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Semi-quantitative visual assessment of hepatic tumor burden can reliably predict survival in neuroendocrine liver metastases treated with transarterial chemoembolization

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Abstract

Objectives To evaluate the accuracy and reproducibility of semi-quantitative visual assessment of hepatic tumor burden (HTB) on MRI and to investigate its prognostic value in predicting overall survival (OS) in neuroendocrine liver metastases (NELMs) treated with transarterial chemoembolization (TACE).

Methods Three independent readers blinded to the quantitative HTB measurement reviewed baseline MRI in 111 NELM patients treated with TACE. Readers visually assessed and semi-quantitatively categorized HTB using the European Neuroendocrine Tumor Society (ENETS) guidelines. Quantitative HTB measured by manual segmentation was used as the reference standard. Agreements between quantitative and semi-quantitative measurement of HTB, as well as intra- and inter-reader reproducibility, were evaluated using weighted kappa coefficient and intraclass correlation coefficient (ICC). Survival analysis included the Kaplan-Meier curves and Cox regression. Harrell C-index was calculated to evaluate the prognostic value of semi-quantitative HTB for predicting OS.

Results According to quantitative HTB, 41, 29, 25, and 16 patients were categorized into ≤ 10%, 11–25%, 26–50%, and > 50% groups, respectively. Agreements between quantitative and semi-quantitative measurement of HTB by each reader (weighted kappa, 0.82–0.96), intra-reader agreement (weighted kappa, 0.95), and inter-reader agreements (weighted kappa, 0.84–0.91; ICC, 0.98) were at least substantial to almost perfect. Semi-quantitative HTB was an independent prognostic factor in NELMs treated with TACE (multivariate Cox regression, $p < 0.001$), with prognostic value comparable to that of quantitative HTB (Harrell C-index, 0.735 for both semi-quantitative and quantitative HTB in multivariate regression).

Conclusion Semi-quantitative visual assessment of HTB using MRI is accurate and reproducible and could reliably predict OS in NELMs treated with TACE.

Key Points

- *Semi-quantitative visual assessment of HTB using MR imaging is considerably accurate, reproducible, and efficient.*
- *Visually assessed semi-quantitative HTB serves as an independent predictor of OS in NELMs treated with TACE.*

Keywords Liver neoplasms · Magnetic resonance imaging · Neuroendocrine tumors · Reproducibility of results · Tumor burden

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Abbreviations

ENETS	European Neuroendocrine Tumor Society
HTB	Hepatic tumor burden
ICC	Intraclass correlation coefficient
NELMs	Neuroendocrine liver metastases
OS	Overall survival
TACE	Transarterial chemoembolization

Introduction

Neuroendocrine neoplasms are frequently metastatic at initial diagnosis, with liver representing the most vulnerable site of metastases [1]. The reported prevalence of neuroendocrine liver metastases (NELMs) is 40–96% in specialized centers [2]. Curative-intent surgery remains the mainstay of treatment for NELMs. However, up to 80–90% of patients are unresectable at the time of presentation due to multifocal and bilobar involvement of the liver [3]. In these patients, transarterial chemoembolization (TACE) is a promising palliative treatment option, as stated in multiple guidelines [2, 4, 5].

The extent of liver involvement with metastases, or the hepatic tumor burden (HTB), is acknowledged as an important negative prognostic factor in NELMs treated with TACE [6–8]. Low HTB is associated with prolonged survival and favorable treatment response [6–8]. Furthermore, HTB has been shown to provide crucial information regarding tumor resectability and it plays a critical role in patient management [2, 5, 9, 10]. For example, for patients with low HTB (≤ 10%), octreotide is recommended, while lanreotide is preferred in patients with high HTB [2, 5, 9]. For asymptomatic patients with HTB > 25%, a previous study has suggested that intraarterial therapy (IAT) might be more appropriate, since this subgroup of patients benefited least from surgical treatment [11].

To date, no standardized quantitative method exists for fast and reliable measurement of HTB, which is usually expressed as the ratio of liver tumor volume to total liver volume. Traditionally, the volume can be measured by manual tracing of the tumor or liver contours on each computed tomography (CT) or magnetic resonance (MR) imaging section and then summing the volume of each section. Despite considerable accuracy, the manual tracing process is time-consuming. As a result, in previous studies [6, 8, 10, 12], the assessment of HTB was mainly based on a semi-quantitative visual approach. Yet the accuracy and reproducibility of this semi-quantitative visual estimation remain unknown. In addition, previous studies adopted various cut-off values to categorize HTB, making comparison across researches difficult [13–15].

Recently, the European Neuroendocrine Tumor Society (ENETS) consensus guidelines suggested that a semi-quantitative visual estimation of HTB categorized as ≤ 10%, 11–25%, 26–50%, and > 50% could be considered in NELM patients [16, 17]. The ENETS guidelines also favored the use of MR imaging in the examination of NELMs given its superior soft tissue contrast [16, 17].

Therefore, the aims of our present study were to evaluate the accuracy and reproducibility of semi-quantitative visual assessment of HTB using MR imaging categorized as per the ENETS guidelines and to investigate the prognostic value of semi-quantitative HTB for predicting overall survival (OS) in NELMs treated with TACE.

Materials and methods

This retrospective study was approved by our institutional review board. Informed patient consent was waived.

Patient population

NELM patients who underwent TACE at our institution between November 2005 and March 2015 were reviewed. Patients were included in the present study if they were liver-directed therapy-naïve and underwent multiparametric MR imaging before TACE. A multidisciplinary liver tumor board determined which patients were candidates for TACE. Standardized TACE procedures including conventional TACE (cTACE) and TACE with drug-eluting beads (DEB-TACE) were performed in accordance with our institutional protocol as previously described [18]. Demographic, clinical, and MR imaging data were collected.

MR imaging protocol

MR imaging was performed at 1.5 T and 3 T (Magnetom Avanto, Siemens Healthcare, Magnetom Verio, Siemens Healthcare and Signa HDx, GE Healthcare) using a phased-array torso coil. The protocol consisted of axial T2-weighted fast spin echo images with and without fat saturation (repetition time ms/echo time ms, 2000–4500/90–100; section thickness, 4–6 mm), axial breath-hold echo-planar diffusion-weighted images (1100–3500/45–75; section thickness, 8 mm; b values 0, 50, 500, and 750 s/mm^2), and axial breath-hold unenhanced and dynamic contrast-enhanced (gadopentetate dimeglumine (Magnevist, Bayer HealthCare) at 0.1 mmol/kg body weight) T1-weighted three-dimensional fat-suppressed spoiled gradient-echo imaging (3.95–5.77/1.35–2.77; field of view, 320–400 mm; section thickness, 2.5 mm) in the arterial, portal venous, and delayed phases (20, 70, and 180 s after intravenous administration of contrast agent, respectively).

MR imaging analysis

Quantitative measurement of HTB was performed on Advantage Workstation Volume Viewer 4.5 (GE Healthcare). Two independent MR researchers both with 2 years of experience in volumetric image analysis performed quantitative measurement of HTB in 30 randomly selected cases in our cohort. Inter-reader agreement was excellent (ICC, 0.996; differences between two readers within 4%). Thus, the remaining cases were measured by a single MR researcher. The last multiparametric MR examination before TACE was utilized for volumetric measurement. Manual delineation of the liver as well as all the hepatic metastases was performed on axial portal venous phase images. If metastatic lesions were not clear on venous phase images, the presence and the boundary of the lesions were verified on the other MR images (including arterial phase, delayed phase, diffusion-weighted, unenhanced T1-weighted, and T2-weighted images). For lesions with ill-defined margins, the tumor borders were decided based on consensus after discussion with a board-certified radiologist with 20 years of experience in abdominal MR imaging. Large vessels such as the inferior vena cava and extrahepatic portal vein and major fissures such as the fissure for the ligamentum teres were carefully excluded. The time required for manual segmentation was recorded for each patient. HTB was calculated from the following formula: HTB = (total tumor volume/total liver volume) × 100%. The quantitative HTB then was used as a reference standard and compared with semi-quantitative HTB.

Three readers with 20 years (reader 1, board-certified radiologist), 4 years (reader 2, MR research fellow), and 1 year (reader 3, MR research fellow) of experience in abdominal MR imaging independently reviewed the last multiparametric MR images before TACE and visually assessed HTB by a semi-quantitative approach. For this, readers were asked to go through all the MR image slices using the aforementioned MR sequences (including pre- and post-contrast-enhanced T1-weighted, T2-weighted, and diffusion-weighted imagings) and provide subjective estimation of HTB categorized as ≤ 10%, 11–25%, 26–50%, and > 50% in accordance with the ENETS guidelines [16, 17]. Although this semi-quantitative subjective estimation of HTB was based on reader's personal perspective, before the semi-quantitative assessment, all readers were provided with 20 examples (five examples in each category) that had been quantitatively measured and were not part of our study as a training session (Fig. 1). All readers were blinded to the results of quantitative measurement and the results of other readers. To determine intra-reader reproducibility of semi-quantitative assessment, reader 2 reassessed HTB in all patients after a period of 1 month to reduce recall bias. Discrepancies among three readers were resolved through consensus discussion and the final semi-quantitative assessment of HTB was used to stratify patients for survival analysis.

Statistical analysis

Agreement between quantitative measurement and semi-quantitative visual assessment by each reader, in addition to inter- and intra-reader agreement, was evaluated using weighted kappa values. Intraclass correlation coefficient (ICC) was used to assess agreement among three readers. The strength of agreement based on weighted kappa values can be interpreted as follows: 0–0.2, slight; 0.21–0.4, fair; 0.41–0.60, moderate; 0.61–0.8, substantial; and 0.81–1, almost perfect [19]. Similarly, higher ICC values indicate better agreement, with ICC < 0.4 indicating poor agreement, 0.4–0.59 indicating fair agreement, 0.6–0.74 indicating good agreement, and 0.75–1 indicating excellent agreement [19].

Survival time and its 95% confidence interval (95% CI) were estimated by the Kaplan-Meier method and survival difference was determined by the log-rank test. Cox proportional hazards regression model was used to detect independent prognostic factors for OS. To evaluate the prognostic value

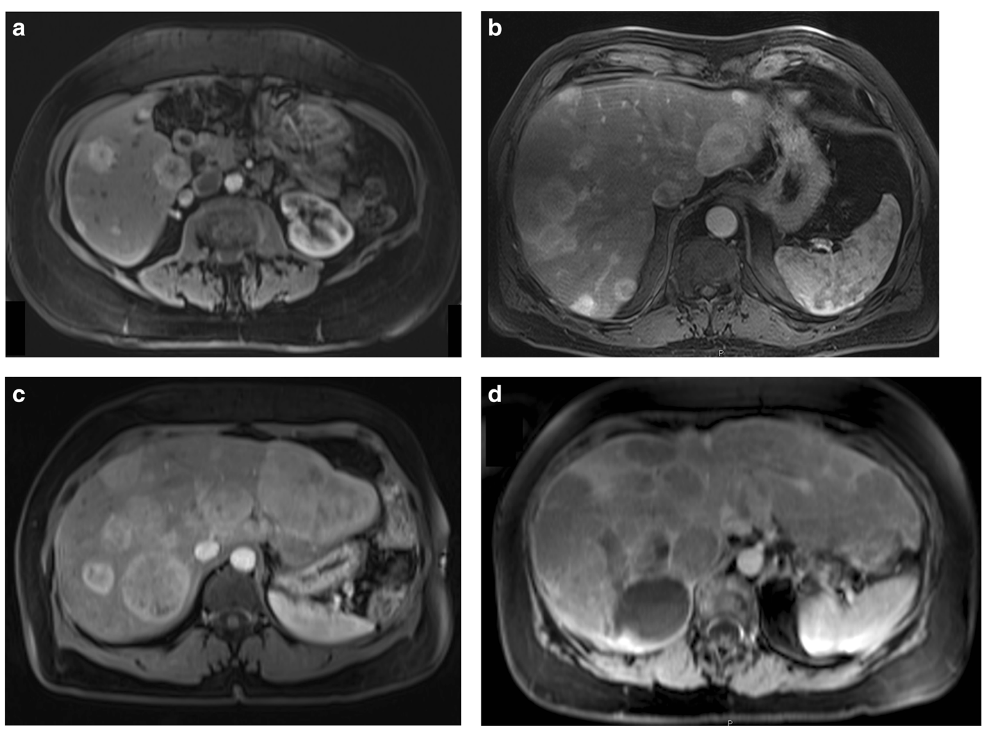


Fig. 1 Examples of hepatic tumor burden quantitatively measured by manual segmentation methods. **a** hepatic tumor burden ≤ 10%. **b** Hepatic tumor burden 11–25%. **c** Hepatic tumor burden 26–50%. **d** Hepatic tumor burden > 50%

of semi-quantitative HTB for predicting OS, Harrell C-index was calculated [20]. OS was calculated as the time interval between the date of first TACE and the date of death from any cause or last follow-up (September 30, 2017). Patients who were alive at last follow-up were censored. Two-tailed p value less than 0.05 was considered statistically significant. Statistical analysis was performed using STATA version 13.1 (StataCorp) software packages.

Results

Patient characteristics

A total of 111 NELM patients (mean age, 60 years; range, 25–87 years) were included in the study. Multifocal (104 out of 111, 94%) and bilobar (96 out of 111, 86%) involvement of liver occurred in the majority of patients. The maximum diameter of the liver metastases ranged from 1.5 to 22.3 cm (median, 5.7 cm). Prior to TACE, 19 patients underwent liver resection. The median time between the baseline MR imaging and the initial TACE session was 15 days (range, 0–60 days). The median follow-up time for our cohort was 29 months (range, 1–147 months). The median OS was 40 months (95%CI 30, 50). At the last follow-up, 77 patients (69%) had died. Additional baseline demographic and clinical characteristics are summarized in Table 1.

Quantitative and semi-quantitative assessments of HTB

Quantitatively measured HTB ranged from 1 to 81% (median, 17%; interquartile range, 4–42%). According to quantitative HTB, 41, 29, 25, and 16 patients were categorized into ≤ 10%, 11–25%, 26–50%, and > 50% groups, respectively (Table 2, Fig. 2). The average time required for manual segmentation of the total liver and all metastatic lesions in each patient was 40 ± 15 min (range, 17–83 min).

Semi-quantitative visual assessments of HTB by three readers are described in Table 2 and Fig. 2. The time spent on semi-quantitative estimation was within 5 min in any patient for all readers. For patients with a discrepancy in the categorization of semi-quantitative HTB, the three readers reached a final consensus after a thorough discussion. Finally, 42, 28, 25, and 16 patients were classified into the four aforementioned categories.

Agreements between quantitative and semi-quantitative assessments

Weighted kappa statistics showed almost perfect agreement between quantitative measurement and semi-quantitative assessment of HTB by reader 1, with a weighted kappa value of 0.96 (95% CI, 0.92–0.99). The agreements between quantitative measurement and semi-quantitative assessments by

Table 1 Baseline demographic and clinical characteristics

Characteristics	Datum
Age (years)*	
All	60 ± 11
Male	59 ± 10
Female	61 ± 13
Sex	
Male	65 (59)
Female	46 (41)
Diagnosis	
Biopsy	91 (80)
Imaging	20 (20)
Primary site	
Pancreas	42 (38)
Gastrointestinal tract	35 (32)
Lung	11 (10)
Other/unknown	23 (21)
Tumor differentiation	
Well-differentiated	78 (70)
Moderately differentiated	4 (4)
Poorly differentiated	9 (8)
Unknown	20 (18)
ECOG performance Score	
0	63 (57)
> 0	48 (43)
Extrahepatic metastases	
Present	37 (33)
Absent	74 (67)
Therapy	
cTACE	83 (75)
DEB-TACE	28 (25)
Primary tumor resection	
Yes	53 (48)
No	58 (52)
Number of metastases	
< 5	17 (15)
5–9	18 (16)
10–19	25 (23)
≥ 20	51 (46)
Maximum diameter of metastases	
< 5 cm	47 (42)
≥ 5 cm	64 (58)

Numbers in parentheses are percentages

ECOG, Eastern Cooperative Oncology Group; *cTACE*, conventional transarterial chemoembolization; *DEB-TACE*, transarterial chemoembolization with drug-eluting beads

*Data are mean ± standard deviation

reader 2 and reader 3 were substantial to almost perfect, weighted kappa values being 0.86 (95% CI, 0.79–0.91) and 0.82 (95% CI 0.75, 0.88), respectively (Table 2).

Compared with quantitative measurement, 29 patients were misclassified by 3 readers (5, 20, and 25 cases by reader 1, reader 2, and reader 3, respectively), and all cases were misclassified into adjacent categories (Table 2). The majority of misclassifications occurred in cases with HTB close to cut-off values (Fig. 2). Overestimation was more frequent than underestimation. The most common misclassification involved classifying a case with tumor burden of 26–50% into the > 50% group (Table 2).

Inter- and intra-reader reproducibility of semi-quantitative assessments

The inter- and intra-reader reproducibility of semi-quantitative assessments of HTB, expressed as weighted kappa coefficients, is shown in Table 3. The inter-reader reproducibility between readers was almost perfect, except for that between reader 1 and reader 3, which was substantial to almost perfect (weighted kappa, 0.84; 95% CI, 0.77–0.90). The overall inter-reader reproducibility among three readers, expressed as ICC (0.98; 95% CI, 0.97–0.99), was excellent.

Reader 2 repeated the semi-quantitative assessment in all patients after an interval of 1 month. Intra-reader reproducibility was almost perfect (Table 3).

Prognostic values of semi-quantitative HTB for predicting OS

Univariate survival analysis

When patients were stratified according to the final consensus on semi-quantitative HTB achieved by three readers for survival analysis, significant differences in median OS were noted (log-rank test, $p < 0.001$) (Fig. 3). Patients with HTB ≤ 10% showed best survival ($n = 42$; median OS, 62 months), while patients with HTB > 50% demonstrated worst prognosis ($n = 16$; median OS, 11 months). For patient subgroups whose HTB ranged 11–25% and 26–50%, median OS was similar (34 months and 35 months, respectively). These two subgroups of patients were also combined for further survival analysis.

Prognostic values, expressed as C-indices, of quantitative HTB as a continuous variable, semi-quantitative HTB, and other potential surrogates for HTB including the number and the maximum diameter of liver metastases are listed in Table 4. On the basis of C-indices, the prognostic value of semi-quantitative HTB assessed by a visual approach was comparable to that of quantitative HTB and was better than those of tumor number and maximum diameter.

Multivariate survival analysis

Tumor differentiation and extrahepatic metastases were the only two clinical variables associated with survival at univariate analysis (Table 5). Given their correlations with quantitative and semi-quantitative HTB (Spearman rank correlation test, $p < 0.001$) and inferior prognostic values for predicting OS, the number of metastases and the maximum diameter of metastases were excluded from multivariate analysis. Quantitative and semi-quantitative HTBs were included in multivariate Cox regression models separately. After controlling for confounding clinical factors, including tumor differentiation and extrahepatic metastases, HTB remained an independent predictor of survival, regardless of assessment approach (quantitative or semi-quantitative) (Table 4). Multivariate survival prediction models consisting of semi-quantitative HTB demonstrated similar or even slightly better prognostic value compared with the model consisting of quantitative HTB (Table 4).

Discussion

To our knowledge, this is the first study to compare the reliability and prognostic value of visually assessed semi-quantitative HTB versus manually segmented quantitative HTB in NELMs. Using the quantitative method as a reference standard, the present study demonstrated that semi-quantitative visual assessment of HTB is considerably accurate, reproducible, and efficient. Furthermore, the prognostic value of semi-quantitative HTB for predicting OS in NELMs treated with TACE is comparable to that of quantitative HTB.

In this study, the overall accuracy of semi-quantitative visual assessments of HTB was good, regardless of experience level. Nevertheless, as expected, better accuracy was noted for readers with greater experience in reading abdominal MR imaging. Less experienced readers tended to overestimate HTB. Likewise, inter-reader agreement was higher between more experienced readers. Similar results were obtained by a recent study evaluating HTB on contrast-enhanced CT images using visual semi-quantitative methods [21]. However, inter- and intra- reader agreements reported in that previous study were poorer than the current study. The higher reproducibility in our study is probably due to the use of multiparametric MR images, instead of CT images in HTB assessment. Owing to its superior tissue contrast resolution, MR imaging is generally accepted as the first-line imaging technique in NELMs. Compared with other imaging techniques including CT, somatostatin receptor scintigraphy, and ultrasonography, MR imaging remains the most sensitive modality in detecting liver metastases [22, 23]. Equivocal metastatic lesions on other images may be better characterized on MR imaging. Multiparametric MR imaging including contrast-enhanced

Table 2 Quantitative and semi-quantitative assessments of hepatic tumor burden

Quantitative measurements	Reader 1				Reader 2–1*				Reader 3				
	≤ 10%	11–25%	26–50%	> 50%	≤ 10%	11–25%	26–50%	> 50%	≤ 10%	11–25%	26–50%	> 50%	Total
≤ 10%	41	0	0	0	40	1	0	0	37	4	0	0	41
11–25%	1	27	1	0	2	23	4	0	3	19	7	0	29
26–50%	0	1	23	1	0	2	13	10	0	2	14	9	25
> 50%	0	0	1	15	0	0	1	15	0	0	0	16	16
Total	42	28	25	16	42	26	18	25	40	25	21	25	111
Weighted kappa	0.96 (0.92, 0.99)				0.86 (0.79, 0.91)				0.82 (0.75, 0.88)				

Data in parentheses are 95% confidence interval

*The first semi-quantitative assessment by reader 2

and diffusion-weighted imaging further facilitates depiction of small metastases [24]. Good detection and delineation of liver metastases on MR images could improve inter- and intra-reader reproducibility. In fact, MR imaging yielded higher inter-reader reproducibility over CT in detecting NELMs in a prior study [22]. Another reason for higher reproducibility in the present study might be due to the training session scheduled for all readers during which examples of various HTB categories were provided to the three readers allowing standardization of HTB assessment in our study.

There are currently no standardized techniques to reliably quantify HTB in NELMs. Different methods have been adopted in previous studies. Manual liver and tumor segmentation, though the gold standard for volume measurement, is not widely used in HTB quantification. This is because the manual tracing process is tedious and time-consuming, especially for multifocal metastases. In our study, the average time spent on manual quantitative measurement is about 10 times longer than semi-quantitative visual assessment. Lately, several semi-automated or automated methods have been proposed for fast volume quantification [25–27]. Mostly based on CT images, these methods generally involve complex algorithms and are still under investigation. Other researchers have used the number as well as the maximum diameter of liver metastases as surrogates for tumor burden [28–31]. However, these two variables may not necessarily reflect HTB, which may also be affected by other factors such as the growth and distribution pattern of liver metastases and total liver volume (prior history of liver resection). That might explain the inconsistent results on the association between these two variables and patient outcomes in NELMs [28–31]. In our study, although the number and the maximum diameter of liver metastases were associated with OS on univariate survival analysis, their prognostic values were inferior to that of HTB. On the other hand, visual semi-quantitative assessment of HTB is work-flow efficient due to ease, time saved, and no requirement of special software. Importantly, it can accurately reflect tumor load and reliably predict OS in NELMs treated with TACE.

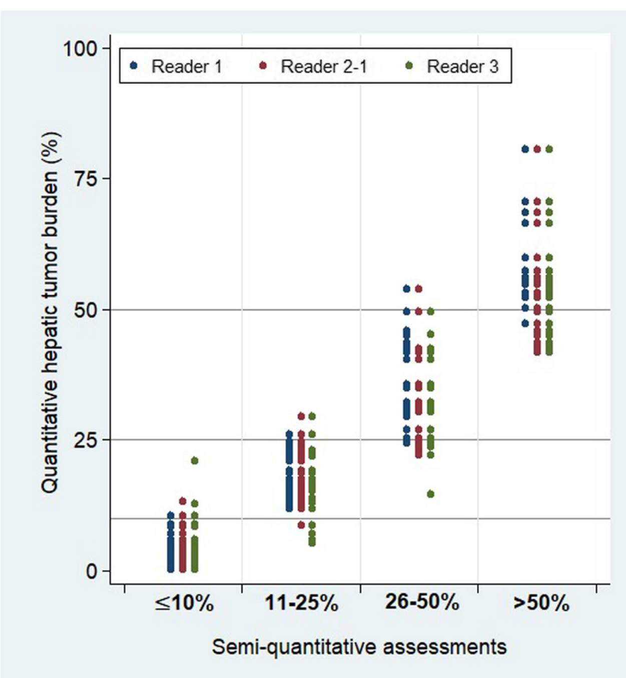


Fig. 2 Quantitative and semi-quantitative assessments of hepatic tumor burden. Reader 2–1 represents the first semi-quantitative assessment by reader 2

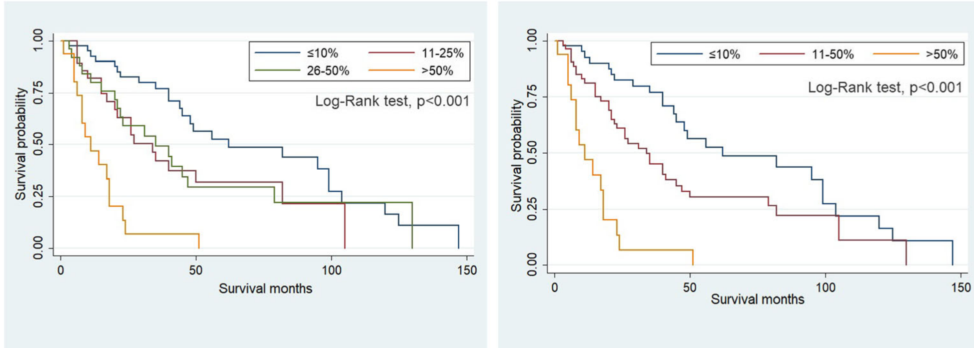
Table 3 Inter- and intra-reader reproducibility of semi-quantitative assessment of hepatic tumor burden

Readers		Weighted kappa (95% CI)
Reader 1	Reader 2–1*	0.89 (0.83, 0.94)
	Reader 3	0.84 (0.77, 0.90)
Reader 2–1*	Reader 3	0.91 (0.86, 0.95)
	Reader 2–2°	0.95 (0.91, 0.98)

*The first semi-quantitative assessment by reader 2

° The second semi-quantitative assessment by reader 2

Fig. 3 Kaplan-Meier curves of overall survival according to semi-quantitative hepatic tumor burden categorized into four groups (**a**) and three groups (**b**)



In the current study, visually assessed semi-quantitative HTB (categorized as ≤ 10%, 11–25%, 26–50%, and > 50%, in accordance with ENETS guidelines) and quantitative HTB as a continuous variable were similar in predicting OS in NELMs treated with TACE. OS was similar in patients with HTB of 11–25% and 26–50%. Combining these two groups did not affect prognostic value of semi-quantitative HTB. Consistent with our results, previous studies have shown that aforementioned cut-off values (10%, 25%, and 50%) of HTB can add prognostic information in patients with NELMs [6, 32, 33]. Although other cut-off values (33% and 75%) were also used, those studies failed to demonstrate the predictive value of HTB [15, 34]. This might be because inappropriate dichotomization of the continuous variable (HTB) affects the statistical power in survival analysis [35]. By adhering to the cut-offs suggested in the ENETS guidelines, we ensured that the thresholds used had a clinical rationale.

The exact role of TACE in the treatment of NELMs is still unclear due to the lack of prospective RCTs with large sample size. Previous retrospective studies have demonstrated that TACE is a promising treatment option to palliate symptoms and might improve prognosis in unresectable NELMs, and therefore multiple guidelines support its use [2, 4, 5]. Although the aim of the current study was not to evaluate the therapeutic efficacy of TACE, we found that visually assessed semi-quantitative HTB categorized as per the ENETS guidelines serves as an independent predictor of OS in NELMs treated with TACE. Low semi-quantitative HTB was associated with improved prognosis. This semi-quantitative visual assessment of HTB as per the ENETS guidelines could be employed in risk stratification of patients in the future prospective trials investigating the efficacy of TACE in unresectable NELMs.

Table 4 Prognostic values of hepatic tumor burden for predicting overall survival

	Univariate analysis			Multivariate analysis		
Variable	HR (95% CI)	*p* value	C-index	HR (95% CI)	*p* value	C-index
Quantitative tumor burden (continuous)	1.03 (1.01, 1.04)	< 0.001	0.675	1.03 (1.02, 1.04)	< 0.001	0.735
Semi-quantitative tumor burden (4 categories)			0.673			0.735
≤ 10%	1			1		
11–25%	1.97 (1.06, 3.64)	0.031		2.25 (1.19, 4.26)	0.013	
26–50%	1.83 (0.99, 3.40)	0.054		2.11 (1.13, 3.95)	0.020	
> 50%	7.27 (3.62, 14.61)	< 0.001		9.34 (4.48, 19.48)	< 0.001	
Semi-quantitative tumor burden (3 categories)			0.672			0.739
≤ 10%	1			1		
11–50%	1.90 (1.13, 3.21)	0.016		2.17 (1.27, 3.72)	0.005	
> 50%	7.26 (3.61, 14.58)	< 0.001		9.33 (4.48, 19.47)	< 0.001	
Number of metastases			0.614			
< 5	1					
5–9	1.43 (0.56, 3.66)	0.455				
10–19	1.72 (0.73, 4.06)	0.218				
≥ 20	2.89 (1.34, 6.23)	0.007				
Maximum diameter of metastases (continuous)	1.11 (1.04, 1.19)	0.003	0.604			

Table 5 Univariate Cox proportional hazards model of clinical parameters

Variable	Univariate analysis	
	HR (95% CI)	*p* value
Age (continuous)	1.01 (0.99, 1.03)	0.333
Sex		
Male	1	
Female	0.91 (0.57, 1.45)	0.693
Primary site		
Pancreas	1	
Gastrointestinal tract	0.94 (0.54, 1.62)	0.818
Lung	1.40 (0.61, 3.22)	0.426
Other/unknown	1.20 (0.65, 2.20)	0.565
Tumor differentiation		
Well	1	
Moderate/poor	2.87 (1.47, 5.61)	0.002
Unknown	0.87 (0.49, 1.56)	0.645
ECOG performance score		
0	1	
> 0	1.16 (0.70, 1.92)	0.570
Extrahepatic metastases		
Absent	1	
Present	1.71 (1.08, 2.71)	0.021
Therapy		
cTACE	1	
DEB-TACE	1.45 (0.86, 2.45)	0.165
Primary tumor resection		
No	1	
Yes	0.78 (0.50, 1.23)	0.294

ECOG, Eastern Cooperative Oncology Group; *cTACE*, conventional transarterial chemoembolization; *DEB-TACE*, transarterial chemoembolization with drug-eluting beads

Our study has several limitations. One limitation was the lack of radiologic-histopathological correlations. Ideally, HTB should be calculated based on histopathological examinations. However, since our patients were not surgical candidates, histopathological examinations for HTB quantification were not possible in our study. Instead, the reference standard for the current study was HTB measured using manual segmentation on multiparametric MR imaging, which is currently the most sensitive imaging technique for detecting NELMs. Thus, we believed this was the best possible approach to quantify HTB in vivo. Second, we investigated the prognostic value of visually assessed semi-quantitative HTB categorized according to the ENETs guidelines in a subgroup of NELM patients treated with TACE. Its use in other NELM treatment subgroups might need to be validated. The same visual semi-quantitative approach has been shown to predict prognosis in NELMs receiving octreotide [10]. However, NELM patients undergoing surgical treatment theoretically should have lower HTB than our cohort, and thus different cut-off values for semi-quantitative HTB might be needed. Third, since this was a single-institution study, cross-validation from a different institution was not achieved. Future multicenter studies are needed to cross-validate the accuracy and reproducibility of visual semi-quantitative HTB assessment. Last, examples were provided before the visual semi-quantitative assessment of HTB, which might have improved the accuracy as well as inter- and intra-reader agreement in our study. However, our study did demonstrate that after training with some cases (for example, 20 cases in the current study), readers with certain experience could use visual semi-quantitative method to assess HTB with considerable accuracy and reproducibility. According to our results, we advocate training before HTB assessment, especially in less-experienced readers and in future multicenter studies.

In conclusion, semi-quantitative visual assessment of HTB using multiparametric MR imaging is accurate, reproducible, and efficient compared with quantitative assessment using manual segmentation. Visually assessed semi-quantitative HTB serves as an independent predictor of OS in NELMs treated with TACE. As the ENETs guidelines suggested, semi-quantitative visual assessment of HTB categorized as ≤ 10%, 11–25%, 26–50%, and > 50% could be used in NELM clinical trials.

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Compliance with ethical standards

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Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in a previously published paper (Gowdra HV et al Neuroendocrine liver metastasis treated by using intraarterial therapy: volumetric functional imaging biomarkers of early tumor response and survival. Radiology 2013; 266:502–513). We have reported on 55 out of 111 patients included in the current study. However, the prior report focused on the volumetric changes in multiparametric MR post TACE. The current study doubled the sample size and focused on a completely different aspect, the assessment of hepatic tumor burden.

Methodology
• Retrospective
• Diagnostic or prognostic study
• Performed at one institution

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