Volumetric Enhancing Tumor Burden at CT to Predict Survival Outcomes in Patients with Neuroendocrine Liver Metastases after Intra-arterial Treatment

Jessica Assouline, MD • Roberto Cannella, MD • Giorgia Porrello, MD • Louis de Mestier, MD •
Marco Dioguardi Burgio, MD, PhD • Lucas Raynaud, MD • Olivia Hentic, MD • Jérôme Cros, MD, PhD •
Lambros Tselikas, MD • Philippe Ruszniewski, MD, PhD • Marie-Pierre Vullierme, MD • Valérie Vilgrain, MD, PhD •
Rafael Duran, MD, PhD • Maxime Ronot, MD, PhD

Purpose: To investigate whether liver enhancing tumor burden (LETB) assessed at contrast-enhanced CT indicates early response and helps predict survival outcomes in patients with multifocal neuroendocrine liver metastases (NELM) after intra-arterial treatment.

Materials and Methods: This retrospective study included patients with NELM who underwent intra-arterial treatment with transarterial embolization (TAE) or chemoembolization (TACE) between April 2006 and December 2018. Tumor response in treated NELM was evaluated by using the Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST (mRECIST). LETB was measured as attenuation 2 SDs greater than that of a region of interest in the nontumoral liver parenchyma. Overall survival (OS); time to unTA(C)Eable progression, defined as the time from the initial treatment until the time when intra-arterial treatments were considered technically unfeasible, either not recommended by the multidisciplinary tumor board or until death; and hepatic and whole-body progression-free survival (PFS) were evaluated using multivariable Cox proportional hazards analyses, the Kaplan-Meier method, and log-rank test.

Results: The study included 119 patients (mean age, 60 years ± 11 [SD]; 61 men) who underwent 161 treatments. A median LETB change of –25.8% best discriminated OS (83 months in responders vs 51 months in nonresponders; $P = .02$) and whole-body PFS (18 vs 8 months, respectively; $P < .001$). A –10% LETB change best discriminated time to unTA(C)Eable progression (32 months in responders vs 12 months in nonresponders; $P < .001$) and hepatic PFS (18 vs 8 months, respectively; $P < .001$). LETB change remained independently associated with improved OS (hazard ratio [HR], 0.56), time to unTA(C)Eable progression (HR, 0.44), hepatic PFS (HR, 0.42), and whole-body PFS (HR, 0.47) on multivariable analysis. Neither RECIST nor mRECIST helped predict patient outcome.

Conclusion: Response according to LETB change helped predict survival outcomes in patients with NELM after intra-arterial treatments, with better discrimination than RECIST and mRECIST.

Supplemental material is available for this article.

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Neuroendocrine neoplasms (NENs) include a broad spectrum of tumors that stem from neuroendocrine cells. Liver metastases are found at diagnosis in 40%–73% of gastroenteropancreatic NENs and have important predictive value regardless of the primary tumor site (1,2). In historical series, the 5-year survival rate was 13%–54% in patients with neuroendocrine liver metastases (NELM), compared with 75%–99% in those without hepatic involvement (2,3).

The therapeutic management of NELM is challenging. Although the best 5-year survival rate is obtained with surgical resection (60%–80%), this is indicated in only a small number of patients with slow-growing, well-differentiated NELM without extrahepatic disease (4). Up to 80%–90% of patients have unresectable disease at presentation due to multifocal and bilobar hepatic involvement (2). The numerous therapeutic options for these patients include systemic medical treatment with somatostatin analogs, chemotherapy, oral targeted therapies, peptide receptor radionuclide therapy, liver intra-arterial treatments with transarterial embolization (TAE) or transarterial chemoembolization (TACE), and, more recently, radioembolization. Intra-arterial treatments are well suited to NENs, which are slow-growing, richly vascularized tumors. According to the European Neuroendocrine Tumor Society, intra-arterial treatments may be used in patients with progressive or symptomatic predominant liver metastases not suitable for surgical resection (5).

Summary

Changes in liver enhancing tumor burden, quantified at contrast-enhanced CT, were independently associated with improved overall survival, time to unTA(C)Eable progression, hepatic progression-free survival, and whole-body progression-free survival after intra-arterial treatment in patients with multifocal neuroendocrine liver metastases.

Key Points

- On per-patient multivariable analysis, tumor grade (hazard ratio [HR], 1.72; $P = .03$), visual tumor burden (HR, 0.30; $P = .048$), and response according to changes in liver enhancing tumor burden (LETB) (HR, 0.56; $P = .03$) remained independently associated with overall survival, whereas tumor grade (HR, 1.42; $P = .046$), multiple intra-arterial treatments (HR, 0.63; $P = .03$), and response according to LETB change (HR, 0.44; $P = .001$) were independently associated with time to unTA(C)Eable progression.
- Per-treatment analysis showed that previous treatments (HR, 2.15; $P < .001$) and response according to LETB change (HR, 0.42; $P < .001$) were independently associated with hepatic progression-free survival, whereas tumor grade (HR, 1.37; $P = .047$), previous treatments (HR, 1.71; $P = .002$), and response according to LETB change (HR, 0.47; $P < .001$) were independently associated with whole-body progression-free survival.
- Neither Response Evaluation Criteria in Solid Tumors (RECIST) nor modified RECIST were predictors of overall survival, time to unTA(C)Eable progression, or hepatic or whole-body progression-free survival ($P > .1$ for all outcomes).

Keywords

CT, Chemoembolization, Embolization, Abdomen/GI, Liver

At present, tumor response following intra-arterial treatments is evaluated with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (6), which monitors changes in the sum of the largest diameters of target lesions. Tumor response can also be assessed with the modified RECIST (mRECIST) (7), which evaluates the components of the largest enhancing target tumors, although use of these criteria has not yet been validated in NENs. According to these criteria, treatment response leads to symmetrical and spherical changes in tumor size and/or their enhancing components. In practice, liver metastases often show heterogeneous changes following intra-arterial treatments.

Volumetric tumor enhancement assessment has been shown to help predict survival in patients with cancer (8–16). Rather than a lesion-by-lesion volumetric analysis, volumetric assessment of metastatic disease in the entire liver, also known as the liver enhancing tumor burden (LETB), is a more comprehensive marker of tumor response in NELM after intra-arterial treatments (17,18). Quantitative assessment of LETB by using MRI seems to reliably help predict overall survival (OS) following intra-arterial treatment therapy in patients with NELM, with better discriminatory power than RECIST (17,18). To our knowledge, studies evaluating volumetric assessment of LETB after intra-arterial treatments

have all used MRI (17,18). In clinical practice, contrast-enhanced CT is frequently used to assess response to intra-arterial treatments in NELM (19). Assessment of volumetric enhancement using this modality may help predict survival outcomes with greater accuracy compared with conventional one-dimensional criteria.

The purpose of this study was to investigate whether LETB assessed at contrast-enhanced CT could be an early response marker and help predict survival outcomes in patients with multifocal neuroendocrine liver metastases after TAE or TACE.

Materials and Methods

This retrospective study, together with a retrospective chart review, was performed according to the Declaration of Helsinki convention and following institutional review board approval (approval no. CRM-2003–081). Written informed consent from patients was waived. There was no industry support for this study. The authors had control of the data and information submitted for publication.

Patients

We searched the medical records at our tertiary referral care center for the treatment of liver disease to select adult patients with pathologically proven NENs and liver metastases who underwent intra-arterial treatments between April 2006 and December 2018. Inclusion criteria were the following: *(a)* intra-arterial treatments performed with TAE or TACE, *(b)* available pretreatment (within 3 months before intra-arterial treatment) and posttreatment (1–4 months after intra-arterial treatment) CT scans, and *(c)* CT scans that included at least precontrast and hepatic arterial-phase acquisitions. The initial study sample included 191 patients who underwent 423 intra-arterial treatments. Patients with pulmonary NENs ($n = 3$), inadequate CT scans (eg, absence of unenhanced and/or arterial-phase images or severe motion artifacts), or posttreatment CT scans acquired outside the required time (ie, >4 months after intra-arterial treatments) ($n = 69$) were excluded (Fig 1).

Patients had a consultation with interventional radiologists within 4 weeks before intra-arterial treatments. The following data were collected from pretreatment consultations: age, sex, primary tumor origin, histopathologic grade, date of initial diagnosis, presence of extrahepatic metastases, carcinoid syndrome and carcinoid heart disease, and previous or concurrent antitumor treatment, including surgery of the primary tumor and/or metastases. All pathologic samples were reviewed onsite by expert pathologists, and the histopathologic grade (World Health Organization 2019 classification) was determined centrally on the basis of the Ki-67 index, as recommended (20).

Additional data were collected after intra-arterial treatments, including the number and date of treatment, time between imaging and intra-arterial treatments, type of intra-arterial agent used, and procedural complications graded according to the Interventional Radiology Adverse Event Severity Scale (21).

Intra-arterial Treatments

Intra-arterial treatments were performed in patients with NELM and unresectable hepatic-dominant disease that was

191 adult patients with neuroendocrine neoplasm treated by TAE or TACE between April 2006 and December 2018

3 patients excluded due to primary pulmonary neuroendocrine neoplasm

69 patients excluded due to CT exams with inadequate protocol or CT exams performed more than three months before treatments or more than four months after treatments

119 patients undergoing 161 intraarterial treatments 241 TAE or TACE procedures

88 patients undergoing a single intraarterial treatment

21 patients undergoing two intraarterial treatments

9 patients undergoing three intraarterial treatments

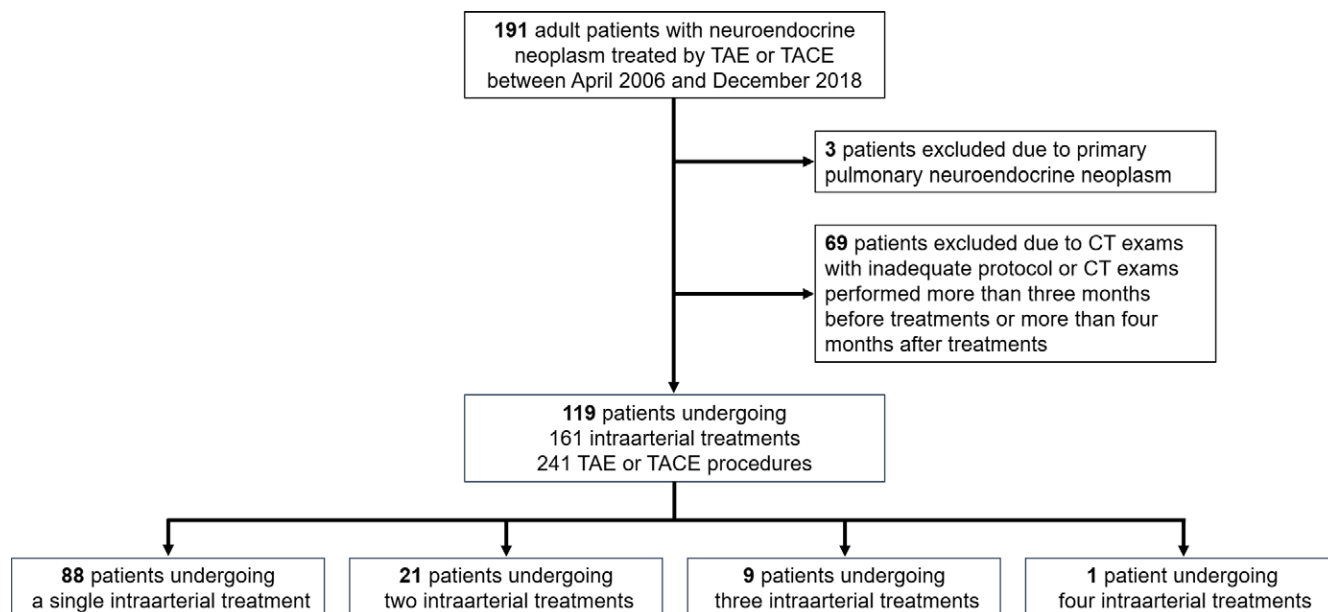**1** patient undergoing four intraarterial treatments

Figure 1: Flowchart of the study patients. TACE = transarterial chemoembolization, TAE = transarterial embolization.

symptomatic or progressive, with an Eastern Cooperative Oncology Group performance status of 0–2; adequate hepatic, renal, and hematologic function; and at least partial patency of the portal venous system. In our institution, patients with bowel NELM are usually treated with TAE, whereas those with pancreatic tumors undergo TACE. All indications were discussed and validated by our European Neuroendocrine Tumor Society center–certified multidisciplinary tumor board.

We routinely segmented the hepatic volume into two or three different parts that were treated successively to optimize tolerance, especially in cases of high liver burden, with a delay of 4–8 weeks between each partial procedure. Thus, each patient could undergo multiple intra-arterial treatments targeting different lesions, and each intra-arterial treatment could include more than one TAE or TACE procedure, depending on the target tumor burden and pretreatment planning. Different procedures were considered to be part of the same treatment if they were performed within a maximum of 6 months.

Intra-arterial treatments were performed by our team of interventional radiologists using a standardized approach. Briefly, the common femoral artery was accessed via the Seldinger technique. The celiac axis was selected with a 5.0-F catheter (Simmons 1 or Cobra C2). After the hepatic arterial anatomy was identified at angiography, a microcatheter was advanced into the tumor-feeding vessels. An emulsion of streptozotocin (1500 mg/m²) was infused in a 1:2 mixture with iodized oil (Lipiodol; Guerbet) for conventional TACE, followed by an injection of gelfoam (Gelita-spon [Gelita Medical] or Curaspon [Cura Medical]) or occasionally by 100–300-μm microspheres (Embospheres; Merit). An injection of gelfoam, or occasionally 100–300-μm microspheres, was performed for TAE. The end point of embolization was clearance of the intra-arterial contrast agent column at the tip of the microcatheter within two to five heartbeats. Complete occlusion was avoided to maintain arterial patency to repeat treatment.

All patients were followed up with CT of the chest, abdomen, and pelvis every 3–6 months, and imaging findings were regularly discussed within our multidisciplinary tumor board. Any progression was validated by the multidisciplinary board. Date of death or last available follow-up was recorded until May 30, 2020.

CT Technique

Imaging was performed with 64-channel CT scanners (LightSpeed VCT or Revolution; GE Medical Systems). A standard liver protocol with the same imaging parameters before and after intra-arterial treatments was used for consistent image acquisition and timing. The protocol included precontrast, late hepatic arterial (acquired at 30–35 seconds using the bolus tracking technique), and portal venous (70–90 seconds) phases after the intravenous administration of an iodinated contrast agent, with an iodine concentration of 350 g/L (iomeprol [Iomeron; Bracco Diagnostics] or iobitridol [Xenetix; Guerbet]) injected with a power injector at a rate of 3–4 mL/sec. The scanning parameters were 1.25-mm section thickness reconstruction and 120-kVp tube potential with automatic milliampere modulation.

Qualitative Image Analysis

Image analysis was performed using a picture archiving and communication system (Vue PACS; Philips Healthcare) by an abdominal radiologist (reader 1, J.A., with 6 years of experience in abdominal imaging) and a resident senior radiologist (reader 2, R.C., with 4 years of experience in abdominal imaging) to evaluate interreader agreement. These readers, who independently reviewed all CT images, were aware of the treated liver segments but blinded to patient outcome.

At pretreatment CT, readers visually assessed the pattern of tumor enhancement on hepatic arterial-phase images (reported as hyperenhancement or iso- to hypoenhancement) and the tumor
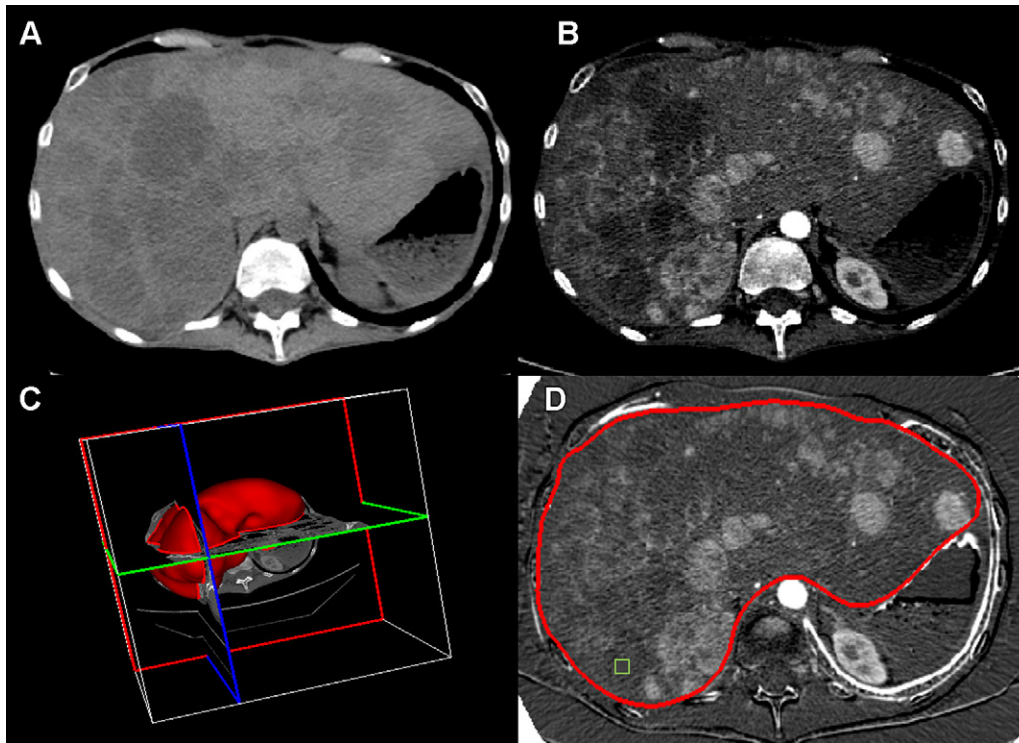
Figure 2: Pretreatment liver enhancing tumor burden (LETB) quantification in a 41-year-old woman with pancreatic neuroendocrine liver metastases. CT images show **(A)** precontrast, **(B)** arterial phase, **(C)** three-dimensional segmentation mask of the whole liver, and **(D)** subtracted images with the 0.5-cm^3 region of interest placed in the nontumoral liver parenchyma to quantify the LETB. The segmentation mask to determine the whole liver volume is shown as the red borders of the liver. Total liver volume, volume of enhancing tumor, and LETB were 4495 cm^3, 2012 cm^3, and 44.8%, respectively.

burden (classified as <25%, 25%–50%, >50%–75%, >75%, depending on the percentage of involved liver parenchyma). The response of treated liver metastases was evaluated by comparing pretreatment and first posttreatment CT scans according to RECIST 1.1 (6) and mRECIST considering hyperenhancing lesions (7). Patients were classified as having a complete response to treatment (disappearance of all lesions [RECIST] or no intratumoral arterial enhancement [mRECIST]), a partial response (≥30% decrease in size of the sum of diameters of target lesions [RECIST] or of intratumoral enhancement [mRECIST]), stable disease (neither partial response nor disease progression), and disease progression (>20% increase in size of the sum of diameters of target lesions [RECIST] or viable target lesions [mRECIST] and/or appearance of new lesions). Patients with a complete or partial response were considered to have an objective response.

Quantitative Image Analysis

LETB was quantified at pretreatment and first posttreatment CT. First, the whole liver was segmented during the hepatic arterial phase using prototype software (Medisys; Philips Research). A three-dimensional segmentation mask of the entire liver was created with the software. Then, LETB was calculated with another prototype software (qEASL3D; Medisys) that measures three-dimensional enhancement using voxel attenuation thresholds. The precontrast CT images were subtracted from the hepatic arterial-phase images to remove any contribution of background liver parenchyma and intralesional iodized oil deposition. A radiologist (G.P., with 5 years of experience)

who was not involved in imaging analysis and was blinded to patient outcomes placed a 0.5-cm^3 (in patients with extensive tumoral involvement and limited nontumoral parenchyma) or 1-cm^3 region of interest on the nontumoral liver parenchyma for image normalization (Fig 2). The software generated liver volume (in cubic centimeters), the volume of the enhancing tumor (in cubic centimeters), defined as the viable tumor tissue more than 2 SDs from the region of interest average, and the LETB, defined as the percentage of enhancing tumor within the liver volume (17). The region of interest was placed three times in the nontumoral liver parenchyma, and the mean of the three consecutive measurements was recorded. This approach has been validated in previous studies and shown to have the best reproducibility and agreement with histopathologic results, without being affected by the presence of nontumoral intrahepatic vessels (17,22,23). Moreover, a strong correlation of measured volumes has been shown with multimodal imaging (MRI, cone-beam CT, and CT) (22,24,25). The change in LETB (percentage) was calculated using the following formula: $[(LETB_{post} - LETB_{pre})/LETB_{pre}] \times 100$, where $LETB_{pre}$ and $LETB_{post}$ were the pre- and posttreatment LETB, respectively.

Statistical Analysis

Categorical variables are presented as numbers, proportions, and percentages, and continuous variables are presented as means ± SDs and ranges or medians and IQRs, after testing for normal distribution by the Shapiro–Wilk test. Changes in LETB were compared using the Mann–Whitney U or Kruskal–Wallis test,
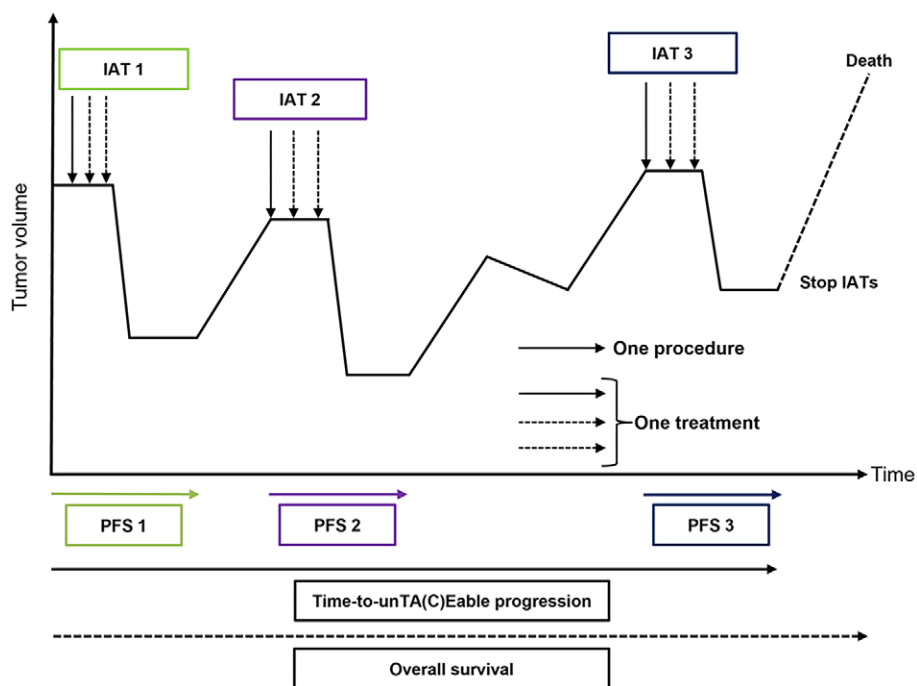
Figure 3: Tumor volume change over time according to intra-arterial treatments (IATs) and corresponding survival outcomes. Notably, each patient could undergo multiple IATs during the course of the disease, and each treatment could include more than one transarterial embolization (TAE) or transarterial chemoembolization (TACE) procedure. Overall survival and time to unTA(C)Eable progression were recorded per patient, whereas progression-free survival (PFS) (hepatic or whole body) was recorded per each treatment. Time to unTA(C)Eable progression is defined as the time from the initial treatment until the time when intra-arterial treatments were considered technically unfeasible, either not recommended by the multidisciplinary tumor board or until death.

as appropriate. The Cohen κ test was used to assess interreader agreement of image analysis. Agreement was reported to be poor (κ < 0.00), slight (κ = 0.00–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), substantial (κ = 0.61–0.80), or almost perfect (κ = 0.81–1.00). The intraclass correlation coefficient with 95% CIs was calculated to assess the reproducibility of LETB.

OS and time to unTA(C)Eable progression were calculated for each patient, and hepatic and whole-body progression-free survival (PFS) were assessed for each treatment, as tumor progression (according to RECIST) could occur numerous times throughout the patient's oncologic history (Fig 3). OS was calculated from the date of the first treatment to the date of death. Time to unTA(C)Eable progression was defined as the time from the initial treatment until the time when intra-arterial treatments were considered technically unfeasible, either not recommended by the multidisciplinary tumor board or until death. Patients were considered to have unTA(C)Eable disease if they developed impaired liver function or hepatotoxicity, hepatic progression not technically treatable by TAE or TACE, progression following repeat TAE or TACE procedures, new vascular invasion, or clinical progression with Eastern Cooperative Oncology Group performance status greater than 2. Hepatic PFS was recorded after each intra-arterial treatment until the date of hepatic disease progression or death. Whole-body PFS was considered because of the possible extrahepatic tumor progression despite hepatic disease control, and it was calculated from each date of intra-arterial treatment to the date of disease progression on follow-up

CT scans of the chest, abdomen, and pelvis (hepatic or extrahepatic) or death. Patients were censored if they were alive at the date of the last follow-up.

Kaplan-Meier curves were plotted to compare survival outcomes according to RECIST, mRECIST, and LETB change. Median estimated survival was reported for responders and nonresponders with 95% CIs. Response according to LETB change was defined as a change that was greater than a predefined threshold. Because there is no validated cutoff to define responders according to the LETB change, several possible thresholds were tested. The nonlinearity of responses according to the LETB was tested considering the LETB quartile. Curves were compared using the log-rank test. Multivariable Cox proportional hazards analyses with the backward elimination technique were used to select parameters independently associated with survival outcomes. Because of the collinearity between changes in LETB and conventional one-dimensional response criteria (ie, RECIST and mRECIST), multivariable analysis was performed including the response according to LETB change, RECIST, or mRECIST. Hazard ratios (HRs) with their 95% CIs were determined for statistically significant variables at multivariable analyses. The goodness of fit of the predictive model and the calibration curves of the predictive models were evaluated with the Wald test, Harrell C statistic, and Akaike information criteria.

A P value less than .05 was considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS software, version 20.0 (IBM).

Table 1: Patient and Tumor Characteristics

Characteristic	Data
Age (y)	
All patients	60 ± 11 (35–84)
Men	59 ± 11 (35–84)
Women	61 ± 11 (35–83)
Sex	
Men	61/119 (51)
Women	58/119 (49)
Primary tumor location	
Small bowel	59/119 (50)
Pancreas	45/119 (38)
Other (stomach, colon, rectum)	7/119 (6)
Unknown primary location	8/119 (7)
Tumor grade	
G1	36/119 (30)
G2	74/119 (62)
G3	5/119 (4)
Unknown	4/119 (4)
Other disease characteristics	
Extrahepatic metastases	68/119 (57)
Carcinoid syndrome	49/119 (41)
Carcinoid heart disease	24/119 (20)
Previous surgery	
Primary tumor resection	76/119 (64)
Liver resection	14/119 (12)
Previous treatments for metastatic disease	
None	20/119 (17)
Somatostatin analogs	50/119 (42)
Treatments other than somatostatin analogs	22/119 (18)
Somatostatin analogs plus other treatments	27/119 (23)

Note.—Based on 119 patients. Continuous variables (age) are expressed as means ± SDs, with ranges in parentheses, after testing for normal distribution. Categorical variables are expressed as proportions, with percentages in parentheses.

Table 2: Treatment Characteristics of Study Patients

Characteristic	Data
Type of treatment	
Transarterial chemoembolization	89/161 (55)
Transarterial embolization	72/161 (45)
No. of procedures per treatment	
1	91/161 (56.5)
2	61/161 (37.9)
3	8/161 (5.0)
4	1/161 (0.6)
Pretreatment tumor burden	
<25%	16/161 (10)
25%–50%	42/161 (26)
>50%–75%	44/161 (27)
>75%	59/161 (37)
Adverse events*	41/241 (17)
Grade 2	33/241 (14)
Grade 3	6/241 (2)
Grade 4	2/241 (1)
Grade 5	0/241 (0)

Note.—Based on 161 treatments. Categorical variables are expressed as proportions, with percentages in parentheses.
* Adverse events were graded according to the Society of Interventional Radiology classification (21).

Results

Patients and Treatment Characteristics

The study cohort included 119 patients (mean age, 60 years ± 11; 61 men [51%]). Patient and tumor characteristics are reported in Table 1. The most common primary tumor locations were small bowel (*n* = 59 [50%]) and pancreas (*n* = 45 [38%]). NENs were most frequently classified as G2 (*n* = 74 [62%]) or G1 (*n* = 36 [30%]). Twenty (17%) patients were naive to any treatment before intra-arterial treatment, whereas 99 of 119 (83%) had previously received treatment before hepatic progression (Table 1).

Patients underwent 161 treatments, including 241 TAE or TACE procedures. Eighty-nine of 161 (55%) treatments included TACE and 72 of 161 (45%) included TAE. Ninety-one (56%) treatments were performed in a single procedure and 44% included two procedures or more. Eight (3%) adverse events of grade 3 or higher were observed following intra-arterial treatment (Table 2).

Follow-up and Survival

The median follow-up after the first procedure was 48 months (IQR, 21–70 months). Sixty of 119 patients (50%) died during follow-up. Median OS was 65 months (95% CI: 50.5, 79.4). Tumor progression untreatable by intra-arterial treatment occurred in 107 of 119 (90%) patients after a median of 28 months (95% CI: 22, 33.9).

Progression occurred following 122 of the 161 included treatments (76%), with 106 of 161 (66%) hepatic progressions. Median hepatic PFS was 16 months (95% CI: 13.2, 18.7), and median whole-body PFS was 12 months (95% CI: 10.2, 13.7).

Image Analysis

Hepatic metastases usually manifested with a hyperenhancing pattern (112 of 161 [70%]) and a hepatic tumor burden greater than 50% (103 of 161 [64%]) was identified on visual pretreatment CT assessment (Table S1).

A complete response, a partial response, stable disease, and progressive disease according to RECIST were reported on the
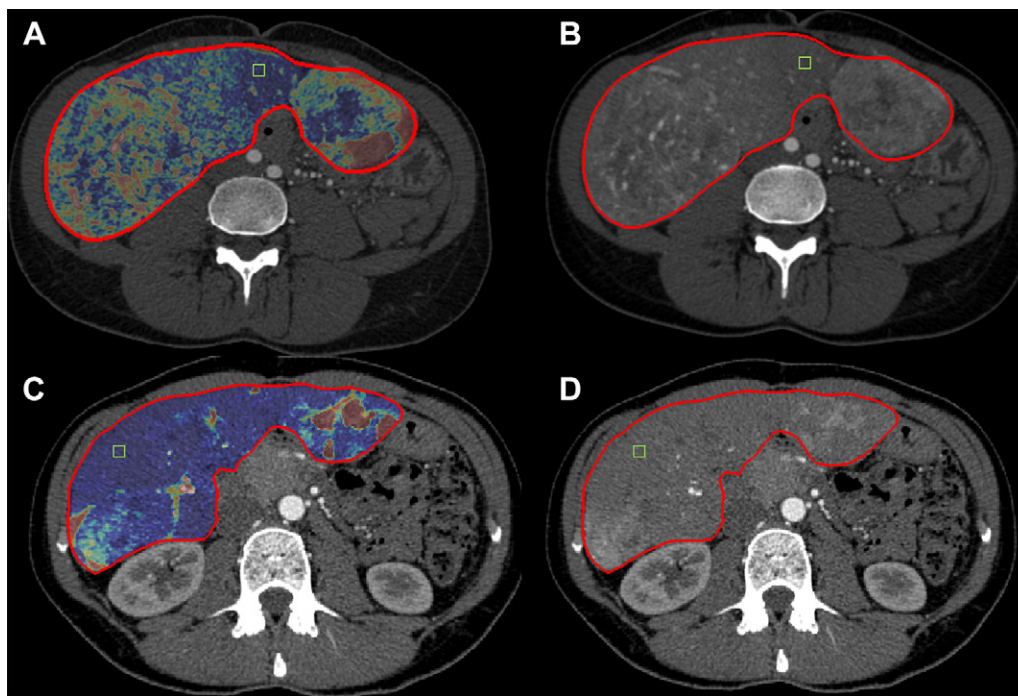
Figure 4: Changes in liver enhancing tumor burden (LETB) in a 36-year-old woman with pancreatic neuroendocrine liver metastases treated with transarterial chemoembolization. **(A, B)** Pretreatment CT showed a total hepatic volume of 2823 cm³, a volume of enhancing tumor of 1035 cm³, and an LETB of 36.6%. **(C, D)** Posttreatment CT showed a total hepatic volume of 1607 cm³, a volume of enhancing tumor of 354 cm³, and an LETB of 22%. LETB dropped by 41%. Hepatic and whole-body progression-free survivals were each 11 months, and overall survival was 21 months. Note: The segmentation mask to determine the whole liver volume is shown as the red borders of the liver. The green box represents the 0.5-cm³ region of interest placed in the nontumoral liver parenchyma to quantify the LETB.

first posttreatment CT scan in 0 of 161 (0%), 42 of 161 (26%), 114 of 161 (71%), and five of 161 (3%) treatments, respectively. A complete response, a partial response, stable disease, and progressive disease according to mRECIST were reported on the first posttreatment CT scan in 16 of 161 (10%), 73 of 161 (45%), 66 of 161 (41%), and six of 161 (4%) treatments, respectively. An objective response according to mRECIST was present in 89 of 161 (55%) treatments.

Interreader agreement was substantial for visual enhancement (κ = 0.73) and fair for visual assessment of tumor burden (κ = 0.32), RECIST (κ = 0.25), and mRECIST (κ = 0.33).

LETB Change

Median pretreatment LETB was 17% (IQR, 13.5%–28%), and median posttreatment LETB was 12% (IQR, 9%–12.5%). LETB showed a median change between pre- and posttreatment CT scans of –25.8% (IQR, –38.3% to –11.1%) (Fig 4). The reproducibility of LETB in three consecutive measurements was good, with an intraclass correlation coefficient of 0.87 (95% CI: 0.84, 0.89). Distribution of LETB change according to visual analysis is presented in Table S1.

Survival Analyses

Survival analyses according to RECIST and mRECIST are presented in Table 3. We found no evidence of differences in OS, time to unTA(C)Eable progression, hepatic PFS, or whole-body PFS between patients with and without (stable

or progressive disease) an objective response. The comparison between patients with an objective response and stable disease only (but not progressive disease) is presented in Table S2.

Survival analyses according to different LETB change thresholds are reported in Table 4. In addition, survival analyses according to the quartiles of LETB change are provided in Table S3. The median (–25.8%) LETB change provided the best separation of OS (P = .02) and whole-body PFS curves (P < .001) between responders (LETB change < –25.8%) and nonresponders (LETB change ≥ –25.8%).

The best discrimination of time to unTA(C)Eable progression (P < .001) and hepatic PFS (P < .001) between responders (LETB change < –10%) and nonresponders (LETB change ≥ –10%) was identified with an LETB change of –10%. Differences in hepatic PFS curves were also best discriminated by a median LETB change of –25.8% (P = .001).

The Kaplan-Meier curves corresponding to the optimal LETB thresholds are presented in Figure 5. Hepatic PFS and whole-body PFS significantly differed between responders and nonresponders for all LETB change thresholds less than zero (Table 4). Survival analyses limited to the subset of patients with iso- to hypoenhancing metastases on visual analysis (n = 49) are reported in Table S4.

Multivariable analyses for variables associated with survival outcomes including LETB change are reported in Table 5, Table S5, and Table S6 (optimal, median, and quartile LETB change thresholds, respectively). Tumor grade (HR, 1.72 [95% CI:

Table 3: Differences in Overall Survival, Time to UnTA(C)Eable Progression, Hepatic PFS, and Whole-Body PFS between Objective Responders and Nonresponders according to RECIST and mRECIST

Criteria	N+	N–	Median Response (mo)		Difference (mo)	Log-Rank P Value
			Objective Responders	Nonresponders		
Overall survival (n = 119 patients)						
RECIST	34	85	86.0 (45.1, 126.8)	64.0 (48.5, 79.5)	22.0	.42
mRECIST	67	52	65.0 (51.6, 78.4)	72.0 (43.2, 100.7	−7.00	.57
Time to unTA(C)Eable progression (n = 119 patients)						
RECIST	34	85	22.0 (16.3, 27.7)	32.0 (25.6, 38.3)	−10.0	.53
mRECIST	67	52	25.0 (18.4, 31.6)	32.0 (18.7, 45.3)	−7.0	.38
Hepatic PFS (n = 161 treatments)						
RECIST	42	119	20.0 (12.9, 27.1)	15.0 (12.4, 17.5)	5.0	.16
mRECIST	89	72	18.0 (13.4, 22.6)	14.0 (11.1, 16.9)	4.0	.28
Whole-body PFS (n = 161 treatments)						
RECIST	42	119	14.0 (6.7, 21.2)	11.0 (8.9, 13.1)	3.0	.10
mRECIST	89	72	12.0 (9.4, 14.5)	10.0 (6.8, 13.2)	2.0	.40

Note.—Response was based on assessment by an experienced abdominal radiologist (reader 1). Estimated median survivals are expressed in months, with 95% CIs in parentheses. N+ indicates number of objective responses (complete or partial response); N– indicates nonresponders (stable or progressive disease). Time to unTA(C)Eable progression is defined as the time from the initial treatment until the time when intra-arterial treatments were considered technically unfeasible, either not recommended by the multidisciplinary tumor board or until death. mRECIST = modified RECIST, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors.

1.06, 2.79]; P = .03), visual burden (HR, 1.30 [95% CI: 1.00, 1.69]; P = .048), and response according to LETB change (HR, 0.56 [95% CI: 0.33, 0.95]; P = .03) remained independently associated with OS (Table 5). Tumor grade (HR, 1.42 [95% CI: 1.00, 2.00]; P = .046), multiple intra-arterial treatments (HR, 0.63 [95% CI: 0.42, 0.95]; P = .03), and response according to LETB change (HR, 0.44 [95% CI: 0.28, 0.70]; P = .001) were independently associated with time to unTA(C)Eable progression (Table 5). Previous treatment (HR, 2.15 [95% CI: 1.44, 3.20]; P < .001) and response according to LETB change (HR, 0.42 [95% CI: 0.29, 0.67]; P < .001) were independently associated with hepatic PFS, whereas tumor grade (HR, 1.37 [95% CI: 1.00, 1.88]; P = .047), previous treatment (HR, 1.71 [95% CI: 1.22, 2.40]; P = .002), and response according to LETB change (HR, 0.47 [95% CI: 0.34, 0.66]; P < .001) were independently associated with whole-body PFS (Table 5). The models demonstrated good calibration and discrimination (Table S7; Figs S1 and S2). Neither RECIST nor mRECIST were identified by multivariable analysis (Tables S8 and S9).

Discussion

We showed that LETB changes assessed by using a quantitative comparison of pretreatment and early posttreatment arterial-phase CT images helped predict survival outcomes in patients with NELM treated with TAE or TACE. In particular, response according to the LETB change was independently associated with improved OS (HR, 0.56), time to unTA(C)Eable progression (HR, 0.44), hepatic PFS (HR, 0.42), and whole-body PFS (HR, 0.47).

Early prediction of patient outcome after intra-arterial treatment is challenging. Size-based response criteria such as RECIST are often limited by minimal or delayed changes in tumor size (26), whereas criteria based on tumor enhancement, such as mRECIST, are limited by heterogeneous modifications. Our study showed no evidence of a difference in survival between patients with and without an objective response according to RECIST or mRECIST, which is consistent with previous reports assessing early response in patients with multiple NELM (10,17). Moreover, these criteria are based on one-dimensional measurements of a maximum of two target lesions per organ, which could markedly underestimate hepatic tumor burden and bias the assessment of response in patients with multiple hepatic metastases, which often have discordant evolution. In our study, most patients presented with extensive tumor burden (>50% of liver involvement in 64% of patients). A large number of metastases per patient complicates the identification of target lesions and could explain the fair interreader agreement. Another limitation of conventional criteria is the well-known inaccuracy in predicting the extent of tumor necrosis, which is often heterogeneously distributed throughout the tumor and may be hidden by iodized oil deposition at early posttreatment contrast-enhanced CT.

A volumetric approach may solve many of these problems. Indeed, no target lesion selection is needed because the entire tumor volume is quantified regardless of response heterogeneity, avoiding subjective bias inherent to the choice of the targets. In our study, precontrast CT images were subtracted from hepatic arterial-phase images; thus, the volume of the arterially enhancing tumor was generated. This approach offers the advantage of quantifying the tumor burden of the entire liver with good measurements for reproducibility, without being influenced by

Table 4: Overall Survival, Time to UnTA(C)Eable Progression, Hepatic PFS, and Whole-Body PFS according to Response Based on Different Thresholds of Changes in Liver Enhancing Tumor Burden

LETB Change Threshold Used to Define Responders	N+	N–	Median Time (mo)		Difference	Log-Rank *P* Value
			Responders (Below Threshold)	Nonresponders (Above Threshold)		
Overall survival (*n* = 119 patients)						
+10%	103	16	70.0 (53.4, 86.5)	56.0 (34.2, 77.8)	14.0	.60
0%	94	25	70.0 (53.7, 86.2)	56.0 (33.9, 78.1)	14.0	.24
−10%	88	31	75.0 (55.8, 94.1)	56.0 (27.8, 84.2)	19.0	.14
−20%	71	48	78.0 (54.3, 106.6)	50.0 (31.1, 68.8)	28.0	.07
−25.8%*	61	58	83.0 (57.3, 108.6)	51.0 (34.7, 67.2)	32.0	.02†
−30%	54	65	75.0 (50.8, 99.2)	53.0 (35.4, 70.6)	22.0	.04†
−40%	29	90	62.0 (55.5, 68.5)	72.0 (50.3, 93.7)	−10.0	.86
Time to unTA(C)Eable progression (*n* = 119 patients)						
+10%	103	16	28.0 (21.9, 34.0)	14.0 (0.00, 51.2)	14.0	.17
0%	94	25	30.0 (23.4, 36.6)	12.0 (4.6, 19.3)	18.0	.008†
−10%	88	31	32.0 (24.2, 39.7)	12.0 (4.7, 19.2)	20.0	.001†
−20%	71	48	31.0 (23.2, 38.8)	25.0 (10.8, 39.2)	6.0	.05
−25.8%*	61	58	30.0 (22.8, 37.2)	25.0 (9.2, 40.7)	5.0	.05
−30%	54	65	30.0 (23.3, 36.7)	25.0 (10.6, 39.3)	5.0	.09
−40%	29	90	24.0 (22.0, 33.9)	29.0 (19.2, 38.7)	−5.0	.2
Hepatic PFS (*n* = 161 treatments)						
+10%	141	20	17.0 (14.2, 19.8)	7.0 (2.8, 11.1)	10.0	.003†
0%	130	31	18.0 (15.1, 20.9)	8.0 (5.7, 10.3)	10.0	.001†
−10%	122	39	18.0 (15.2, 20.8)	8.0 (7.0, 8.9)	10.0	<.001†
−20%	96	65	19.0 (16.4, 21.5)	10.0 (6.8, 31.1)	9.0	.002†
−25.8%*	80	81	20.0 (17.2, 22.8)	10.0 (7.7, 12.3)	10.0	.001†
−30%	71	90	19.0 (15.8, 22.2)	10.0 (7.9, 12.0)	9.0	.001†
−40%	37	124	21.0 (15.1, 26.9)	13.0 (10.4, 15.6)	8.0	.02†
Whole-body PFS (*n* = 161 treatments)						
+10%	141	20	12.0 (9.8, 14.2)	6.0 (1.6, 10.4)	6.0	.07
0%	130	31	13.0 (10.9, 15.1)	6.0 (1.6, 10.3)	7.0	.003†
−10%	122	39	14.0 (11.9, 16.1)	6.0 (3.9, 8.0)	8.0	<.001†
−20%	96	65	15.0 (12.4, 17.6)	8.0 (6.4, 9.5)	9.0	<.001†
−25.8%*	80	81	18.0 (14.9, 21.1)	8.0 (7.3, 8.6)	10.0	<.001†
−30%	71	90	18.0 (14.8, 21.2)	8.0 (6.9, 9.1)	10.0	<.001†
−40%	37	124	19.0 (16.6, 21.3)	10.0 (8.7, 11.2)	9.0	.01†

Note.—Estimated median survivals are expressed in months, with 95% CIs in parentheses. N+ indicates the number of patients or treatments below the threshold, classified as responders according to volumetric enhancement threshold; N– indicates the number of patients or treatments equal to or above the threshold, classified as nonresponders. Differences in survival between responders and nonresponders according to the volumetric enhancement threshold are expressed in months. Time to unTA(C)Eable progression is defined as the time from the initial treatment until the time when intra-arterial treatments were considered technically unfeasible, either not recommended by the multidisciplinary tumor board or until death. PFS = progression-free survival.
* Threshold based on the median decrease of volumetric arterial enhancement.
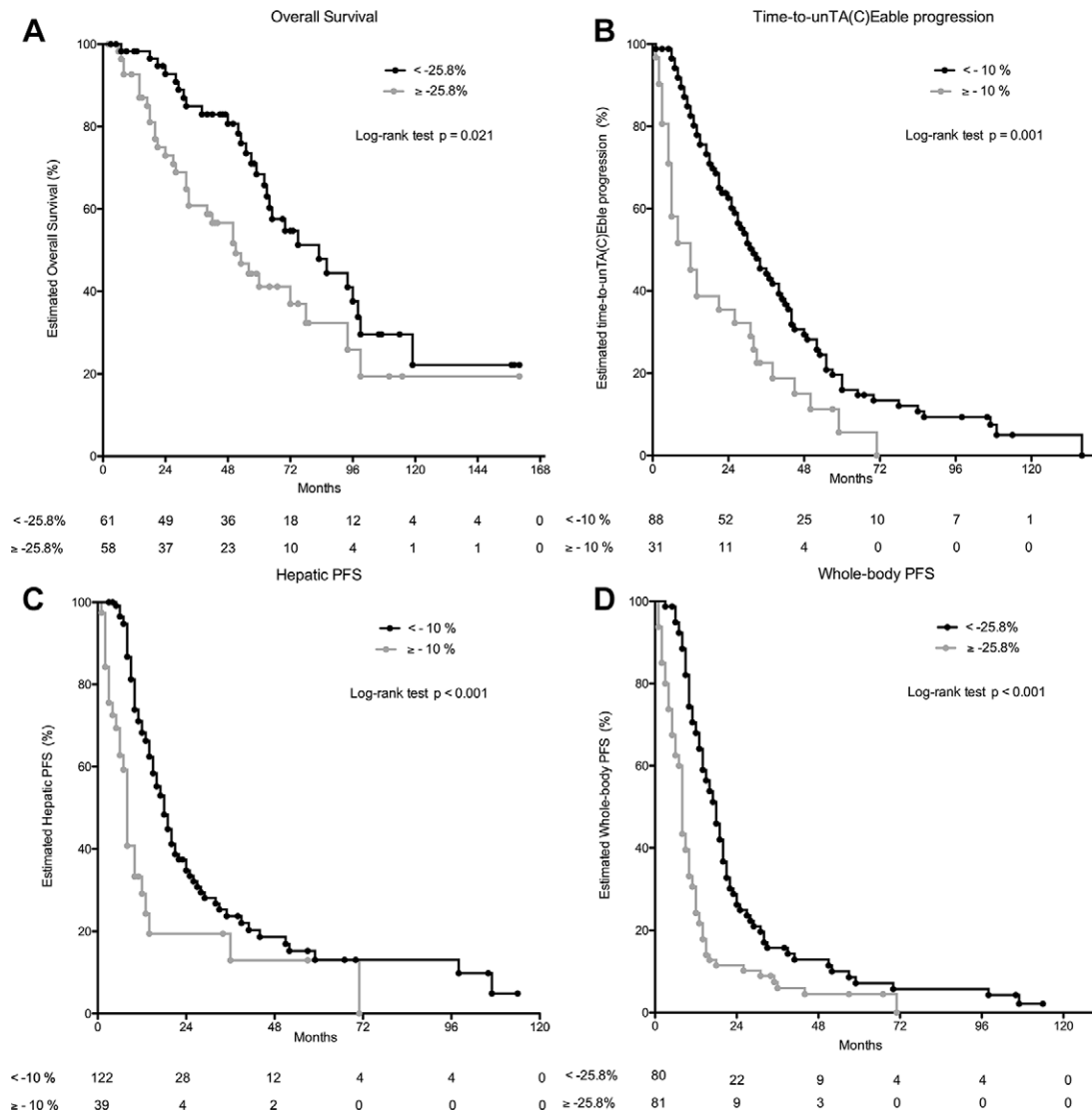† Statistically significant (*P* < .05).

Figure 5: Kaplan-Meier curves according to optimal response threshold of liver enhancing tumor burden for **(A)** overall survival, **(B)** time to unTA(C)Eable progression, **(C)** hepatic progression-free survival (PFS), and **(D)** whole-body PFS. Time to unTA(C)Eable progression is defined as the time from the initial treatment until the time when intra-arterial treatments were considered technically unfeasible, either not recommended by the multidisciplinary tumor board or until death.

background liver parenchyma enhancement or intratumoral iodized oil deposits following therapy. Moreover, LETB takes into account the volume of the involved liver parenchyma, which is important because the amount of residual nontumoral liver parenchyma may also influence patient survival.

Previous studies have investigated the value of MRI-monitored volumetric tumor enhancement to predict OS as the primary end point, with promising results (17,18). In clinical practice, contrast-enhanced CT remains the most frequently used imaging technique to evaluate patients with NEN metastases, because both hepatic and extrahepatic disease can be evaluated at CT in a single test. Thus, we chose to focus on CT. Although OS remains the primary end point to assess cancer-related outcomes, treatment decisions are often based on the evidence of tumor progression. Patients with NELM are treated with multiple lines of local or systemic therapy, which could each potentially influence patient survival. Thus, we also considered hepatic

and whole-body PFS. All survival indexes were associated with a change in LETB.

There is no generally accepted cutoff of LETB to define responders. In our study, patients were stratified as responders and nonresponders on the basis of Kaplan-Meier analyses. A median LETB change of –10% was the best cutoff to stratify patients as responders or nonresponders according to hepatic PFS and time to unTA(C)Eable progression, whereas –25.8% was the best change for whole-body PFS and OS. The latter threshold was also found to be an independent predictor of survival in multivariable analyses and was similar to the values reported for MRI applied in other cohorts (10,17). Gowdra Halappa et al (10) reported that patients with a decrease in volumetric arterial enhancement of greater than 25% in target lesions had significantly longer OS (40 vs 16 months in patients with a decrease of <25%). However, only one lesion per patient was assessed (10). Sahu et al (17) found a significant

Table 5: Multivariable Cox Proportional Hazards Analyses for Prediction of Overall Survival, Time to UnTA(C)Eable Progression, Hepatic PFS, and Whole-Body PFS

Variable	Overall Survival		Time to unTA(C)Eable Progression		Hepatic PFS		Whole-Body PFS	
	HR	P Value	HR	P Value	HR	P Value	HR	P Value
Age	...	.18	...	.09	...	.76	...	.95
Sex	...	.40	...	.16	...	.75	...	.23
Primary location	...	.87	...	.95	...	.32	...	.26
Tumor grade	1.72 (1.06, 2.79)	.03*	1.42 (1.00, 2.00)	.046*		.56	1.37 (1.00, 1.88)	.047*
Previous treatments	...	.86	...	.57	2.15 (1.44, 3.20)	<.001*	1.71 (1.22, 2.40)	.002*
Multiple IATs	...	.96	0.63 (0.42, 0.95)	.03*	...	.22	...	.66
Extrahepatic metastases	...	.56	...	.17	...	.73	...	.99
Visual enhancement	...	.15	...	.06	...	.76	...	.42
Visual burden	1.30 (1.00, 1.69)	.048*	...	.21	...	.21	...	.65
Response according to LETB change								
−25.8%	0.56 (0.33, 0.95)	.03*	...	...	...	...	0.47 (0.34, 0.66)	<.001*
−10%	...	...	0.44 (0.28, 0.70)	.001†	0.42 (0.29, 0.67)	<.001*	...	...

Note.—Data in parentheses are 95% CIs. Analyses were performed using stepwise selection with backward elimination. An optimal threshold of −25.8% of liver enhancing tumor burden (LETB) was used to improve prediction of overall survival and whole-body progression-free survival (PFS); an optimal threshold of −10% of LETB was used to predict time to unTA(C)Eable progression and hepatic PFS. Time to unTA(C)Eable progression is defined as the time from the initial treatment until the time when intra-arterial treatments were considered technically unfeasible, either not recommended by the multidisciplinary tumor board or until death. HR = hazard ratio, IAT = intra-arterial treatment.
* Statistically significant (P < .05).

difference in OS with all tested thresholds of LETB change (−30%, −50%, and −65%), with the best survival found with the 50% cutoff at MRI. In our study, there was a significant difference in hepatic PFS or whole-body PFS between responders and nonresponders for any of the selected LETB thresholds less than zero. This suggests that any level of decrease in LETB is associated with an improved PFS. Nevertheless, a deeper tumor response was needed to predict OS, because only patients with a −25.8% or −30.0% decrease in LETB showed improved OS compared with nonresponders. Notably, the small number of patients showing response when the LETB cutoff of −40% was selected could have limited the assessment of OS differences in patients with deeper responses.

This study was limited by its retrospective design, which included patients with different clinical histories due to numerous different treatments before intra-arterial treatments that may have influenced baseline tumor enhancement and survival outcomes. However, intra-arterial treatments are not frequently performed as first-line treatment, and in the current study, previous treatments were not significantly associated with survival outcomes in multivariable analyses. Moreover, intra-arterial treatments included both TAE and TACE. Nevertheless, there is no clear evidence that one treatment is more effective than another for NELM (27–31). Patients with incomplete CT protocols were excluded from the study sample, which may have created a selection bias. Finally, in about one-third of cases, NELM was found to be iso- to hypoenhancing before treatment, which may have limited the assessment of response criteria. Nevertheless, differences in OS and whole-body PFS according to LETB change were also confirmed in the subset of patients with iso- to hypoenhancing tumors on visual analysis, as the software allows quantification of subtle internal enhancing components of lesions that appear hypoenhancing on visual assessment.

In conclusion, the assessment of tumor response after intra-arterial treatments using a quantified LETB is feasible at contrast-enhanced CT. Our study shows that early assessment of CT response according to LETB change helps predict survival outcome in patients with NELM after intra-arterial treatments, with better discrimination than RECIST and mRECIST between responders and nonresponders. Whether these findings could be generalized to assess the efficacy of other treatment modalities and systemic therapies remains to be determined.

References

1. Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. Int J Cancer 2016;139(12):2679–2686.

2. Frilling A, Sotiropoulos GC, Li J, Kornasiewicz O, Plöckinger U. Multimodal management of neuroendocrine liver metastases. HPB (Oxford) 2010;12(6):361–379.

3. Rindi G, D'Adda T, Froio E, Fellegara G, Bordi C. Prognostic factors in gastrointestinal endocrine tumors. Endocr Pathol 2007;18(3):145–149.

4. Elias D, Lasser P, Ducreux M, et al. Liver resection (and associated extrahepatic resections) for metastatic well-differentiated endocrine tumors: a 15-year single center prospective study. Surgery 2003;133(4):375–382.

5. Pavel M, Baudin E, Couvelard A, et al; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012;95(2):157–176.

6. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–247.

7. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30(1):52–60.

8. Halappa VG, Bonekamp S, Corona-Villalobos CP, et al. Intrahepatic cholangiocarcinoma treated with local-regional therapy: quantitative volumetric apparent diffusion coefficient maps for assessment of tumor response. Radiology 2012;264(1):285–294.

9. Li Z, Bonekamp S, Halappa VG, et al. Islet cell liver metastases: assessment of volumetric early response with functional MR imaging after transarterial chemoembolization. Radiology 2012;264(1):97–109.

10. Gowdra Halappa V, Corona-Villalobos CP, Bonekamp S, et al. Neuroendocrine liver metastasis treated by using intraarterial therapy: volumetric functional imaging biomarkers of early tumor response and survival. Radiology 2013;266(2):502–513.

11. Chapiro J, Duran R, Lin M, et al. Identifying staging markers for hepatocellular carcinoma before transarterial chemoembolization: comparison of three-dimensional quantitative versus non-three-dimensional imaging markers. Radiology 2015;275(2):438–447.

12. Chapiro J, Duran R, Lin M, et al. Early survival prediction after intra-arterial therapies: a 3D quantitative MRI assessment of tumour response after TACE or radioembolization of colorectal cancer metastases to the liver. Eur Radiol 2015;25(7):1993–2003.

13. Tacher V, Lin M, Duran R, et al. Comparison of existing response criteria in patients with hepatocellular carcinoma treated with transarterial chemoembolization using a 3D quantitative approach. Radiology 2016;278(1):275–284.

14. Zhao Y, Duran R, Bai W, et al. Which criteria applied in multi-phasic CT can predict early tumor response in patients with hepatocellular carcinoma treated using conventional TACE: RECIST, mRECIST, EASL or qEASL? Cardiovasc Intervent Radiol 2018;41(3):433–442.

15. Luo Y, Pandey A, Ghasabeh MA, et al. Prognostic value of baseline volumetric multiparametric MR imaging in neuroendocrine liver metastases treated with transarterial chemoembolization. Eur Radiol 2019;29(10):5160–5171.

16. Doemel LA, Chapiro J, Laage Gaupp F, et al. Reliable prediction of survival in advanced-stage hepatocellular carcinoma treated with sorafenib: comparing 1D and 3D quantitative tumor response criteria on MRI. Eur Radiol 2021;31(5):2737–2746.

17. Sahu S, Schernthaner R, Ardon R, et al. 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? Radiology 2017;283(3):883–894.

18. Luo Y, Ameli S, Pandey A, et al. Semi-quantitative visual assessment of hepatic tumor burden can reliably predict survival in neuroendocrine liver metastases treated with transarterial chemoembolization. Eur Radiol 2019;29(11):5804–5812.

19. Sundin A, Vullierme MP, Kaltsas G, Plöckinger U; Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. Neuroendocrinology 2009;90(2):167–183.

20. WHO Classification of Tumours. Digestive System Tumours. Lyon, France: IARC, 2019.

21. Khalilzadeh O, Baerlocher MO, Shyn PB, et al. Proposal of a new adverse event classification by the society of Interventional Radiology Standards of Practice Committee. J Vasc Interv Radiol 2017;28(10):1432–1437.e3. [Published correction appears in J Vasc Interv Radiol 2018;29(1):146.]

22. Chapiro J, Wood LD, Lin M, et al. Radiologic-pathologic analysis of contrast-enhanced and diffusion-weighted MR imaging in patients with HCC after TACE: diagnostic accuracy of 3D quantitative image analysis. Radiology 2014;273(3):746–758.

23. Chockalingam A, Duran R, Sohn JH, et al. Radiologic-pathologic analysis of quantitative 3D tumour enhancement on contrast-enhanced MR imaging: a study of ROI placement. Eur Radiol 2016;26(1):103–113.

24. Tacher V, Lin M, Chao M, et al. Semiautomatic volumetric tumor segmentation for hepatocellular carcinoma: comparison between C-arm cone beam computed tomography and MRI. Acad Radiol 2013;20(4):446–452.

25. Wang Z, Lin M, Lesage D, et al. Three-dimensional evaluation of lipiodol retention in HCC after chemoembolization: a quantitative comparison between CBCT and MDCT. Acad Radiol 2014;21(3):393–399.

26. de Mestier L, Zappa M, Hentic O, Vilgrain V, Ruszniewski P. Liver transarterial embolizations in metastatic neuroendocrine tumors. Rev Endocr Metab Disord 2017;18(4):459–471.

27. Pitt SC, Knuth J, Keily JM, et al. Hepatic neuroendocrine metastases: chemo-or bland embolization? J Gastrointest Surg 2008;12(11):1951–1960.

28. Maire F, Lombard-Bohas C, O'Toole D, et al. Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumors: a prospective randomized study. Neuroendocrinology 2012;96(4):294–300.

29. Fiore F, Del Prete M, Franco R, et al. Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors. Endocrine 2014;47(1):177–182.

30. Pericleous M, Caplin ME, Tsochatzis E, Yu D, Morgan-Rowe L, Toumpanakis C. Hepatic artery embolization in advanced neuroendocrine tumors: Efficacy and long-term outcomes. Asia Pac J Clin Oncol 2016;12(1):61–69.

31. Touloupas C, Faron M, Hadoux J, et al. Long term efficacy and assessment of tumor response of transarterial chemoembolization in neuroendocrine liver metastases: a 15-year monocentric experience. Cancers (Basel) 2021;13(21):5366.