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MAGNETIC RESONANCE

Prognostic value of baseline volumetric multiparametric MR imaging in neuroendocrine liver metastases treated with transarterial chemoembolization

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Abstract

Objectives To determine whether baseline multiparametric MR imaging can predict overall survival (OS) and hepatic progression-free survival (HPFS) in patients with neuroendocrine liver metastases (NELMs) treated with transarterial chemoembolization (TACE).

Methods This retrospective study included 84 NELMs patients treated with TACE. Tumor volume and volumetric measurements of arterial enhancement (AE), venous enhancement (VE), and apparent diffusion coefficient (ADC) were performed on baseline MR imaging. A maximum of one, two, and five index lesions were selected in each patient. OS was the primary endpoint and HPFS was the secondary endpoint. Prognostic values of volumetric multiparametric MR parameters for predicting OS and HPFS considering a maximum of one, two, and five index lesions were assessed.

Results Prognostic values of volumetric multiparametric MR parameters for predicting OS and HPFS were similar regardless of the maximum number of index lesions. Multivariate survival analysis showed that baseline dominant tumor volume ≥ 73 cm^3, volumetric mean AE ≥ 45%, and mean VE ≥ 73% were independent prognostic factors for OS (HR 2.73; 95% CI 1.45, 5.15; HR 0.32; 95% CI 0.17, 0.63; HR 0.35; 95% CI 0.17, 0.72, respectively) and HPFS (HR 2.30, 95% CI 1.38, 3.84; HR 0.46, 95% CI 0.25, 0.84; HR 0.36, 95% CI 0.19, 0.57, respectively). OS and HPFS were similar in patients with low and high volumetric mean ADC.

Conclusion Volumetric enhancement values and tumor volume of the dominant lesion on baseline MR imaging may act as prognostic factors for OS and HPFS in NELMs patients treated with TACE.

Key Points

- *High volumetric mean AE and VE, and low tumor volume of the dominant lesion on baseline MR imaging were associated with favorable OS and HPFS in NELMs patients treated with TACE.*
- *Evaluation of multiple lesions does not provide additional information as compared to single lesion evaluation.*

Keywords Chemoembolization · Liver neoplasms · Magnetic resonance imaging · Neuroendocrine tumors · Prognosis

Abbreviations

ADC	Apparent diffusion coefficient
AE	Arterial enhancement
DWI	Diffusion-weighted imaging
EASL	European Association for the Study of the Liver
HPFS	Hepatic progression-free survival
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
NELMs	Neuroendocrine liver metastases
OS	Overall survival
PFS	Progression-free survival
TACE	Transarterial chemoembolization
VE	Venous enhancement

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Introduction

Neuroendocrine tumors (NETs) comprise a spectrum of neoplasms arising from amine precursor uptake and decarboxylation (APUD) cells throughout the body. The reported annual age–adjusted incidence of NETs has increased to 5.25 out of 100,000 subjects, while the estimated prevalence reached 35 out of 100,000 subjects in the USA [1]. Despite the relatively indolent nature of NETs, roughly one fifth of patients present with synchronous distant metastasis at initial diagnosis, with the liver being the most common site [2]. Hepatic metastases occur in 46–93% patients with NETs during the disease course [3], and are acknowledged as an important negative prognostic factor, irrespective of the primary sites [4, 5]. Surgery remains the only potentially curative treatment for neuroendocrine liver metastases (NELMs). However, only a small percentage of patients are eligible for surgical resection due to multifocal and bilobar involvement of the liver. For those deemed unsuitable candidates for resection, transarterial chemoembolization (TACE) is an appropriate option to palliate symptoms and improve prognosis, as stated in multiple guidelines [4–6].

Assessing treatment response, especially early response post TACE is crucial in clinical practice. Conventional anatomic tumor response evaluation metrics, including World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST), have been proven to be inadequate in intra-arterial therapy scenarios, which induce tumor necrosis rather than size shrinkage [7]. Functional magnetic resonance (MR), such as contrast-enhanced and diffusion-weighted imaging (DWI), is able to monitor post-treatment changes in tumor microenvironment before any morphological change is visible [8, 9]. Reliable assessment of therapeutic response mainly focuses on pre- and post-TACE changes in functional MR imaging parameters. For example, European Association for the Study of the Liver (EASL) and modified RECIST (mRECIST) criteria, which are based on changes in bi-dimensional and uni-dimensional diameter of viable enhancing tumor, respectively, have shown good correlation with survival outcome in patients treated with TACE [10]. On the other hand, DWI-derived apparent diffusion coefficient (ADC) change is also considered a promising imaging biomarker of tumor response following loco-regional therapy in primary and secondary hepatic malignancies [9, 11, 12].

Identifying patient subgroups who would benefit from TACE preferably before treatment is desired for the personalized management of NELMs patients. Recent studies have suggested a possible association between pretreatment ADC and therapeutic outcome in different tumors [13–16]. Vascularization evaluated on preprocedure contrast-enhanced images might also serve as a predictor of prognosis in patients receiving intra-arterial therapy [17–19].

Volumetric assessment enables comprehensive evaluation of the whole lesion and improves interobserver reproducibility, and thus is advocated in oncologic imaging [20, 21]. In fact, in early prediction of therapeutic outcomes, volumetric changes of functional MR imaging have been demonstrated to be more accurate than current measurements based on single axial section region of interest (ROI) [22–24]. To our knowledge, no prior study addressed the prognostic role of pretreatment functional MR imaging in NELMs using volumetric approaches.

Our present study aims to determine whether baseline volumetric diffusion-weighted and contrast-enhanced MR imaging are of prognostic value in predicting overall survival (OS) and hepatic progression-free survival (HPFS) in NELMs patients treated with TACE.

Materials and methods

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

Patient population

NELMs patients who underwent TACE between November 2005 and March 2015 were identified from our institutional imaging database. Patients were included if they were liver-directed therapy naïve and underwent standard multiparametric MR imaging within 6 weeks before TACE. Database search identified 152 patients; 68 patients were excluded because of prior liver-directed therapy ($n = 28$) or inadequate MR imaging ($n = 40$) (Fig. 1). Patients who received prior systemic therapy (somatostatin analogues, interferon,

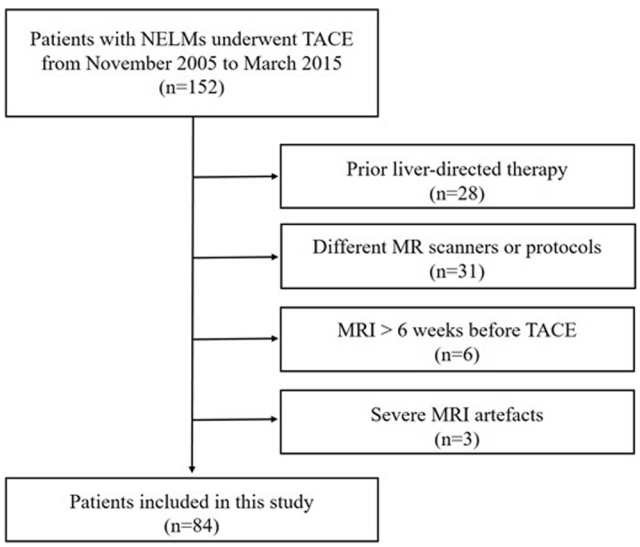

Fig. 1 Flow chart of the study population selection

chemotherapy, or molecular-targeted medicine) or liver resection were included. We did not exclude patients with prior systemic treatment, because TACE is considered as a second-line option in unresectable NELMs, which might appear metachronously years after the initial diagnosis and treatment of the primary tumor. The final study population consisted of 84 patients. Demographic, clinical, and imaging data were recorded.

TACE procedure

A multidisciplinary liver tumor board determined whether patients were eligible for TACE, which included conventional TACE (cTACE) and TACE with drug-eluting beads (DEB-TACE) and was performed in accordance with standardized protocols that have been previously described elsewhere [9] (Supplementary Data).

MR imaging protocol

All imaging was performed on a 1.5T MR scanner (MagnetomAvanto; Siemens) with a phased-array torso coil using a standard liver imaging protocol. The protocol included axial breath-hold diffusion-weighted echo-planar imaging (repetition time msec/echo time msec, 3000/69; matrix, 128 × 128, section thickness, 8 mm; intersection gap, 2 mm; *b* values, 0 and 750 s/mm^2) and axial breath-hold unenhanced and dynamic contrast-enhanced (0.1 mmol of intravenous gadopentetate per kilogram of body weight [Magnevist; Bayer]) T1-weighted three-dimensional fat-suppressed spoiled gradient-echo imaging (5.77/2.77; field of view, 320–400 mm; matrix, 192 × 160; section thickness, 2.5 mm; flip angle, 10°) in the hepatic arterial, portal venous, and delayed phases (20, 70, and 180 s after intravenous administration of contrast agent, respectively).

MR image analysis

MR image analysis was performed by a researcher with 4 years of experience in abdominal MR imaging using proprietary software (MRArithmetric and Multiparametric Analysis; Siemens Medical Solutions USA Inc.). First, Digital Imaging and Communications in Medicine (DICOM) data including pre-contrast, arterial, and portal-venous phase images were loaded into MRArithmetric prototype and co-registered with a non-rigid algorithm to create arterial enhancement (AE) and venous enhancement (VE) map. AE and VE were calculated from the following formulae $[(A-P)/P]\times 100\%$ and $[(V-P)/P]\times 100\%$, respectively, where, *A* denotes the signal intensity (SI) in hepatic arterial phase, *V* denotes the SI in portal-venous phase, and *P* denotes the SI in pre-contrast phase. Next, the portal-venous phase images, the previously computed AE and VE maps, the low *b* value ($b = 0$ s/mm^2) DW images, and the ADC map were loaded into the multiparametric analysis prototype and elastically co-registered. An interactive semiautomatic "Random-Walker" three-dimensional segmentation technique was used to segment the index tumor on the fused multiparametric MR images, as described in prior studies [24, 25]. Finally, the software calculated and output volumetric statistics for ADC, AE, and VE as well as tumor volume. Given that the majority of patients in our cohort had multifocal hepatic metastases, a maximum of the largest one, two, and five index lesions that had been treated during the first session of TACE were selected in each patient. Tumor volumes and volumetric measurements of AE, VE, and ADC were calculated accordingly. The index lesions were at least 2 cm in diameter for volumetric evaluation [25].

Follow-up MR imaging was performed at 3–7 weeks after TACE procedure, subsequently at an interval of 2–6 months for the first 2 years and at least annually thereafter until death or loss to follow-up. Follow-up images were reviewed in all patients. Treatment response was assessed according to mRECIST criteria [7]. Progressive disease was defined as an increase of at least 20% in the sum of the longest diameters in the enhancing target lesions or an appearance of one or more new lesions [7]. Date of the first follow-up images demonstrating radiological progression was recorded to calculate HPFS.

Statistical analysis

Volumetric measurements of mean ADC, AE, and VE among the largest one, two, and five index lesions were compared using Friedman test. Mann-Whitney test was performed to determine if baseline tumor volume and volumetric mean ADC, AE, and VE were significantly different between patients with and without prior systemic treatment.

OS was calculated from the date of first TACE to the date of death from any cause or last follow-up (September 30, 2017), or until 90 months after initial TACE, which is approximately twice the previously reported median OS of NELMs patients treated with TACE [26, 27]. HPFS was calculated from the date of first TACE to the date of progression or death or last follow-up. For survival analysis, median values of tumor volume and each of the volumetric multiparametric MR imaging parameters were used to dichotomize patients into two groups. Median OS, median HPFS, and their 95% confidence intervals (CIs) were estimated by Kaplan-Meier method and survival difference was determined by log-rank test. Multivariate Cox proportional hazards regression model was used to detect independent prognostic factors of patient outcomes. Variables with $p < 0.1$ at univariate analysis were included into multivariate analysis. Harrell C-index was calculated for each survival prediction model considering the largest one, two, and five index lesions, respectively, to assess the prognostic value and to identify the optimal number of index lesions needed for an accurate assessment [28, 29]. Two-tailed

$p < 0.05$ was considered statistically significant. Statistical analysis was performed using STATA (version 13.1) software packages.

Results

Demographic data

A total of 84 patients (51 men; mean age, 59 years; range, 25–87 years) were included into this study. The majority of patients (78 out of 84, 93%) had multifocal metastases. In total, 227 TACE procedures were performed, with a median of three sessions per patient (range, one to nine). The median time interval between baseline MR imaging and first TACE procedure was 12 days (range, 0–40 days). Prior to TACE, 46 patients received systemic treatment, with somatostatin analogues being the most commonly used medicine in 32 patients, chemotherapy in 6 patients, and combination therapy in 8 patients. Baseline patient characteristics are summarized in Table 1.

Overall survival and hepatic progression-free survival data

The median follow-up time was 28 months (range, 1–90 months). At the time of the last follow-up, 49 patients (58%) had died. Radiological progression of liver metastases was observed in 71 patients (85%). The median OS and HPFS of all patients was 40 months (95% CI 28, 52) and 16 months (95% CI 8, 23), respectively.

Baseline tumor volume and volumetric multiparametric MR measurements

The maximum number of index lesions was one in 18 patients (21%), two in 12 patients (14%), and three or more in 54 patients (64%). No significant difference was noted in the volumetric mean ADC ($p = 0.259$), AE ($p = 0.120$), and VE ($p = 0.934$), when the largest one, two, or five index lesions were selected. Baseline tumor volume and volumetric measurements were not significantly different between patients with and without prior systemic treatment (Fig. 2).

Prognostic values of tumor volume and volumetric multiparametric MR metrics for OS

Univariate survival analysis

Patients were stratified based on median tumor volume, and volumetric mean ADC, AE, and VE for survival analysis. When using the largest one index lesion, univariate analysis revealed a significantly better prognosis in patients with low tumor volume (< 73cm^3) compared to patients with high tumor

Table 1 Baseline patient characteristics

Characteristics	Datum
Age (year)*	
All	59 ± 12
Male	60 ± 10
Female	59 ± 14
Sex	
Male	51 (61)
Female	33 (39)
Ethnicity	
White	66 (79)
Africa American	14 (17)
Other	4 (5)
Diagnosis	
Biopsy	67 (80)
Imaging	17 (20)
Tumor type	
Islet cell tumors	34 (40)
Carcinoid	28 (33)
Small cell type	5 (6)
Unknown primary	17 (20)
Tumor differentiation	
Well differentiated	60 (71)
Moderately differentiated	1 (1)
Poorly differentiated	6 (7)
Unknown	17 (20)
Plasma Chromogranin A	
Normal	24 (29)
Elevated	48 (57)
Unknown	12 (14)
ECOG performance Score	
0	51 (61)
> 0	33 (39)
Extrahepatic metastases	
Present	32 (38)
Absent	52 (62)
Therapy	
cTACE	59 (70)
DEB-TACE	25 (30)
Prior treatment	
Primary tumor resection	38 (45)
Systemic therapy	46 (55)
Liver resection	12 (14)
Concurrent somatostatin analogues treatment	
Yes	44 (52)
No	40 (48)

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

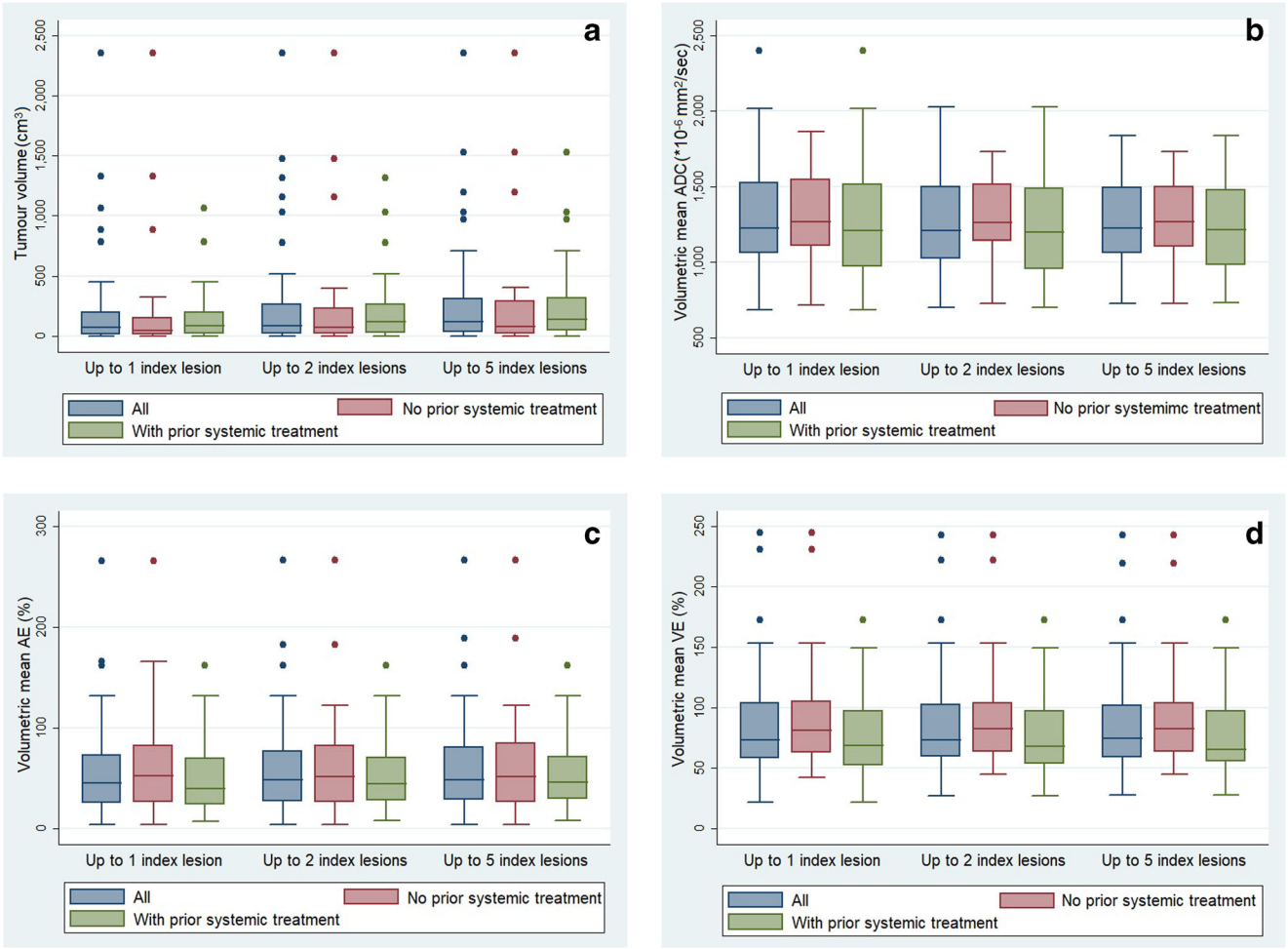

Fig. 2 Box and whisker plots of baseline tumor volume and volumetric MR functional metrics. The horizontal line inside each box represents the median value. The top and bottom of each box represent 25% and 75% percentile, respectively. Circles represent outliers. **a** Baseline tumor volume, **b** baseline volumetric mean ADC, (**c**) baseline volumetric mean AE, and **d** baseline volumetric mean VE. The median baseline tumor volume was 73, 88, and 116 cm^3 for the largest one, two, and five index lesions, respectively ($p < 0.001$). Volumetric mean ADC, AE, and VE were similar when the largest one, two, or five index lesions were selected (p value, 0.259, 0.120, and 0.934, respectively)

volume (≥ 73 cm^3) (median OS, 48 months vs. 20 months, $p = 0.014$). High baseline volumetric mean enhancements were significantly associated with a prolonged median OS. Patients who demonstrated a volumetric mean AE $\geq 45\%$ or VE $\geq 73\%$ showed an improved survival compared to patients who had volumetric mean enhancements below thresholds (AE: median OS, 50 months vs. 22 months, $p = 0.003$; VE: median OS, 48 months vs. 22 months, $p = 0.017$). Baseline volumetric mean ADC, by contrast, failed to show a significant impact on OS (median OS of 41 and 40 months in patients with low ($< 1226 \times 10^{-6}$ mm^2/s) and high ADC ($\geq 1226 \times 10^{-6}$ mm^2/s), respectively, $p = 0.400$) (Figs. 3 and 4).

Likewise, when using the largest two and five index lesions, low tumor volume and high volumetric mean AE and VE were significant prognostic factors for a prolonged survival. Prognostic abilities of each parameter, expressed as c-indices, were similar when measuring the largest one, two, and five index lesions (Table 2).

Multivariate survival analysis

According to the results of univariate analysis (Table 3), baseline tumor volume and volumetric mean enhancements, as well as clinical variables including extrahepatic metastases, treatment number, tumor differentiation, and tumor type, were analyzed in multivariate survival analysis. After adjusting for confounding clinical factors, baseline tumor volume and volumetric mean AE, and VE were independent predictors of OS, regardless of the maximum number of index lesions (Table 4).

Prognostic values of tumor volume and volumetric multiparametric MR metrics for HPFS

Similar to the results of OS, significantly longer HPFS was noted for patients with low baseline tumor volume, and high volumetric mean AE and VE in both univariate and multivariate survival analysis, regardless of the maximum number of

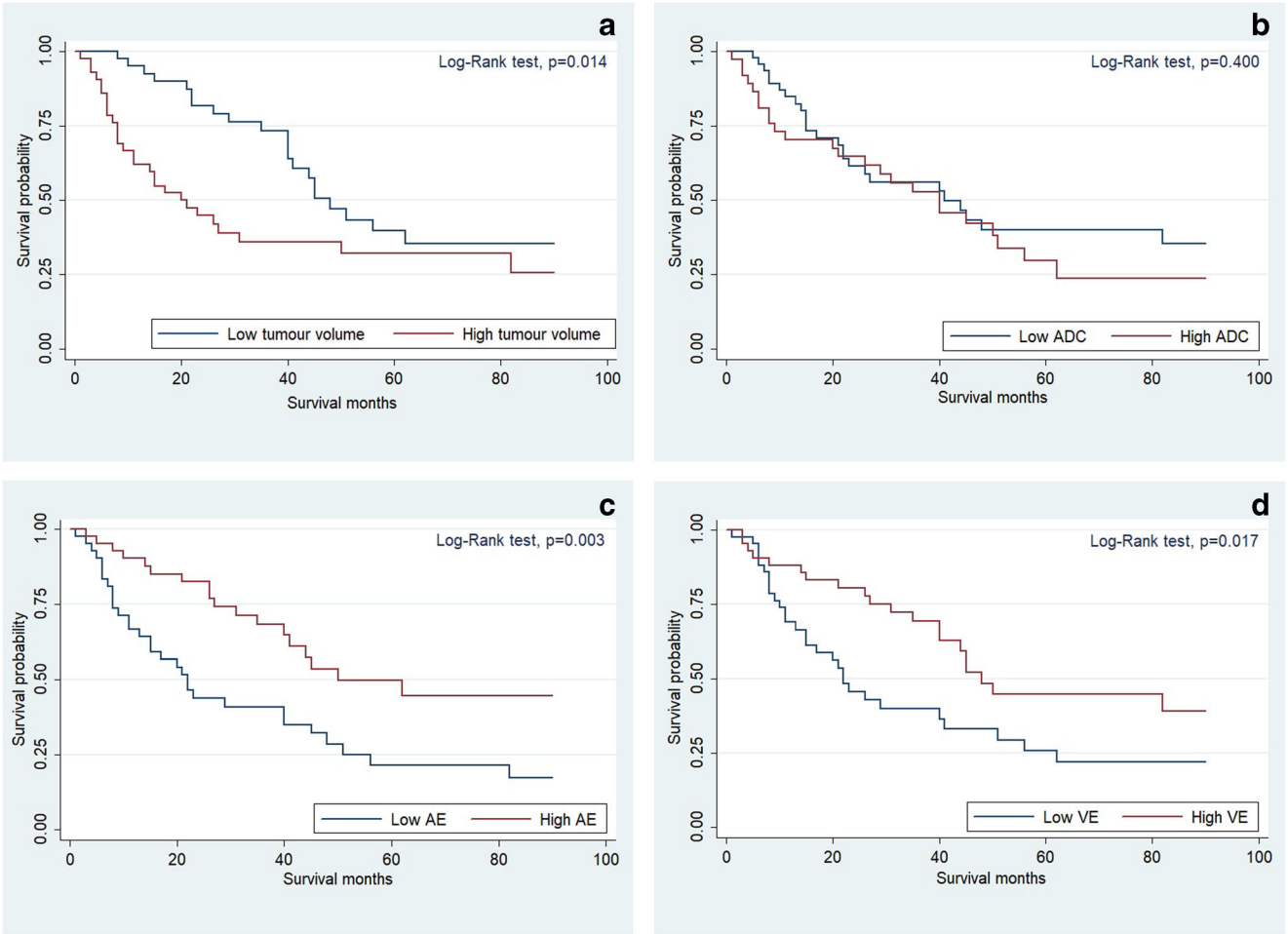

Fig. 3 Kaplan-Meier curves of overall survival using the largest one index lesion. Patients were dichotomized according to (**a**) baseline tumor volume (< 73 and ≥ 73 cm^3), (**b**) baseline volumetric mean ADC (< 1226 and ≥ 1226×10^{-6} mm^2/s), (**c**) baseline volumetric mean AE (< 45% and ≥ 45%), and (**d**) baseline volumetric mean VE (< 73% and ≥ 73%)

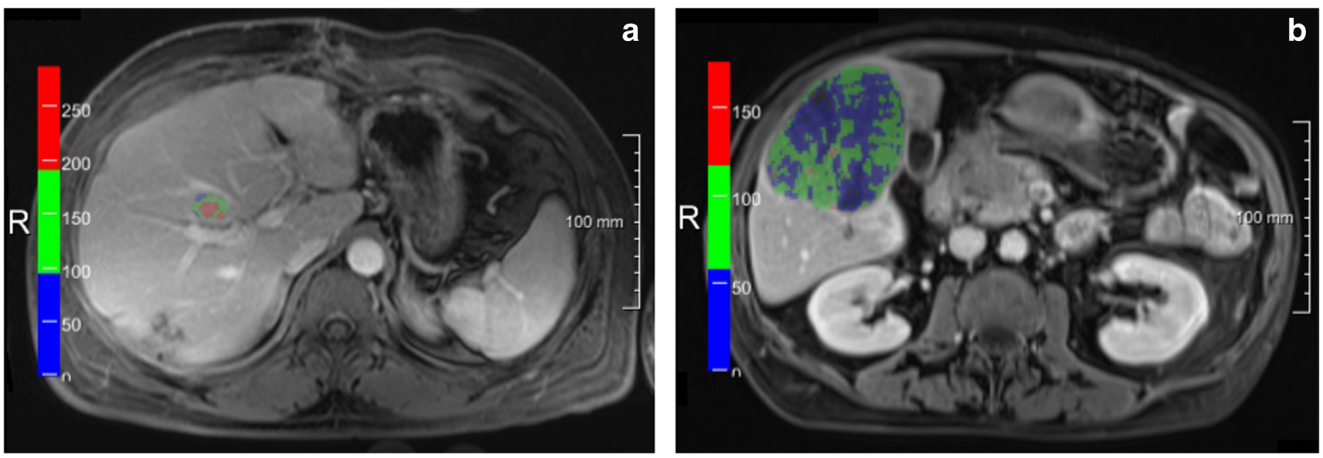

Fig. 4 MR image (**a**) in a 42-year-old male patient with neuroendocrine liver metastases demonstrating low baseline tumor volume (6.3 cm^3) and high baseline volumetric enhancements (AE = 162%; VE = 150%). OS was 90 months and HPFS was 42 months. MR image (**b**) in a 60-year-old male patient with neuroendocrine liver metastases demonstrating high baseline tumor volume (208 cm^3) and low enhancements (AE = 30%; VE = 63%). Patient died 7 months post TACE with a HPFS of 4 months. Segmented lesions with voxelwise VE are shown in axial venous phase contrast-enhanced MR image

Table 2 Prognostic values of baseline tumor volume and volumetric multiparametric MR metrics for OS and HPFS

		Up to 1 index lesion	Up to 2 index lesions	Up to 5 index lesions
Tumor volume	Median values (cm^3)	73	88	116
	C-index for OS	0.637 (0.570, 0.705)	0.652 (0.587, 0.718)	0.651 (0.587, 0.716)
	C-index for HPFS	0.602 (0.537, 0.667)	0.614 (0.551, 0.676)	0.625 (0.564, 0.686)
Baseline volumetric mean AE	Median values (%)	45	49	49
	C-index for OS	0.600 (0.523, 0.676)	0.605 (0.529, 0.682)	0.605 (0.529, 0.682)
	C-index for HPFS	0.595 (0.532. 0.660)	0.611 (0.549, 0.674)	0.611 (0.549, 0.674)
Baseline volumetric mean VE	Median values (%)	73	73	75
	C-index for OS	0.623 (0.550, 0.695)	0.636 (0.564, 0.707)	0.636 (0.564, 0.707)
	C-index for HPFS	0.591 (0.524. 0.659)	0.605 (0.540, 0.670)	0.605 (0.540, 0.670)
Baseline volumetric mean ADC	Median values ($\times 10^{-6}$ mm^2/s)	1226	1210	1225
	C-index for OS	0.534 (0.453, 0.614)	0.497 (0.417, 0.578)	0.480 (0.400, 0.561)
	C-index for HPFS	0.546 (0.475, 0.616)	0.519 (0.448, 0.590)	0.534 (0.464, 0.604)

Numbers in parentheses are 95% CI

OS, overall survival; *HPFS*, hepatic progression-free survival; *AE*, arterial enhancement; *VE*, venous enhancement; *ADC*, apparent diffusion coefficient

index lesions (Fig. 5, Tables 2 and 4). HPFS was similar in patients with low and high volumetric mean ADC. Prognostic values of tumor volume and volumetric mean ADC, AE, and VE in predicting HPFS were similar when considering the largest one, two, and five index lesions (Table 2).

Discussion

The current study is the first study to the best of our knowledge investigating the prognostic value of baseline volumetric multiparametric MR imaging in NELMs treated with TACE. Identifying non-invasive imaging biomarkers associated with prolonged survival before TACE might improve cost-effectiveness and reduce the possible side effect of TACE. Our study demonstrated that high volumetric mean AE and VE, and low tumor volume of the dominant lesion on baseline MR imaging correlated with favorable OS and HPFS in NELMs patients treated with TACE. Furthermore, evaluation of multiple lesions does not provide additional information as compared to single lesion evaluation.

The rationale for TACE is based on the intra-arterial delivery of chemotherapeutic drugs and embolic agents, which causes occlusion of tumor blood supply and retention of chemotherapeutic drugs within the tumor, and eventually leads to tumor necrosis. Tumor vascularity, reflected by enhancement on radiological images, plays a vital role in this delivery process. Previous studies on hepatocellular carcinoma (HCC) reported an association between avid enhancement before TACE and near-complete lesion necrosis in post-treatment pathological examinations [30]. Similarly, preprocedure hyperenhancement was found to be a predictor of delayed progression in NELMs treated with TACE and radioembolization [18, 31], while hypoenhancement was associated with early progression [32]. However, tumor enhancement was assessed qualitatively in those previous studies. Employing a volumetric quantitative method, we demonstrated that high enhancement on baseline MR imaging was an independent prognostic factor for OS and HPFS after TACE in NELMs patients, which was in accordance with the basis of TACE and those previous reports.

Regarding the role of pretreatment ADC in predicting patient outcomes, conflicting results exist. Negative correlations between pretherapy ADC and progression-free survival (PFS) were found in newly diagnosed glioblastoma treated with bevacizumab [33]. On the contrary, low pretreatment ADC was associated with poor PFS in recurrent glioblastoma treated with bevacizumab [34]. Similarly, studies on HCC receiving TACE yielded inconclusive results [13, 35]. Although Min et al found that baseline ADC might be a predictor of OS in hepatic NETs (including both primary and secondary) [36], our current study showed no correlation between pretreatment ADC and therapeutic outcomes in NELMs treated with TACE. Consistent with our findings, one study showed that baseline ADC was not able to predict OS or PFS in colorectal liver metastases treated with chemotherapy [37]. The discordances may be due to the differences in the tumor entities and treatments investigated, in the inclusion and exclusion criteria employed (whether patients with previous treatment were excluded), and in the *b* values used to calculate ADC. Future studies with larger database or prospective design may be needed to investigate the relationship between pretreatment ADC and survival after TACE in NELMs patients; after all, survival represents an objective endpoint and is also the ultimate goal of treatment.

Hepatic tumor burden is considered a prognostic factor for survival and treatment response in NELMs [38–40]. However, due to the lack of a reliable quantitative method to calculate hepatic tumor burden, in most of the studies [38–40],

Table 3 Univariate Cox proportional hazard model of clinical parameters for OS and HPFS

	OS		HPFS	
Variable	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.01(0.98, 1.03)	0.566	1.00 (0.98, 1.02)	0.979
Sex				
Male	1	0.103	1	0.098
Female	0.61(0.33, 1.11)		0.67 (0.41, 1.08)	
Tumor type				
Islet cell tumors	1		1	
Carcinoid	0.65 (0.32, 1.34)	0.242	0.72 (0.41, 1.26)	0.252
Small cell type	3.88 (1.40, 10.78)	0.009	2.47 (0.93, 6.54)	0.069
Unknown	1.22 (0.60, 2.51)	0.581	0.75 (0.39, 1.44)	0.385
Tumor differentiation				
Well	1		1	
Moderate/poor	2.83 (1.17, 6.87)	0.021	2.44 (1.08, 5.51)	0.031
Unknown	0.65 (0.30, 1.40)	0.267	0.54 (0.28, 1.03)	0.060
Plasma chromogranin A*				
Normal	1		1	
Elevated	1.21 (0.81, 1.82)	0.358	1.04 (0.74, 1.46)	0.834
ECOG performance Score				
0	1	0.993	1	0.386
> 0	1.00 (0.53, 1.91)		1.26 (0.74, 2.15)	
Extrahepatic metastases				
Absent	1	0.020	1	0.218
Present	1.96 (1.11, 3.45)		1.36 (0.83, 2.21)	
Therapy				
cTACE	1	0.787	1	0.537
DEB-TACE	1.09 (0.58, 2.07)		1.18 (0.69, 2.03)	
Primary tumor resection				
No	1	0.705	1	0.784
Yes	1.11 (0.64, 1.95)		1.07 (0.67, 1.71)	
Prior systemic therapy				
No	1	0.781	1	0.660
Yes	0.92 (0.52, 1.63)		1.11 (0.69, 1.78)	
Concurrent somatostatin analogues treatment				
No	1	0.469	1	0.346
Yes	0.81 (0.46, 1.43)		1.25 (0.78, 2.01)	
Treatment number	0.84 (0.68, 1.03)	0.095	0.93 (0.79, 1.10)	0.428

ECOG, Eastern Cooperative Oncology Group; *OS*, overall survival; *HPFS*, hepatic progression-free survival; *cTACE*, conventional transarterial chemoembolization; *DEB-TACE*, transarterial chemoembolization with drug-eluting beads

*Data available for 72 patients

the estimation of tumor burden was based on a semi-quantitative visual approach and various threshold values were adopted. Recently, the reproducibility of this semi-quantitative visual assessment of tumor burden was evaluated in NELMs and interobserver agreement was reached in only 58% of the cases [41]. Here we found that tumor volume of index lesions generated automatically during volumetric multiparametric MR imaging analysis enabled prognostic stratification of NELMs treated with TACE. Tumor volume might serve as a surrogate before the development of a new quantitative method to measure tumor burden accurately.

Similar to our findings, Sahu et al [42] showed that enhancing tumor burden could be used as an imaging biomarker in NELMs treated with TACE. However, the current study is different from the study by Sahu et al in the following aspects. Firstly, the MR parameters used in our study were different.

Table 4 Multivariate Cox proportional hazard model of baseline tumor volume and volumetric multiparametric MR metrics for OS and HPFS

		OS		HPFS	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Tumor volume	Up to 1 index lesion	3.57 (1.80, 7.07)	< 0.001	2.30 (1.38, 3.84)	0.001
	Up to 2 index lesions	4.96 (2.44, 10.09)	< 0.001	3.37 (1.96, 5.79)	0.000
	Up to 5 index lesions	4.26 (2.15, 8.45)	< 0.001	3.56 (2.02, 6.25)	0.000
Baseline volumetric mean AE	Up to 1 index lesion	0.33 (0.17, 0.65)	0.001	0.46 (0.25, 0.84)	0.012
	Up to 2 index lesions	0.27 (0.13, 0.55)	< 0.001	0.43 (0.23, 0.79)	0.007
	Up to 5 index lesions	0.27 (0.13, 0.55)	< 0.001	0.43 (0.23, 0.79)	0.007
Baseline volumetric mean VE	Up to 1 index lesion	0.36 (0.18, 0.74)	0.005	0.36 (0.19, 0.67)	0.001
	Up to 2 index lesions	0.35 (0.17, 0.72)	0.004	0.32 (0.18, 0.60)	0.000
	Up to 5 index lesions	0.35 (0.17, 0.72)	0.004	0.32 (0.18, 0.60)	0.000

OS, overall survival; *HPFS*, hepatic progression-free survival; *AE*, arterial enhancement; *VE*, venous enhancement

The previous study by Sahu et al used single parameter, enhancing tumor burden, which was defined as the volume of tumor that was more than two standard deviations the signal intensity of a region of interest in normal liver [42]. Our study on the other hand used multiple parameters including tumor volume, and volumetric mean AE and VE, with AE and VE

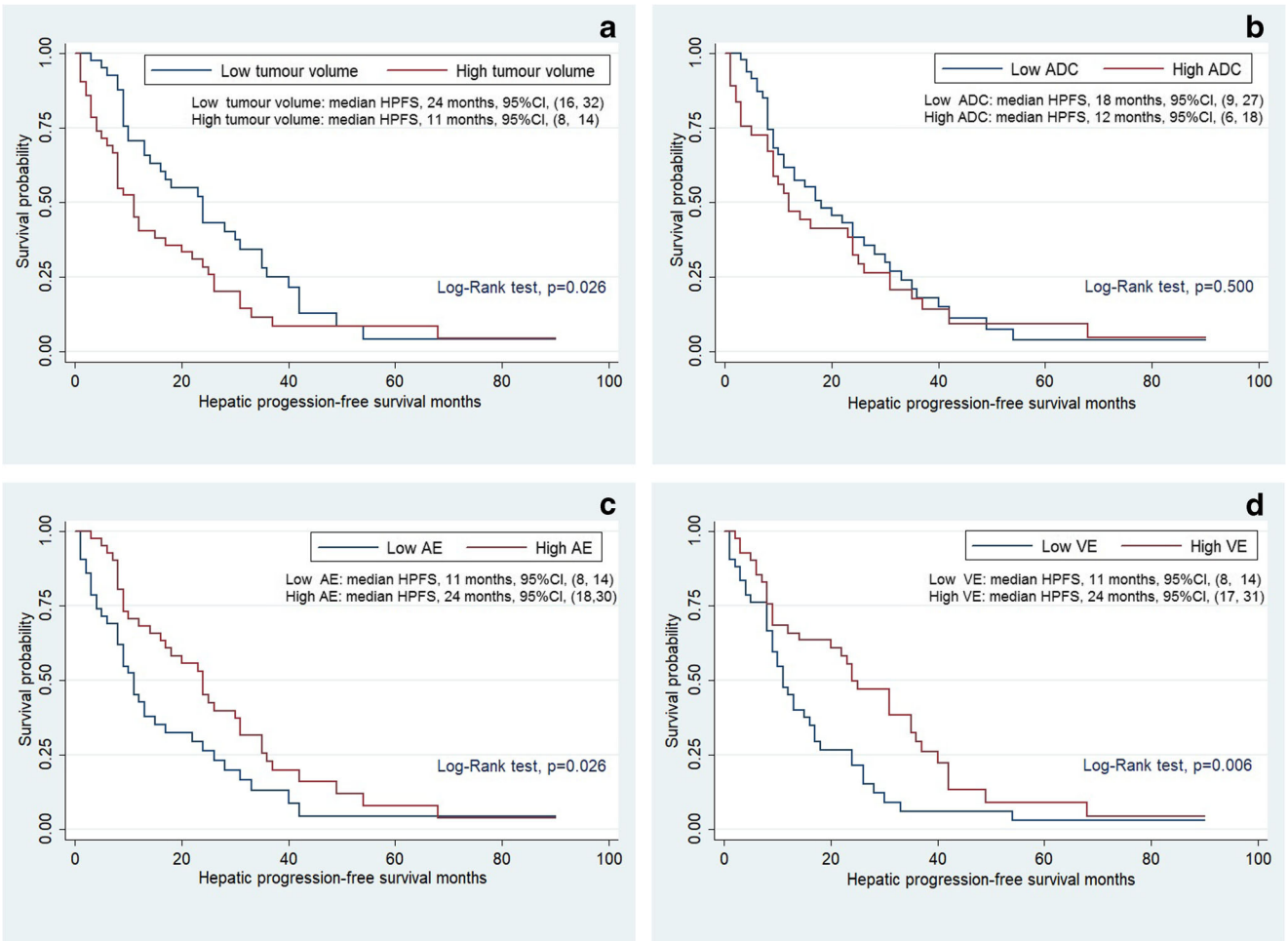

Fig. 5 Kaplan-Meier curves of hepatic progression-free survival using the largest one index lesion. Patients were dichotomized according to (**a**) baseline tumor volume (< 73 and ≥ 73 cm^3), (**b**) baseline volumetric mean ADC (< 1226 and ≥ 1226×10^{-6} mm^2/s), **c** baseline volumetric mean AE (< 45% and ≥ 45%), and (**d**) baseline volumetric mean VE (< 73% and ≥ 73%)

representing the degree of enhancement. Secondly, our study focused on the prognostic value of baseline (pre-TACE) MR imaging parameters while Sahu et al relied on the change between baseline and post-TACE MR imaging. Last, the previous study did not involve diffusion-weighted imaging which allows functional assessment without the use of contrast enhancement. The current study on the other hand evaluated whether baseline volumetric mean ADC could predict OS and HPFS in NELMs treated with TACE.

Worthy of note, volumetric assessment of the dominant lesion reliably predicts patient outcomes and provides similar prognostic value as the assessment of multiple lesions. In line with our results, previous studies [28, 43] suggested that the largest one index lesion was adequate to reflect the overall tumor burden as a representative in multifocal HCC undergoing TACE. Kim et al showed that response of the largest one target lesion was able to predict OS with accuracy similar to that of the response of multiple as well as all the lesions [28]. A similar conclusion was reported in a prior study investigating the predictive role of enhancing tumor volume in patient survival [43]. Therefore, we suggest that volumetric assessment of the largest one index lesion may be sufficient, avoiding dispensable multiple measurements.

There are several limitations to our study. First, since no guidelines exist for tumor volume and volumetric multiparametric MR parameters, the cohort derived median values were used to dichotomize patients in our single-center data; their use in other studies need to be validated. Second, because of the retrospective nature of this study, information on tumor differentiation was incomplete in some patients. Another potential prognostic factor, Ki-67 [4], was not available in the majority of our patients; future prospective studies are warranted to include these parameters as well as volumetric multiparametric MR metrics in the prognosis prediction model. Third, we included a relatively heterogeneous population with different previous systemic treatment history, which might potentially influence the baseline volumetric MR parameters. Nevertheless, our study found no significant difference in the volumetric measurements between patients with and without prior systemic therapy. That might be explained by the fact that patients usually received TACE after treatment failure of previous systemic therapy. And it would be impractical to exclude patients with prior systemic treatment, as TACE serves as a second-line option in unresectable NELMs and somatostatin analogues are generally used to control the symptoms of carcinoid syndrome; therefore, a considerable percentage of patients would have received systemic therapy before TACE as previously reported [38].

In conclusion, volumetric enhancement values and tumor volume of the dominant lesion on baseline MR imaging may act as prognostic factors for OS and HPFS in NELMs patients treated with TACE.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

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 intra-arterial therapy: volumetric functional imaging biomarkers of early tumor response and survival. Radiology 2013; 266:502–513). We have reported on 55 out of 84 patients included in the current study. However, the prior report focused on the prognostic value of pre- and post-TACE changes in volumetric multiparametric MR imaging of the dominant lesion for predicting overall survival. The current study included a larger sample size and evaluated whether baseline volumetric MR imaging only can predict overall survival and hepatic progression-free survival. Also, the prognostic values of baseline volumetric MR metrics using three different numbers of index lesions (one, two, and five) were compared in the current study.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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