Imaging Biomarkers of Tumor Response in Neuroendocrine Liver Metastases Treated with Transarterial Chemoembolization: Can Enhancing Tumor Burden of the Whole Liver Help Predict Patient Survival?[1]

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Purpose: To investigate whether whole-liver enhancing tumor burden (ETB) can serve as an imaging biomarker and help predict survival better than World Health Organization (WHO), Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), and European Association for the Study of the Liver (EASL) methods in patients with multifocal, bilobar neuroendocrine liver metastases (NELM) after the first transarterial chemoembolization (TACE) procedure.

Materials and Methods: This HIPAA-compliant, institutional review board–approved retrospective study included 51 patients (mean age, 57.8 years ± 13.2; range, 13.5–85.8 years) with multifocal, bilobar NELM treated with TACE. The largest area (WHO), longest diameter (RECIST), longest enhancing diameter (mRECIST), largest enhancing area (EASL), and largest enhancing volume (ETB) were measured at baseline and after the first TACE on contrast material–enhanced magnetic resonance images. With three-dimensional software, ETB was measured as more than 2 standard deviations the signal intensity of a region of interest in normal liver. Response was assessed with WHO, RECIST, mRECIST, and EASL methods according to their respective criteria. For ETB response, a decrease in enhancement of at least 30%, 50%, and 65% was analyzed by using the Akaike information criterion. Survival analysis included Kaplan-Meier curves and Cox regressions.

Results: Treatment response occurred in 5.9% (WHO criteria), 2.0% (RECIST), 25.5% (mRECIST), and 23.5% (EASL criteria) of patients. With 30%, 50%, and 65% cutoffs, ETB response was seen in 60.8%, 39.2%, and 21.6% of patients, respectively, and was the only biomarker associated with a survival difference between responders and nonresponders (45.0 months vs 10.0 months, 84.3 months vs 16.7 months, and 85.2 months vs 21.2 months, respectively; $P < .01$ for all). The 50% cutoff provided the best survival model (hazard ratio [HR]: 0.2; 95% confidence interval [CI]: 0.1, 0.4). At multivariate analysis, ETB response was an independent predictor of survival (HR: 0.2; 95% CI: 0.1, 0.6).

Conclusion: Volumetric ETB is an early treatment response biomarker and surrogate for survival in patients with multifocal, bilobar NELM after the first TACE procedure.

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Metastatic disease to the liver develops in 67%–91% of patients with neuroendocrine tumors and substantially reduces 5-year survival rates from 60%–88% to 15%–30%. Largely owing to the diffuse nature of neuroendocrine liver metastasis (NELM), only 10%–20% of patients are eligible for resection. For patients with multifocal, bilobar NELM, embolotherapy such as transarterial chemoembolization (TACE) is the standard of care (1–5).

The two most utilized imaging response assessment systems for NELM are the Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO) criteria, which measure tumor diameters in one dimension and two dimensions, respectively (6,7). Because of the slow-growing nature of neuroendocrine tumors (5), size reductions are rarely observed after treatment including life-prolonging therapies (8,9). Tumor shrinkage is also a rare phenomenon soon after embolotherapy and not always associated with its clinical benefits (10–13).

To assess the efficacy of embolotherapy, enhancement-based assessment systems such as modified RECIST (mRECIST) (13) and European Association for the Study of the Liver (EASL) (12) were introduced. They measure one- and two-dimensional tumor enhancement, respectively. Although developed for hepatocellular carcinoma, these assessment systems have been applied to hypervascular liver metastases such as NELM (5,11,14). These criteria assume that tumors undergo symmetrical and spherical alterations in enhancement after treatment when instead tumors exhibit heterogeneous changes in enhancement and necrosis (15,16).

Volumetric measurements of tumor enhancement are more representative of tumor necrosis and have been shown to help predict survival (11,14,17,18). In general, volumetric analysis has been applied on a lesion-by-lesion basis. However, this is impractical in most patients with NELM who present with multifocal, bilobar disease (3,19) and are treated with lobar TACE. A volumetric assessment of the entire liver could be a more comprehensive biomarker for tumor response because it would eliminate the subjectivity associated with lesion-based analysis and account for tumor heterogeneity and tumor burden (2,20–22). The purpose of our study was to investigate whether whole-liver enhancing tumor burden (ETB) could serve as an early response biomarker and help predict patient survival better than WHO, RECIST, mRECIST, and EASL criteria in patients with multifocal, bilobar NELM after the first TACE procedure.

Advance in Knowledge

- In patients with multifocal, bilobar neuroendocrine liver metastases (NELM) treated with their first transarterial chemoembolization (TACE) procedure, volumetric changes in enhancing tumor burden (ETB) showed a correlation with survival (hazard ratio: 0.2; 95% confidence interval: 0.1, 0.6) and helped identify a survival difference between responders and nonresponders (45.0 months vs 10.0 months, respectively; $P < .01$); non–three-dimensional (3D) imaging biomarkers (World Health Organization, Response Evaluation Criteria in Solid Tumors [RECIST], modified RECIST, and European Association for the Study of the Liver methods) could not help differentiate responders from nonresponders on the basis of patient survival (45.0 months vs 23.3 months [$P = .6$], 45.0 months vs 30.0 months [$P = .99$], 45.0 months vs 23.3 months [$P = .9$], and 45.0 months vs 23.3 months [$P = .7$], respectively).

Implication for Patient Care

- Most patients with NELM undergoing their first TACE procedure have extensive disease burden at baseline; in such patients, volumetric ETB may serve as the ideal response assessment method given its 3D holistic nature, significant correlation with survival, high interreader reliability, and work-flow efficiency.

Materials and Methods

This retrospective, single-institution study was conducted in compliance with the Health Insurance Portability and Accountability Act and approved by the institutional review board. The requirement to obtain informed consent was waived. The study was performed with financial support from the National Institutes of Health (NIH/NCI-R01-CA160771) and Philips Healthcare. Authors who were not funded by sponsors (S.S., R.S., J.C., Y.Z., J.H.S, F.F., J.F.G, and R.D.) had full control of the data and their analysis during the study. R.A. and M.L. are employees of Philips.

Patient Population

A prospectively collected database of patients who underwent TACE from

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Abbreviations:
CI = confidence interval
EASL = European Association for the Study of the Liver
ETB = enhancing tumor burden
HR = hazard ratio
ICC = intraclass correlation coefficient
mRECIST = modified RECIST
NELM = neuroendocrine liver metastases
RECIST = Response Evaluation Criteria in Solid Tumors
ROI = region of interest
TACE = transarterial chemoembolization
3D = three-dimensional
WHO = World Health Organization

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

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

January 2000 to May 2014 was reviewed, and 246 patients with NELM were identified (23). Patients were included if they were liver-directed therapy naive, had multifocal, bilobar NELM (type II or III), and underwent contrast material–enhanced T1-weighted magnetic resonance (MR) imaging within 1 month before TACE and 3 months after TACE. Patients who had liver-directed therapy before their first TACE were excluded to avoid confounding treatment effects (n = 45). Patients with limited disease (type I) were excluded because lesion analysis would have been more applicable than whole-liver assessment (n = 42).

NELM can be divided into three growth patterns: single metastasis (type I), isolated metastatic bulk with smaller deposits involving both liver lobes (type II), and disseminated, bilobar metastatic spread with virtually no normal liver parenchyma (type III) (19). In our study, multifocal, bilobar disease included types II and III, which occur in most patients with NELM (2,3,19). Most patients were excluded because of inadequate imaging (n = 108), that is, the patient underwent computed tomography (CT), imaging was performed more than 3 months after TACE, MR imaging lacked specific sequences (axial breath-hold unenhanced and contrast-enhanced T1-weighted three-dimensional [3D] fat-suppressed spoiled gradient-echo images), there were motion artifacts, or different MR units were used before and after TACE. Excluded cases largely occurred in the first half of the study period, when CT images and longer follow-up periods were more prevalent. Patients who underwent follow-up imaging more than 3 months after TACE were excluded to provide a timely and consistent assessment of therapy response.

The final study cohort comprised 51 patients. Baseline characteristics (age, sex, ethnicity, diagnosis method, tumor cell type and grade, performance status, extrahepatic disease, portal vein thrombosis, hypovascular lesions, previous nonliver-directed treatment, concurrent somatostatin therapy, type and number of TACE procedures, duration between imaging and TACE, and number of deaths) were recorded.

TACE Procedure

A multidisciplinary tumor board determined which patients were eligible for TACE. TACE was performed in patients with NELM with unresectable hepatic-dominant disease that was symptomatic or progressive, Eastern Cooperative Oncology performance status of 0–2, and adequate hepatic, renal, and hematologic function (albumin level >2.5 g/dL, alanine and aspartate aminotransferase levels less than five times the upper limit of normal, total serum bilirubin level <3.0 mg/dL, serum creatinine level <2.0 mg/dL, platelet count ≥50 000/mm^3, international normalized ratio ≤1.5, and at least partial patency of the portal venous system).

TACE was performed by an interventional radiologist (J.F.G., with 18 years of experience) using a standardized approach (24,25). Briefly, the common femoral artery was accessed by using the Seldinger technique. With a 5.0-F glide catheter (Sim1; Terumo, Tokyo, Japan), the celiac axis was selected. After the hepatic arterial anatomy and portal venous patency were determined, a microcatheter was advanced to deliver the chemotherapy in a lobar fashion. For conventional TACE, an emulsion of doxorubicin (50 mg) and mitomycin C (10 mg) in a 1:1 mixture with iodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) was infused and followed by 100–300-μm microspheres (Embospheres; Merit, South Jordan, Utah). For TACE with drug-eluting beads, a 4-mL solution of 100–300-μm DC Bead (Biocompatibles/BTG, Surrey, England) was loaded with up to 100 mg of doxorubicin hydrochloride (25 mg/mL) and mixed with 4 mL of Oxilan (Guerbet, Bloomington, Ind; 300 mg iodine per milliliter). The technical end point was when the intra-arterial contrast material column visible at the tip of the microcatheter cleared within two to five heartbeats; complete occlusion was avoided to maintain arterial patency for repeat treatment (20,24,25). The first TACE was delivered to the right hepatic lobe nonselectively because it typically contains most of the tumor burden in patients with multifocal, bilobar NELM.

MR Imaging Protocol

Patients underwent MR imaging within 1 month before TACE and 1–3 months after TACE with use of a 1.5-T unit (Magnetom Avanto; Siemens, Forchheim, Germany) equipped with a phased-array torso coil. A standard liver protocol with the same imaging parameters before and after TACE was used to ensure consistency in image acquisition and timing. The protocol included axial breath-hold unenhanced and intravenous contrast-enhanced (Omniscan, GE Healthcare, Princeton, NJ; 0.1 mmol/kg of body weight) T1-weighted 3D fat-suppressed spoiled gradient-echo imaging (repetition time msec/echo time msec, 5.1/1.2; field of view, 320–400 mm; matrix size, 192 × 160; section thickness, 4–6 mm; receiver bandwidth, 64 kHz; flip angle, 15°) in the arterial, portal venous, and delayed phases (20, 70, and 180 seconds after intravenous contrast material administration, respectively; a fixed time-delay technique was used).

MR Image Analysis

Two readers (R.D. and S.S., with 9 and 2 years of experience in abdominal imaging, respectively) performed the image analysis independently. Readers did not participate in the TACE procedures and were blinded to survival outcomes. Image analysis was performed after the first TACE procedure.

Non-3D tumor-specific imaging biomarkers.—The two largest lesions treated during the first TACE procedure were selected as index lesions. For each lesion, the longest diameter (RECIST), largest area (WHO criteria), longest enhancing diameter (mRECIST), and largest enhancing area (EASL criteria) were measured on the arterial phase of MR images before and after TACE (6,7,12,13).

ETB measurement.—ETB of the whole liver was calculated at baseline and after TACE. Although a lobar evaluation may better reflect the treatment effects of TACE, a whole-liver assessment was

Figure 1

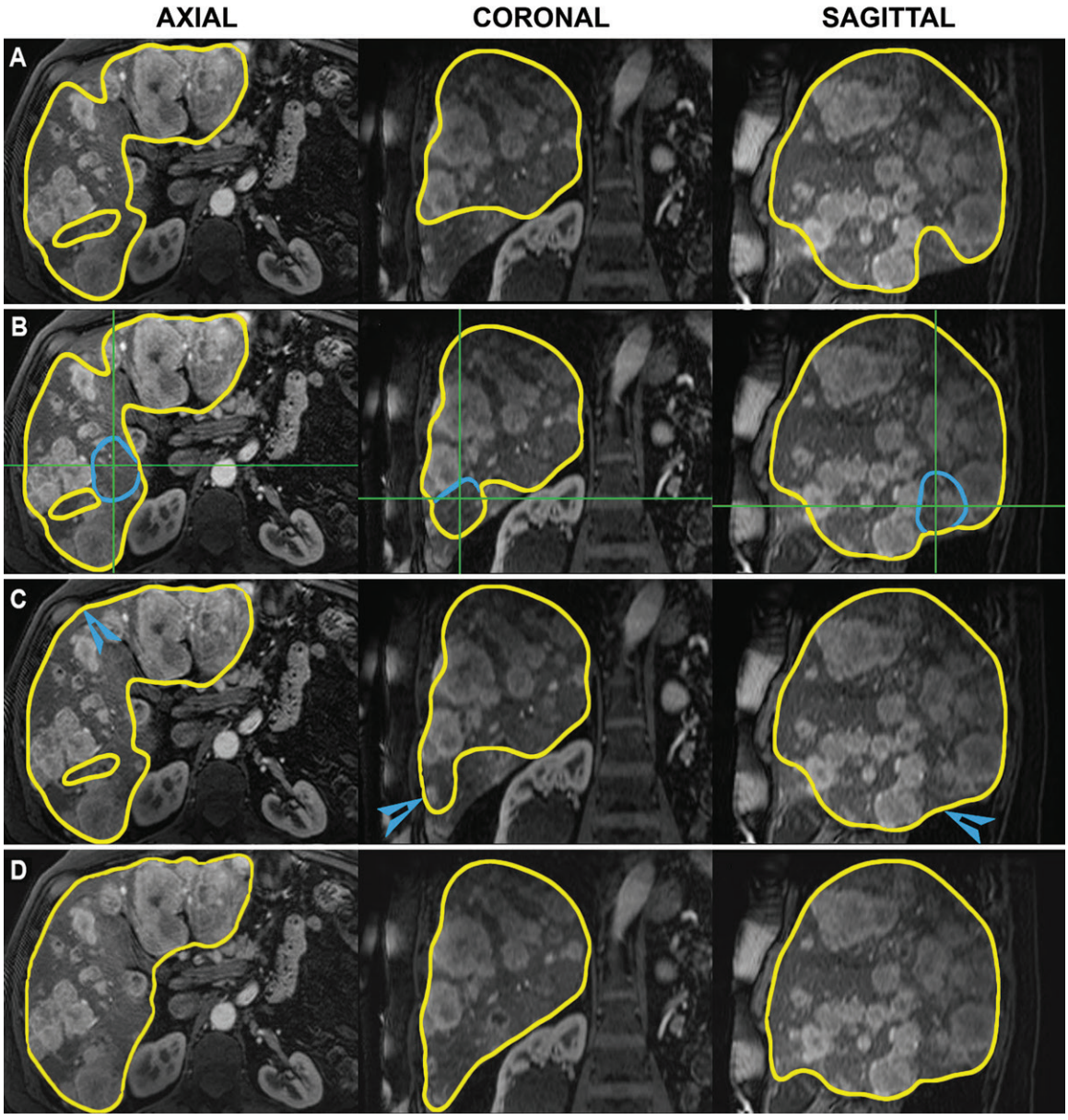

Figure 1: Whole-liver segmentation. Baseline contrast-enhanced arterial phase T1-weighted MR images in 60-year-old man with NELM in axial, coronal, and sagittal planes. *A*, Automatic segmentation produced a 3D liver segmentation mask, which was adjusted semiautomatically in control mode or contour mode. *B*, In control mode, an interactive balloon was expanded or contracted to include or exclude 3D regions. *C*, In contour mode, liver edge was identified with an arrowhead, and the software grew or shrunk the 3D liver mask accordingly. *D*, Images show adjustments made to original segmentation shown in *A*.

selected because tumor burden relates strongly to patient outcome (2,20,21) and because it can capture tumor biology. Indeed, although little to no change is expected in the untreated area (left liver lobe) between the first and the second TACE procedures because most NELM are indolent, in the cases where there is significant progression ETB would incorporate the more aggressive tumor biology.

The first step involved whole-liver 3D segmentation on the arterial phase of MR images. A prototype software (Medisys; Philips Research, Suresnes, France) segmented the liver automatically and produced a 3D segmentation mask (Fig 1, *A*). If needed, readers could revise the segmentation mask semiautomatically by expanding or contracting it around control points (Fig

1, *B*) or defining the liver contour (Fig 1, *C*) to obtain a precise segmentation (Fig 1, *D*). Liver volumes (in cubic centimeters) for each reader and the average segmentation time were recorded. Briefly, automatic liver segmentation was performed by using an anatomic liver model derived from an independent dataset of 50 T1-weighted contrast-enhanced abdominal MR images. Probability maps of the liver's location were determined by the random forest algorithm and weighted by organ atlases (26–29). The liver model then underwent implicit template deformation with a classic principal components analysis. The control point editing was based on non-Euclidean geometry and the theory of radial functions (30), and the liver contour editing relied on voxel signal intensities and an edge-detection algorithm (31). The theories underlying the prototype software (eg, regression forests for organ localization, computed organ probability maps, and implicit template deformation for segmentation) have been previously validated in multiple large imaging databases of diverse organs (26–29).

After liver segmentation, liver ETB was calculated by using a second prototype software (Medisys, Philips Research) that measures 3D enhancement by using voxel intensities. Previous validation studies of this method have reported high interreader reproducibility and radiologic-pathologic accuracy (32–35). To remove background signal, the precontrast T1-weighted MR image was subtracted from the contrast-enhanced arterial phase image (36). The 3D liver segmentation mask (obtained by using the whole-liver segmentation software) was then transposed to the subtracted images and a 0.5- or 1-cm^3 region of interest (ROI) was placed in healthy liver parenchyma for image intensity normalization (Fig 2, *A*). If the ROI had a coefficient of variation greater than 30%, the ROI was repositioned. A 0.5-cm^3 ROI was selected in cases of extensive tumor burden and limited normal liver tissue. The subtraction process and ROI placement mitigated variability between individual MR images. The software generated the volume (in cubic centimeters) of ETB by defining enhancement (viable tumor tissue) as more than 2 standard deviations of the ROI's average signal intensity (12–15) and provided a 3D color map to demonstrate nonenhancing tumor tissue (blue) and enhancing tissue (red) (Fig 2, *B* and *C*).

Imaging Response and Survival

Interreader measurements were averaged to determine the percentage decrease in WHO, RECIST, mRECIST, and EASL measurements; liver volume; and volumetric ETB after TACE and treatment response. Patients were classified as responders (complete and partial response) and nonresponders (stable and progressive disease) according to each response criteria (6,8,12,13). Because no guidelines exist for ETB, cutoff values from the current criteria were assessed and determined to be a decrease in ETB by 30% (RECIST and/or mRECIST), 50% (WHO and/or EASL), and 65% (volumetric version of RECIST and/or mRECIST by using volume = $4/3\pi r^3$, where r is the tumor radius) (7,12–14). Overall survival was calculated from the first TACE date to the death date or February 7, 2015.

Statistical Analysis

Descriptive statistics, such as means and ranges for continuous variables and frequencies and percentages for categoric variables, were used to summarize the data. To determine significant differences between continuous or categoric variables, the Student t test and χ^2 test were implemented, respectively. The two-way mixed-effects intraclass correlation (ICC) was calculated to grade interreader consistency as poor (ICC, <0.50), moderate (ICC, 0.50– 0.74), good (ICC, 0.75–0.89), or excellent (ICC, >0.90) (37). Kaplan-Meier curves were plotted and log-rank tests were performed for responders and nonresponders to determine survival differences. Imaging response and patient demographics were evaluated by using the univariate Cox proportional hazards models. Patients alive at the time of last follow-up (February 7, 2015) were censored. To compare the prognostic ability of the various ETB response cutoffs, the Akaike information criterion was calculated (38). The lower the Akaike information criterion value, the better the cutoff value. Statistically significant univariate covariates were included in the multivariate model. Tests were two tailed. $P < .05$ was considered indicative of a statistically significant difference. Statistical analysis was performed with software (R, version 3.1.1; The R Project for Statistical Computing, Vienna, Austria).

Results

Demographic Data

There were a total of 140 TACE procedures, with an average of 2.7 sessions per patient (range, one to seven sessions). The mean time (±standard deviation) between baseline imaging and the first TACE procedure was 8.2 days ± 8.7 (range, 0–31 days), and the mean time between TACE and follow-up imaging was 33.1 days ± 12.3 (range, 20–69 days). None of the patients died before the first follow-up. Patients were followed up for a mean of 2.5 years ± 2.4 (range, 0.1–9.3 years). At the last follow-up, 34 of the 51 patients (66.7%) had died. The median overall survival was 20.9 months (95% confidence interval [CI]: 12.9, 28.8). Additional baseline characteristics are summarized in Table 1.

Non-3D Tumor-specific Imaging Biomarkers

Mean baseline WHO, RECIST, mRECIST, and EASL measurements were 50.4 cm^2 ± 52.3, 9.7 cm ± 5.3, 8.0 cm ± 4.5, and 33.3 cm^2 ± 41.0, respectively, for reader 1 and 81.6 cm^2 ± 65.6, 13.0 cm ± 5.8, 11.6 cm ± 5.2, and 54.8 cm^2 ± 49.0, respectively, for reader 2. Mean follow-up WHO, RECIST, mRECIST, and EASL values were 48.0 cm^2 ± 58.9, 9.5 cm ± 5.7, 6.8 cm ± 4.9, and 27.7 cm^2 ± 40.6, respectively, for reader 1 and 63.1 cm^2 ± 41.7, 12.4 cm ± 5.9, 9.3 cm ± 5.7, and 40.3 cm^2 ± 45.7, respectively,

Figure 2

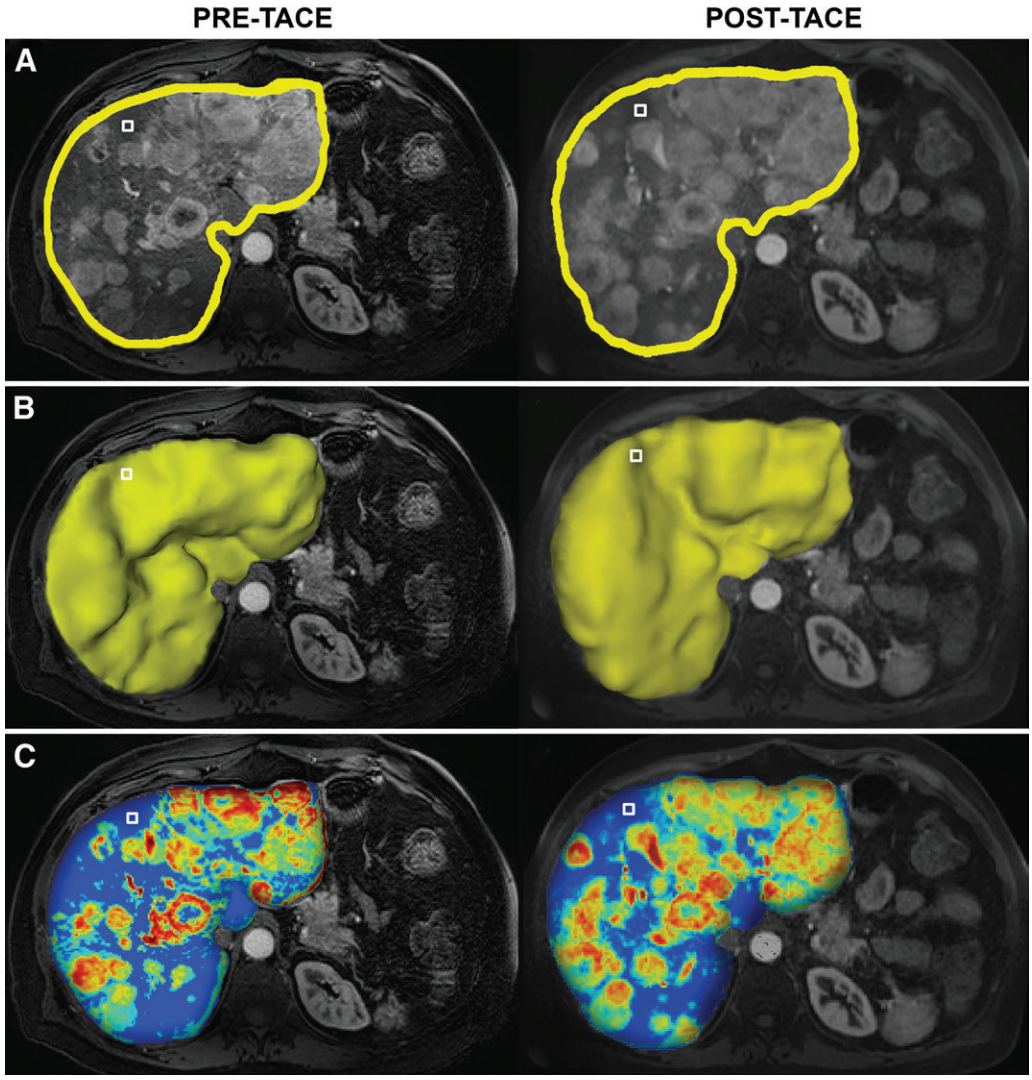

Figure 2: ETB. Pre- and post-TACE contrast-enhanced arterial phase T1-weighted MR images in 70-year-old man with NELM. A 3D ROI, depicted as white box in, *A*, liver segmentation outline and, *B*, 3D mask, was placed in normal liver tissue. *C*, On the basis of the definition of enhancement (>2 standard deviations the ROI's average signal intensity), the software automatically generated 3D color maps of liver, with red representing maximum enhancement and blue representing no enhancement.

for reader 2. Interreader agreement was good for all measurements before and after TACE except for post-TACE WHO measurements, for which there was moderate agreement (ICC = 0.8 and 0.7, respectively, for WHO; 0.8 and 0.8 for RECIST; 0.8 and 0.8 for mRECIST; and 0.8 and 0.8 for EASL, respectively; $P < .01$ for all).

After TACE, there was a significant decrease in the WHO measurement (lesion area) by 15.8%, RECIST measurement (lesion diameter) by 3.9%, mRECIST measurement (enhancing lesion diameter) by 18.3%, and EASL measurement (enhancing lesion area) by 22.8% ($P < .01$ for all). According to WHO, RECIST, mRECIST, and EASL criteria, tumor response occurred in three of the 51 patients (5.9%), one patient (2%), 13 patients (25.5%), and 12 patients (23.5%), respectively. Median overall survival between responders and nonresponders was not significantly different for any of the criteria and was, respectively, 45.0 months versus 23.3 months with WHO criteria ($P = .6$), 45.0 months versus 30.0 months with RECIST ($P = .99$), 45.0 months versus 23.3 months with mRECIST ($P = .9$), and 45.0 months versus 23.3 months with EASL criteria ($P = .7$). As such, Cox regression modeling could not be performed for non-3D tumor-specific imaging biomarkers.

Table 1

Baseline Patient Characteristics

Characteristic	No. of Patients (n = 51)
Sex	
M	28 (55)
F	23 (45)
Ethnicity	
White	35 (69)
African American	13 (25)
Other	3 (6)
Diagnosis	
Biopsy	48 (94)
Imaging	3 (6)
Cell type	
Carcinoid	19 (37)
Islet cell	21 (41)
Unknown primary	11 (22)
Tumor grade	
Well differentiated and/or low grade	30 (59)
Moderately differentiated and/or intermediate grade	2 (4)
Poorly differentiated and/or high grade	1 (2)
Unknown	18 (35)
ECOG performance status	
0	34 (67)
1	13 (25)
2	4 (8)
Hypovascular lesions	7 (13)
Portal vein thrombosis	8 (16)
Extrahepatic disease	28 (55)
Previous treatment	
Primary tumor resection	21 (41)
Liver resection	25 (49)
Therapy	
Conventional TACE	37 (73)
Drug-eluting bead TACE	14 (27)
Concurrent somatostatin treatment	9 (18)

Note.—The mean patient age was 57.8 years ± 13.2 (range, 13.5–85.8 years). Numbers in parentheses are percentages.
ECOG = Eastern Cooperative Oncology Group.

Table 2

ETB Response

Response Cutoff	Responders	Nonresponders
30%	31 (60.8)	20 (39.2)
50%	20 (39.2)	31 (60.8)
65%	11 (21.6)	40 (78.4)

Note.—Data are numbers of patients (n = 51), with percentages in parentheses.

ETB Analysis

Automatic liver segmentation took a mean of 9.2 seconds ± 0.7 and, with user adjustments required, on average, 79 seconds ± 46. Mean liver volume and ETB before TACE were 2737.3 cm^3 ± 1491.6 and 1505.5 cm^3 ± 1634.2, respectively, according to reader 1 and 2728.4 cm^3 ± 1458.0 and 1444.6 cm^3 ± 1470.4, respectively, for reader 2. After TACE, mean liver volumes and ETB were 2633.5 cm^3 ± 1487.3 and 963.8 cm^3 ± 930.4, respectively, according to reader 1 and 2637.3 cm^3 ± 1477.2 and 1019 cm^3 ± 952.8, respectively, according to reader 2. Interreader agreement was excellent for liver volumes and ETB at baseline and follow-up (ICC: 0.99 and 0.99, respectively, for liver volume and 0.93 and 0.94, respectively, for ETB; $P < .01$ for both).

After TACE, liver volume remained stable ($P = .75$), whereas ETB decreased significantly from 1550.1 cm^3 to 693.9 cm^3 ($P < .01$). Table 2 summarizes the number of responders for volumetric ETB according to the various cutoff values. All response cutoff values for ETB showed a significant survival difference between responders and nonresponders (30% cutoff: 45.0 months vs 10.0 months, respectively; 50% cutoff: 84.3 months vs 16.7 months; 65% cutoff: 85.2 months vs 21.2 months; $P < .01$ for all) (Fig 3). Tumor response, regardless of the cutoff, was associated with longer survival in univariate Cox regressions (hazard ratio [HR]: 0.2 for all, $P < .01$) (Table 3). On the basis of the Akaike information criterion, the 50% cutoff for ETB response provided the best univariate survival model (HR: 0.2; 95% CI: 0.1, 0.4). Statistically significant baseline characteristics at univariate analysis included Eastern Cooperative Oncology Group assessments status of at least 1, portal vein thrombosis, and extrahepatic disease (HR: 5.2, 95% CI: 2.4, 10.9; HR: 6.3, 95% CI: 2.6, 15.5; HR: 2.7, 95% CI: 1.3, 5.7, respectively) (Table 4). When controlled for in the multivariate survival model, ETB response with the 50% cutoff remained statistically significant (HR: 0.2; 95% CI: 0.1, 0.6) (Table 5).

Discussion

The main finding of our study is that volumetric ETB of the whole liver can be used as an early imaging biomarker for survival in patients with multifocal, bilobar NELM treated with TACE.

Radiologic response of solid tumors has gained broad acceptance as a surrogate for survival. An early assessment of response is important for timely, effective treatment decisions. Unfortunately, the accepted size-based criteria, WHO and RECIST measurements, have limited utility in both respects for patients with NELM treated with TACE. As our study and others

Figure 3

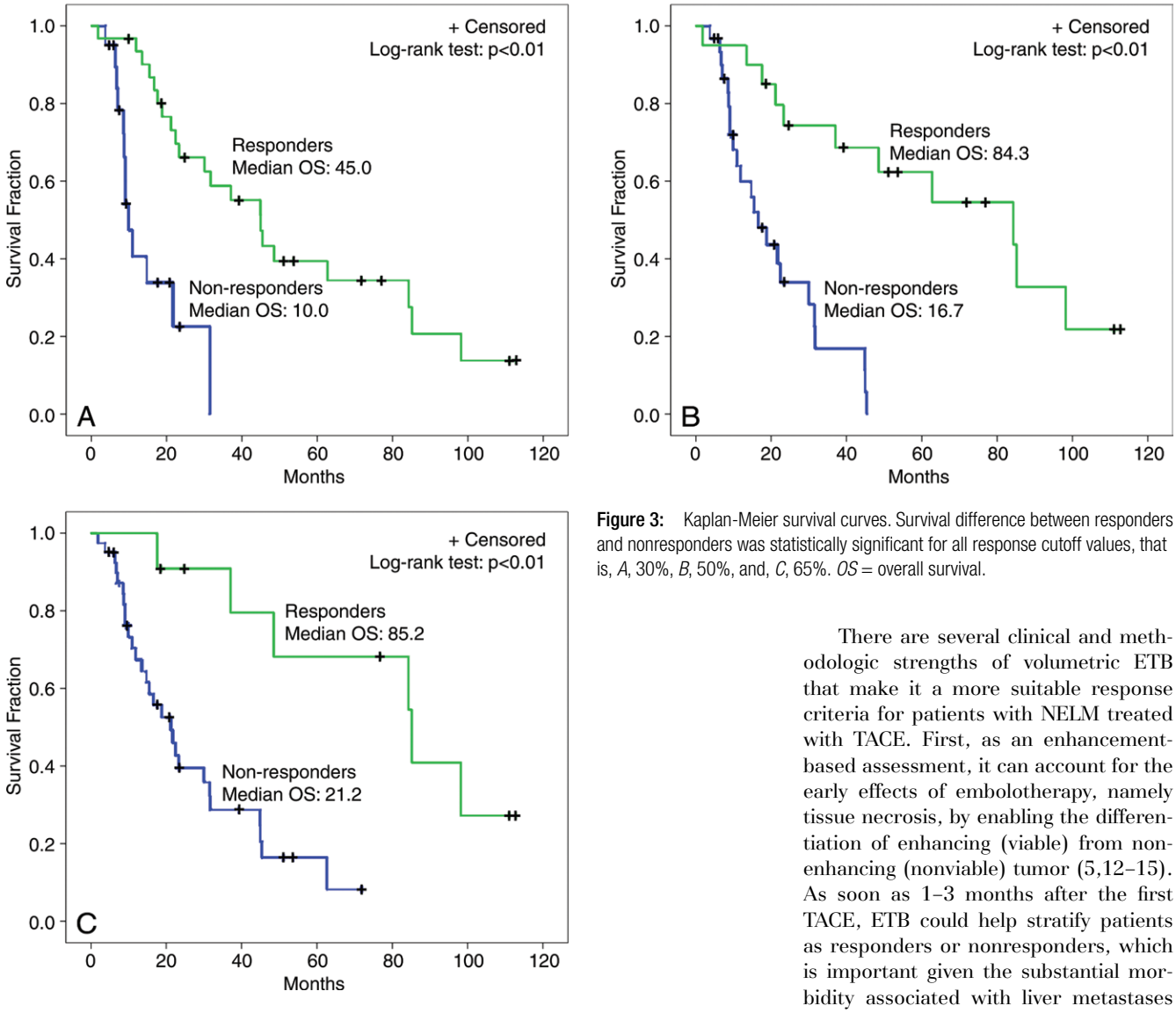

Figure 3: Kaplan-Meier survival curves. Survival difference between responders and nonresponders was statistically significant for all response cutoff values, that is, *A*, 30%, *B*, 50%, and, *C*, 65%. *OS* = overall survival.

Table 3

Univariate Survival Analysis of ETB Response

Variable	HR	95% CI	*P* Value	AIC
ETB response with 30% cutoff	0.2	0.1, 0.5	<.01	198.1
ETB response with 50% cutoff	0.2	0.1, 0.4	<.01	192.6
ETB response with 65% cutoff	0.2	0, 0.5	<.01	198.6

Note.—AIC = Akaike information criterion.

have shown, WHO and RECIST tumor response are poorly associated with survival and result in few responders because the true effect of TACE is tumor necrosis as opposed to shrinkage (10–13).

There are several clinical and methodologic strengths of volumetric ETB that make it a more suitable response criteria for patients with NELM treated with TACE. First, as an enhancement-based assessment, it can account for the early effects of embolotherapy, namely tissue necrosis, by enabling the differentiation of enhancing (viable) from nonenhancing (nonviable) tumor (5,12–15). As soon as 1–3 months after the first TACE, ETB could help stratify patients as responders or nonresponders, which is important given the substantial morbidity associated with liver metastases (19). Second, a volumetric assessment addresses the discordance between lesion diameter or area and volume of tumor tissue—a limitation associated with one- and two-dimensional enhancement-based criteria (mRECIST and EASL, respectively) (14,15,39). Both criteria examine one axial section, which often is not representative of the entire tumor and could explain why mRECIST and EASL were poor biomarkers for survival in our study and other studies (11,14,17,18). Volumetric enhancement–based criteria, however, measure the entire tumor and can account for the

Table 4

Univariate Survival Analysis of Baseline Demographics

Variable	Median OS (mo)	95% CI	HR	95% CI	*P* Value
Treatment age					
<65 y	31.4	18.6, 44.3	1	…	.08
≥65 y	15.4	3.9, 26.9	1.9	0.9, 3.7	…
Sex					
M	21.7	0, 50.6	1	…	.23
F	31.4	19.6, 43.3	0.7	0.3, 1.3	…
Ethnicity					
White	21.7	13.2, 30.2	1	…	.17
African American	48.5	10.4, 86.7	0.5	0.2, 1.2	…
Other	85.2	41.1, 129.3	0.2	0.1, 1.8	…
Tumor type					
Unknown primary	85.2	0, 225.6	1	…	.30
Carcinoid	22.4	16.1, 28.7	2.2	0.8, 6.2	…
Islet cell	30.1	16.8, 43.3	1.6	0.6, 4.4	…
Tumor grade					
Well differentiated	21.7	5.6, 37.8	1	…	.55
Non–well differentiated	7.1	2.7, 16.9	1.4	0.2, 11.0	…
Unknown	31.7	7.1, 56.3	0.7	0.3, 1.4	…
ECOG performance status					
<1	45.5	12.1, 78.9	1	…	<.01
≥1	10.0	6.3, 13.6	5.2	2.4, 10.9	…
Portal vein thrombosis					
Absent	37.1	20.3, 53.9	1	…	<.01
Present	9.1	2.9, 14.3	6.3	2.6, 15.5	…
Extrahepatic disease					
Absent	45.0	33.5, 56.5	1	…	<.01
Present	16.7	8.0, 25.5	2.7	1.3, 5.7	…
Primary tumor resection					
No	23.3	3.1, 43.5	1		.46
Yes	30.1	12.5, 47.7	0.8	0.4, 1.6	
Liver resection					
No	23.3	6.4, 40.2	1	…	.28
Yes	48.5	19.7, 77.4	0.6	0.2, 1.6	…
TACE					
Conventional	31.7	2.5, 60.9	1	…	.40
Drug-eluting bead	23.3	12.6, 34.0	1.4	0.6, 3.3	…
Concomitant somatostatin treatment					
No	22.4	15.7, 29.1	1	…	.25
Yes	44.9	20.0, 69.9	0.7	0.3, 1.3	…
ETB					
<75%	30.1	17.7, 42.5	1		.45
≥75%	17.6	0, 41.3	1.383	0.6, 3.2	

Note.—ECOG = Eastern Cooperative Oncology Group, OS = overall survival.

Table 5

Multivariate Survival Analysis

Variable	HR	95% CI	*P* Value
ETB response with 50% cutoff	0.2	0.1, 0.6	<.01
ECOG performance status ≥1	3.3	1.4, 7.7	<.01
Partial portal vein thrombosis	6.1	2.2, 16.6	<.01
Extrahepatic disease	1.8	0.7, 4.2	.2

Note.—ECOG = Eastern Cooperative Oncology Group.

heterogeneous, nonspherical necrosis that embolotherapy induces (15,39).

Two studies have examined volumetric response in patients with NELM treated with embolotherapy and found that volumetric contrast enhancement and apparent diffusion coefficients of index lesions were predictive of survival (11,40). Although promising, the results of these studies are limited. Li et al (40) included only tumors larger than 2 cm, which is an unconventional size constraint that is used in neither staging nor treatment paradigms, and the response thresholds, 10% (40) and 25% (11), were cohort generated and dependent and lacked clinical reasoning. Perhaps the greatest limitation of these studies is that their findings were based on reader-selected index lesions. Lesion analysis is problematic in patients with NELM when the disease is often diffuse and treated in a lobar fashion rather than selectively. Just as embolotherapy has shown to induce heterogeneous changes in a targeted tumor, the same is to be expected in a targeted liver lobe.

The third and most unique strength of ETB is that it represents a whole-liver approach and thus is capable of providing a holistic assessment of a therapy's effect. Whether the largest (enhancing) lesion represents treatment response or relates to patient outcome remains controversial, whereas tumor burden has been closely linked to prognosis—especially in patients with NELM (2,20–22). As such, WHO and RECIST criteria suggest following up the largest lesion and noting the presence, absence, or unequivocal progression of other lesions (6,7). However, in most patients with NELM and diffuse disease, this can be challenging, time consuming, and prone to error for a reader at one time point and exacerbated by multiple readers across time points (ie, clinical visits). Whole-liver assessment removes these limitations. Index and nonindex lesions do not have to be carefully selected and scrutinized at baseline and follow-up. Instead, the entire tumor burden (treated and untreated regions) is analyzed. If a patient has an aggressive form of

NELM, the progression of untreated lesions may outweigh the necrosis of targeted lesions. Thus, by including the nontreatment area, tumor biology (aggressive vs indolent) is factored into the response assessment.

Several cutoffs for volumetric ETB were explored to find the best point of differentiation between responders and nonresponders. To provide relevance, the explored thresholds were based on a combination of clinical reasoning and validated thresholds rather than cohort generated and dependent cutoffs (11,40). Although the 50% cutoff was statistically the best in our study, we would still recommend a repeat TACE if a patient's ETB decreased by 30% because median overall survival could still improve from 20 to 40 months. In patients who do not show a response to the first TACE, we recommend a second TACE to the same target area on the basis of reported improved outcomes in patients with hepatocellular carcinoma only after the second TACE (41). Our study was designed to identify responders and nonresponders early in the course of treatment (ie, after the first TACE) instead of after multiple sessions to identify patients who benefit from therapy in order to impact patient care in a timely manner. Further studies are needed to evaluate the number of TACE procedures needed before this therapy is abandoned in patients with NELM who are nonresponders.

Our study results were derived from a representative NELM cohort, which favors their utility and reproducibility. The most common pattern of disease (multifocal and bilobar) (2) was examined in a cohort with a median overall survival similar to previously reported outcomes (42). Known prognostic indicators such as performance status, extrahepatic disease, and portal vein thrombosis were confirmed by our results and trended in the expected direction for others, including previous resection, concurrent somatostatin therapy, female sex, primary tumor type, and well-differentiated tumors (1,3,43,44). Importantly, we included challenging situations for one- and two-dimensional response criteria such as arterioportal shunts, hypovascular lesions, or portal vein invasion and/or thrombosis. This highlights the applicability of ETB and supports our suggestion that this new response assessment be included in the personalized treatment of patients with NELM treated with TACE.

Three-dimensional imaging biomarkers are commonly considered holistic assessments, but their adoption has been delayed in large part owing to workflow inefficiency. In our study, we used automatic and semiautomatic segmentation software that required only 9–10 seconds and 0.5–2 minutes, respectively. Automation reduces interreader variability, as confirmed by the high interreader agreement in our study. After liver segmentation, readers simply had to place one ROI in nonmalignant liver tissue, and this is easily implemented in diffuse disease, is time efficient, and has proved sufficient in producing reliable and pathologically accurate results (15,34). Because of the strong association with survival, workflow efficiency, and histologic accuracy, volumetric ETB may be a more advanced and complete imaging response criterion in patients with NELM treated with TACE.

Our study has several limitations. First, the cohort size was small but realistic given the rarity of NELM. Second, our study included only patients who underwent MR imaging, leading to a selection bias. However, accumulation of iodized oil used in TACE in treated areas limits the interpretation of contrast-enhanced CT scans. Third, liver segmentation included intrahepatic vasculature. Although not ideal, the enhancement of the nonembolized vessels before and after TACE has been shown to remain stable and should not have had a substantial effect on our results (45). Future segmentation algorithms should evaluate the exclusion of hepatic vasculature in the response assessment. Fourth, our study lacked radiologic-pathologic validation because patients were not surgical candidates. However, ETB was calculated with software that has proved its radiologic-pathologic accuracy (15). Although the histopathologic accuracy of the liver segmentation remains unknown, our study showed that liver volume was stable after TACE, which indicates that any changes after TACE were due to increases and/or decreases in enhancement rather than volume. Fifth, tumor grade was not available for all patients. This may explain why tumor grade, a well-known prognostic indicator, trended in the expected direction but did not achieve statistical significance. Before the 2010 WHO classification, grading was neither routine nor a requirement (3). As such, tumor grading at our institution was limited and not based on a single classification scheme. This could also explain the smaller proportion of high-grade NELM in our series compared with previously published data (46), as some tumors of unknown grade were likely high grade. Results should therefore be validated with the new WHO classification, however, keeping in mind that this classification provides little information about distant metastatic disease (47).

In conclusion, volumetric ETB is an early treatment response biomarker and surrogate for survival in patients with multifocal, bilobar NELM after the first TACE.

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