which to assess tumor response and identify nonresponders after TACE so that treatment decisions can be made sooner. The 3D quantitative methods used in our study have several methodologic strengths: their accuracy has been validated in a previous radiopathologic study, they are time efficient, and they provide precise volumetric tumor assessment (26,28,34,35). As opposed to fully automated segmentation methods, the semiautomatic approach allows for the dual benefit of fast software-based segmentation while allowing for manual adjustments by a radiologic reader (26).

Our results showed that the mRECIST method performed better than the RECIST and EASL methods by showing statistical significance in the univariate analysis. In the multivariate analysis, mRECIST guidelines showed a clear trend but did not reach statistical significance. This highlights the fact that despite having a better capacity to capture response to therapy when compared with the other nonvolumetric tumor response criteria, the mRECIST method remains a surrogate of the entire viable tumor volume. Moreover, as acknowledged by the panel of experts on mRECIST guidelines, 3D volumetric analysis offers a clear conceptual advantage and should be a priority of future research in patients with HCC (12).

In our study, we directly compared the ability of one-dimensional, two-dimensional, and 3D markers to help identify nonresponders after TACE. Several existing studies described the ability of specific imaging markers (mRECIST, EASL) to attain a significant separation of survival curves between responders and nonresponders, thereby validating their respective unique techniques. However, no data exist that would compare those criteria with an easily reproducible 3D technique.

Our study had some limitations. First, the retrospective design of the study constitutes a classic limitation. Second, the assessment was based only on the primary index tumor and did not include the other target

Figure 4

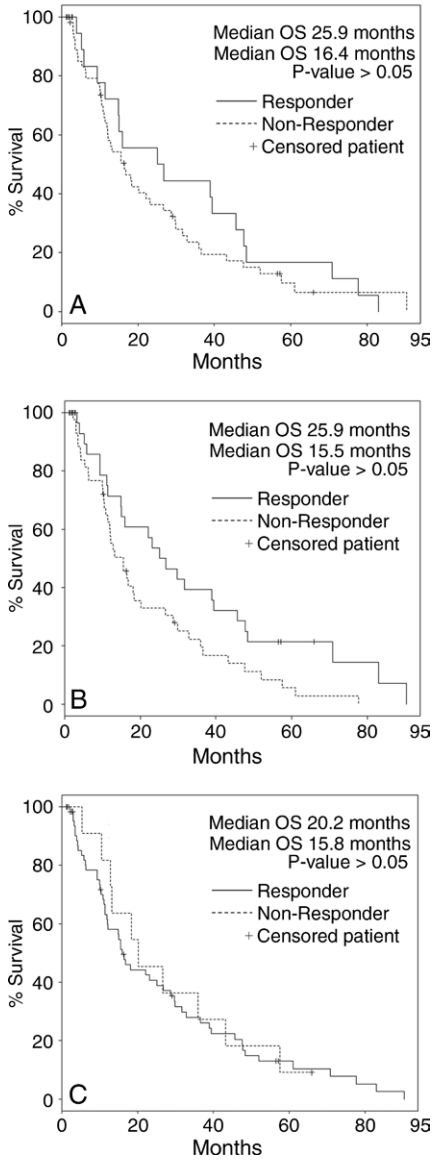


Figure 4: Kaplan-Meier curves used to compare survival between responders and nonresponders according to tumor response after first TACE as defined with the current response assessment methods of, *A*, RECIST; *B*, mRECIST; and, *C*, EASL. On the basis of log-rank test results, RECIST, mRECIST, and EASL methods did not show any differentiation between nonresponders and responders. Of note, the EASL method inverted nonresponders and responders.

Figure 5

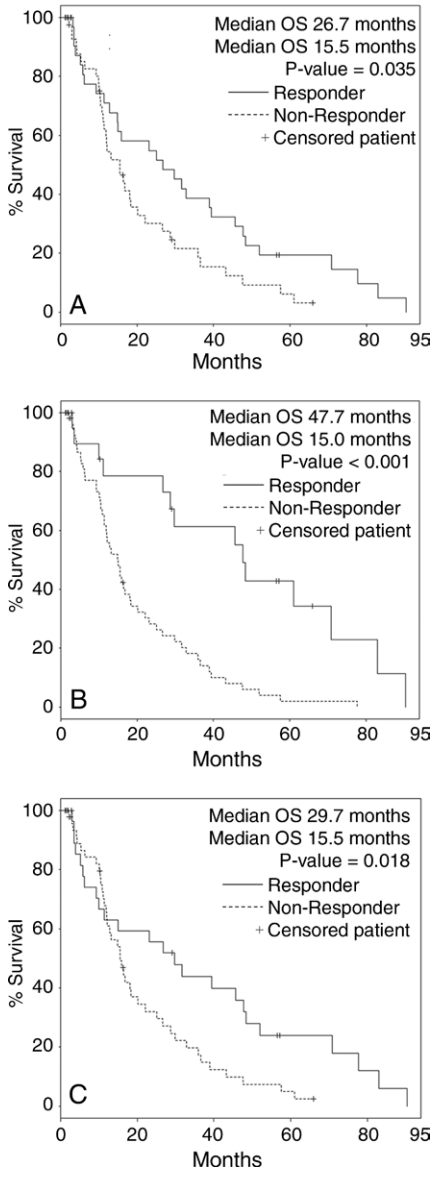


Figure 5: Kaplan-Meier curves used to compare survival between responders and nonresponders according to tumor response after first TACE as defined with the 3D response assessment methods of, *A*, vRECIST; *B*, qEASL (%); and, *C*, qEASL (Vol) methods. On the basis of log-rank test results, vRECIST, qEASL (%), and qEASL (Vol) methods showed a significant ability to help classify responders and nonresponders with accurate survival prediction.

and nontarget tumors. However, this approach has been validated in survival analysis after intraarterial therapy (30,31). While only the tumor number was identified in the univariate analysis as being associated with a significant reduction in OS, it is possible that a different tumor cutoff size (ie, a size other than 5 cm) also could have yielded a significant reduction in OS. However, optimization for cutoff size is out of the scope of our study. Additional study endpoints, such as time to disease-free survival, time to progression, and time to untreatable progression, were not evaluated and could be studied in future works. In our study, we wanted to focus on OS, which is the ultimate maker in cancer research.

In conclusion, vRECIST and qEASL methods were early response markers that could be used to predict survival after initial TACE and thus can be used as a guide for potential therapeutic changes early in the course of treatment. The inclusion of these 3D quantitative tumor response methods may provide new tumor assessment guidelines in patients with HCC who are undergoing TACE in a much better reflection of the tumor biology.

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