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Transarterial Chemoembolization (TACE) for Neuroendocrine Liver Metastasis (NELM): Predictive Value of Volumetric Arterial Enhancement (VAE) on Baseline MRI

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1. Abstract

1.1. Background Neuroendocrine tumors (NETs) belong to a rare family of tumors whose incidence has increased significantly over the past 50 years

Purpose To evaluate the prognostic value of volumetric arterial enhancement (VAE) on baseline magnetic resonance imaging (MRI) for patients with neuroendocrine liver metastasis (NELM) treated using transarterial chemoembolization (TACE).

1.2. Material and Methods Between October 2012 and December 2018, VAE in 37 patients was measured with a semi-automatic volume of Interest (VOI) on subtracted T1 sequence in the arterial phase. Patients underwent 1–3 sectoral lipiodol TACE. Radiologic response using modified Response Evaluation Criteria in Solid Tumors (mRECIST) at the treatment cycle end and progression free survival were determined.

1.3. Results Median age was 68.0 (60.0; 73.0). Twenty-three patients (62%) had a partial response, 10 (27%) had stable disease, four (11%) had progressive disease. VAE was a significant ($p<0.05$) predictor of radiologic response. Median progression free survival was 13 months (IC 95: 8; 16). In univariate analysis, significant predictors of local recurrence were alkaline phosphatase (AP) ($p=0.035$), Ki-67 index ($p=0.014$), and VAE ($p<0.01$). VAE over 500ms and Ki-67 index over 3%were risk factors of progression ($p=<0.01$) in multivariate analysis.

1.4. Conclusion VAE before TACE could be predictive of radiologic response and could be related to oncologic outcomes in patients with NELM.

2. Introduction

Neuroendocrine tumors (NETs) belong to a rare family of tumors whose incidence has increased significantly over the past 50 years [1, 2]. The incidence of liver metastases in these diseases is between 67% and 90% with consequences on overall survival (OS) [3]. Only 10%–20% of patients with liver metastases from NETs are eligible for surgical management [4]. In the course of these pathologies, where patients are often managed over the long term, transarterial chemoembolization (TACE) represents an important therapeutic tool. Recent studies have shown that follow-up based on volumetric enhancement was more relevant than modified Response Evaluation Criteria in Solid Tumors (mRECIST) [5] and significantly related to patient survival more than European Association for the Study of the Liver, RECIST, and the World Health Organization criteria [6]. No previous study has determined whether volumetric arterial enhancement (VAE) measured before the first TACE could be a predictor of radiologic response or survival. The purpose of this study was to evaluate the value of baseline VAE, which is estimated using contrast-enhanced magnetic resonance imaging (MRI) subtracted sequences as a predictive factor of radiologic response and oncologic outcomes for patients with neuroendocrine liver metastasis (NELM) treated with TACE.

3. Material and Methods

This retrospective, single-institution study was approved by the institutional review board.

3.1. Patient population

NELM patients who underwent TACE consecutively at our insti-

tution, between October 2012 and December 2018, were reviewed. Inclusion criteria were patients with multifocal bilobar, age ≥18 years old, an Eastern Cooperative Oncology Group (ECOG) performance status <2, alanine aminotransferase and aspartate aminotransferase <3 times the upper normal limit, total serum bilirubin <3.0 mg/dL, serum creatinine clearance >60 mL/min, platelet count >50,000/mm3, and an international normalized ratio (INR) <1.5. Exclusion criteria were patients in an emergency situation, patients of adult age who were the subject of a legal protection measure or unable to give consent, patients who were pregnant or likely to be pregnant, impossibility to submit to the trial medical follow-up for geographical, social, or psychological reasons, patients with no adequate baseline or follow-up MRI, history of prior liver-directed therapy, and patients with portal vein thrombosis. During this period, a total of 37 patients were included to receive TACE as determined by a multidisciplinary board. A flowchart of patient selection is shown in (Figure 1). All patients included had histopathological evidence of a NET, based on the WHO nomenclature, either with a surgical or image-guided biopsy of the primary site or metastasis. All tumors were well differentiated. Extrahepatic disease was not a contraindication. All patients received a somatostatin analogue either as background therapy or as part of their perioperative preparation. The decision to use a liver directed therapy was based on the progression of one or more liver tumors despite treatment with somatostatin analogues. For patients with extra hepatic tumors, these had to be stable, controlled by somatostatin analogue treatment. Patients who benefited from TACE were only those with isolated uncontrolled progressive liver tumors. The following data were collected regarding patients (age, gender, hepatalgia at diagnosis, and symptoms related to their tumor syndrome), primary cancers (location, disease grade, and extrahepatic disease at time of TACE), liver metastasis (liver burden ≤25% or >25% and ≤50% or >50%), TACE (number of TACEs, and the time between diagnosis and TACE), other treatments (first-line treatment, local progression free survival (LPFS) after first-line treatment, and surgical primary cancer resection), and biological and nuclear imaging data (alkaline phosphatase (AP), Ki-67 index, chromogranin A, 24-hour urinary 5-HIA from the last biological result before the first TACE procedure, and positivity of hepatic metastases on 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT)).

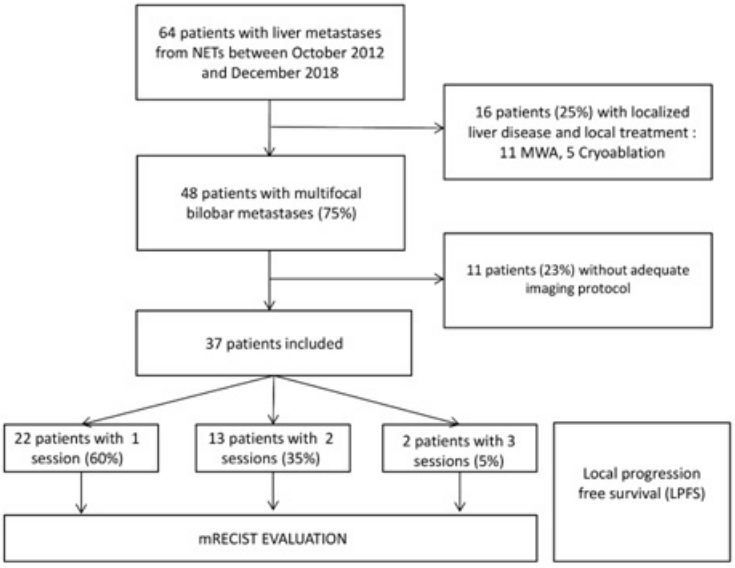

Figure 1: Study Flow chart. *MWA* Microwave ablation

3.2. TACE procedure

TACE indications were decided by a multidisciplinary tumor board (MTB), either for major symptomatic patients or for uncontrolled progressive lesions. No selective subsegmental TACE was carried out; only sectoral TACE was. The decision regarding which regions to target was discussed according to the segments where the progressive lesions were located, i.e., posterior sectoral TACE for progressive lesions in segments VII and/or VI, paramedian sectoral TACE for progressive lesions in segments VIII and/or V, and left liver TACE for progressive lesions in segments II and/or III and/or IV and/or I. If several regions showed progressive lesions, the treatments were carried out in several sessions, thereby achieving a cycle. Regions showing no progressive lesions were not treated. For patients with multiple regions to treat, the disease-dominant region was treated first and then the less affected hepatic region was treated secondarily 5 weeks after so as to restrict the total dose of chemotherapy per session. The decision to continue the protocol was taken after each TACE treatment using MRI performed at 4 weeks. The endpoint was disease control (complete response (CR), partial response (PR), or stable disease (SD)). If the liver disease was controlled according to mRECIST criteria in the first region targeted by TACE, the subsequent TACE was performed 1 week after the MRI. If the first month MRI showed that the disease was uncontrolled in the region targeted by TACE, the treatment cycle was stopped.

Interventions were performed in a standardized way over the duration of the study, according to expert recommendations [7], by three experienced interventional radiologists. The periprocedural preparation protocol consisted of the administration of antibiotics, an-

tiemetics, steroids, and intravenous hydration before TACE. Given that conventional TACE has been used historically with good efficacy, while drug-eluting embolic approaches have not yet been proven to be superior, all patients underwent an iodized oil-based TACE procedure [8]. Under conscious sedation, a selective two-dimensional (2D) or three-dimensional (3D) angiography of the hepatic vascularization with four or five French catheters (Cobra or Simmons, Boston Scientific, Natick, MA, USA, or Terumo, Tokyo, Japan) was performed on an angiographic interventional table (Siemens Artis Zee ® Ceiling; Siemens Medical Solutions, Erlangen, Germany). The operator catheterized the posterior sectoral, paramedian sectoral, or left hepatic artery with a micro-catheter (Progreat, Terumo, Tokyo, Japan). Weight-based epirubicin (Farmorubicin®; Pfizer, USA) was used. The content of the vial of lyophilized powder was dissolved by shaking in 6 mL of physiological solution in the pharmacy laboratory, then emulsified in the angiographic room with iodized oil (Lipiodol; Laboratory André Guerbet, Aulnay-sous-Bois, France), and finally, carefully infused. Immediately after, an additional embolization was performed with absorbable non-calibrated gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Michigan, USA). When a column of contrast material stagnated for 3–5 beats, the procedure was stopped. A complete occlusion was excluded to avoid ischemic complications. All patients were closely monitored by a dedicated anesthesiologist during the procedure and then kept in the recovery room for at least one hour after the procedure. Blood tests including liver enzymes were performed the next day and then between 1 and 3 days apart until normalization.

3.3. MRI protocol for treatment planning and assessment of treatment response

All patients underwent baseline imaging with contrast-enhanced MRI within 30 days before TACE. At the end of the cycle (one or more TACE), 4 weeks after the last TACE, MRI was performed to determine the final mRECIST response. Then, for all patients, an MRI was performed every 3 months to determine tumor progression.

Baseline evaluation and follow-up were performed on a General Electric MRI 1.5T SIGNA Artist (GE Healthcare, Milwaukee, WI, USA). The protocol consisted of: axial T2-weighted fat-suppressed spin-echo in respiratory gating imaging (section thickness 5 mm/1 mm), axial DW echo-planar in respiratory gated imaging (b400-b800; section thickness 5mm/1 mm), axial T1-weighted breath-hold gradient-echo in-phase and out-of-phase imaging (section thickness 5 mm), axial T2-weighted fast breath-hold spin-echo imaging (section thickness 6.5 mm/2 mm), and axial unenhanced and dynamic contrast-enhanced T1-weighted 3D fat-suppressed spoiled breath-hold gradient-echo imaging (section thickness 5 mm), which was obtained with an initial delay of 35 sec (arterial phase) and then at two consecutive intervals, a portal phase (1 minute) and a delayed phase (3 minutes), with intravenous injection of 20 mL of contrast agent (Dotarem®, Guerbet, Roissy, France).

3.4. VAE analysis

On baseline MRI, VAE was estimated on the largest lesion in the TACE-targeted region with a semi-automatic volume of Interest (VOI) on the T1-weighted 3D fat-suppressed subtracted arterial phase sequence. This sequence consisted of an automated subtraction between the T1-weighted arterial phase contrast-enhanced and unenhanced T1-weighted, integrating a system of adjustment to respiratory motion. This enhancement quantification was evaluated using the syngo.MR OncoCare software (Siemens Healthcare, Erlangen, Germany). By circumventing manually four regions of interest (ROIs) on the largest lesion of the treated region, the software created a semi-automatic VOI and determined minimum, maximum, mean enhancement intensity in milliseconds with standard deviation, median enhancement, and a histogram of enhancement values (Figure 2). For patients with multiple or too-numerous-to-count liver lesions, the largest confluent cluster of lesions, if one lesion could not be isolated, was studied. We had decided to take into account the median enhancement value to overcome the heterogeneity of certain lesions presenting a wide range of enhancement values. A double-blind reading was performed by two experienced radiologists with measurement of inter-individual variability.

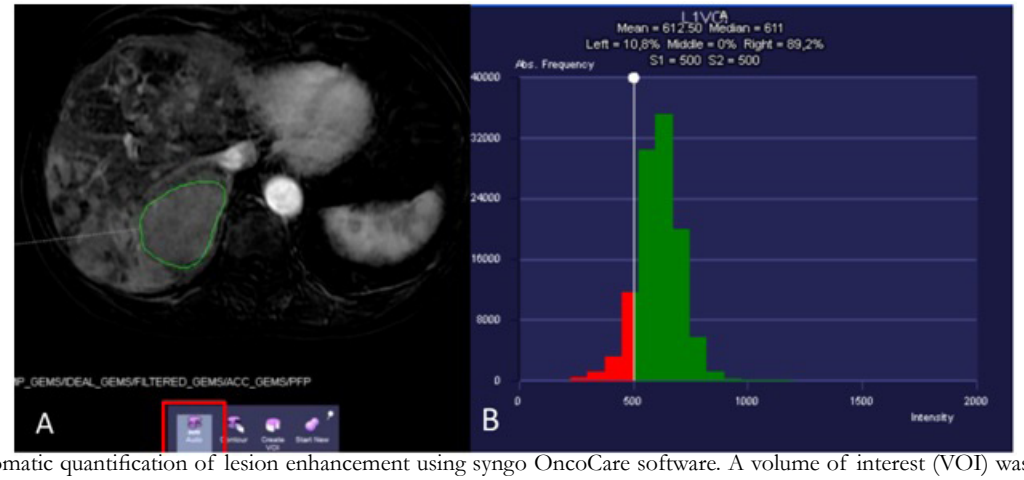

Figure 2: Semi-automatic quantification of lesion enhancement using syngo OncoCare software. A volume of interest (VOI) was determined semi-automatically on the MRI preceding the TACE session on the arterial subtracted sequence between the uninjected T1 sequence and the injected T1 sequence at arterial time. We manually drew the circumference of the main lesion on several slices on axial view (A). Semi-automatic VOI of the lesion was determined (Volume, minimum, maximum, mean and standard deviation, and a histogram of the enhancement values were automatically determined) (B).

3.5. Evaluation of TACE efficacy

Final radiographic response assessment according to mRECIST was evaluated for every patient only at the end of the entire treatment of the region (sectors or lobe) initially planned over one or multiple TACE sessions [9]. The largest enhancing diameters of up to the two most extensive target lesions in the region targeted by TACE were measured and compared using baseline MRI, as recommended in the mRECIST classification. CR was defined as a complete absence of enhancement of lesions targeted by TACE. PR was defined as a decrease in enhanced diameter equal to or greater than 30% of the target lesions. PD was defined as an increase in enhanced diameter greater than or equal to 20% of the target lesions, and SD if the enhancing diameter variation was strictly greater than -20% or strictly less than 30%. A double-blind reading was performed by two different experienced radiologists and confirmed by the MTB. Clinical response assessment was estimated using local progression free survival (LPFS. LPFS was defined for all patients as the date of the first TACE to the date of the first sign of local recurrence (i.e., new growing lesion in the targeted sector or lobe) or the date of the last follow-up.

3.6. Statistical analysis

Quantitative statistics were presented as means and standard deviations or medians and interquartile ranges and compared with each other using the Mann–Whitney U test. Qualitative variables in percentage form were compared with each other using the Student's t and Chi-square tests. LPFS was determined using the Kaplan–Meier method. The influence of prognostic factors on progression free survival was evaluated in univariate analysis with the log-rank test, and multivariate analysis was performed using the Cox proportional-hazards model for variables with statistical significance. Because no guidelines existed, we selected cutoff values based on the median across the entire population to stratify patients concerning quantitative values such as age, VAE, Ki-67 index, and AP. Log-rank tests were performed using the previously obtained thresholds. Agreement between observers was evaluated using the intra-class correlation coefficient (ICC) considering baseline VAE. A value of $p<0.05$ was considered statistically significant. The statistical analysis was performed using Medistica statistical software.pvalue.io (a graphical user interface to the R statistical analysis software for scientific medical publications, 2020).

4. Results

4.1. Demographic data

(Table 1) Median follow up was 26 months (Q25-75: 2, 63). Median age was 68.0 (Q25-75: 60.0; 73.0), and there were 19 females (51%). A large number of patients had a grade 2 disease. 19 patients had a small intestinal origin tumor (5 grade 1, 12 grade 2, 1 grade 3 and 1 unknown) and 2 patients had a colonic origin tumor (2 grade 2). First-line treatments included somatostatin analogs (sandostatin and lanreotide), FOLFOX (folinic acid, fluorouracil, and oxaliplatin), and sunitinib or cisplatin and etoposide. One patient received three prior treatments, five patients received two prior treatments, 26 patients received one prior treatment, and for five patients, TACE was the first-line treatment. Only one patient showed diffuse progression between the first 2 TACEs (progression on the treated territory and on the territory to be treated later) but the patient was not excluded. In practice, a second TACE session was decided to control the tumor secretion and in the study the patient was classified as progressive after the first TACE. Mean number of lesions was 8 (SD: 2), mean tumor diameter was 23mm (SD: 5). No correlation was found between VAE and Ki-67 index (p=0.9) or between VAE and the primary cancer (p=0.6). PFS after first-line treatment was 22.7 months (SD: 28). The ICC of the VAE measurement was 0.85 (95% confidence interval (CI): 0.7; 0.9). Distribution of baseline VAE values was significantly homogeneous considering the initial characteristics of the patients (Table 2).

Table 1: Demographic data

Age, median [Q25-75]		68.0 [60.0; 73.0]
Chromogranine (mg/litre), median [Q25-75]		361 [182; 845]
Time diagnostic/TACE (months), median [Q25-75]		19.0 [12.0; 39.5]
KI67 (%), median [Q25-75]		5 [3; 11.5]
Number of TACE (n), median [Q25-75]		1.00 [1.00; 2.00]
Number of prior treatment (n), median [Q25-75]		1.00 [1.00; 1.00]
PAL (UI/litre), median [Q25-75]		88.5 [75.2; 138]
5HIA urinaire (µmol/24 heures), median [Q25-75]		121 [72.5; 214]
Surgery of primary cancer, (%)	**No**	19 (51%)
	Yes	18 (49%)

Tumor burden, n (%)	**≤25%**	25 (68%)
	>25% and ≤50%	4 (11%)
	>50%	8 (22%)
PET FDG, n (%)	**No**	7 (29%)
	Yes	17 (71%)
Grade of NET, n (%)	**1**	6 (18%)
	2	25 (74%)
	3	3 (8.8%)
Hepatalgia, n (%)	**No**	27 (73%)
	Yes	10 (27%)
Primary tumor, n (%)	**Gastrointestinal**	21 (57%)
	Pancreatic	7 (19%)
	Lung	6 (16%)
	Unknown	3 (8.1%)
Extra hepatic disease, n (%)	**No**	15 (41%)
	Yes	22 (59%)
Sex, n (%)	**F**	19 (51%)
	M	18 (49%)
Symptoms before TACE, n (%)	**No**	14 (39%)
	Yes	22 (61%)

Table 2: Initial characteristics according to baseline VAE. *TACE* Trans arterial chemo embolization, *AP* alkaline phosphatase, *5HIA* 5-Hydroxyindoleacetic acid

			n	**p**
Surgery of primary tumor, median [Q25-75]	**No**	422 [282 - 832]	19	0.6
	Yes	484 [71.8 - 743]	18	-
Liver burden, median [Q25-75]	**≤25%**	366 [135 - 678]	25	0.38
	>25% and ≤50%	481 [244 - 832]	4	-
	>50%	726 [395 - 883]	8	-
PET FDG, median [Q25-75]	**Negative**	598 [244 - 830]	7	0.85
	Positive	525 [166 - 853]	17	-
Grade of NET, median [Q25-75]	**1**	486 [356 - 714]	6	0.17
	2	553 [204 - 865]	25	-
	3	135 [86.5 - 216]	3	-
Hepatalgia, median [Q25-75]	**No**	334 [150 - 671]	27	0.22
	Yes	682 [420 - 899]	10	-

Primary tumor, median [Q25-75]	**Gastrointestinal**	549 [204 - 865]	21	0.65
	Pancreatic	298 [150 - 589]	7	-
	Lung	322 [98.5 - 614]	6	-
	Unknown	598 [432 - 796]	3	-
Extra hepatic disease, median [Q25-75]	**No**	553 [150 - 671]	15	0.96
	Yes	421 [234 - 843]	22	-
Gender, median [Q25-75]	**F**	664 [216 - 952]	19	0.07
	M	324 [113 - 580]	18	-
Symptoms before TACE, median [Q25-75]	**No**	340 [64.2 - 610]	14	0.19
	Yes	488 [234 - 899]	22	-
Age, correlation (IC95)		0.0339 (-0.293; 0.354)	37	0.84
Chromogranine, correlation (IC95)		0.222 (-0.109; 0.510)	37	0.19
Diagnostic/TACE, correlation (IC95)		0.103 (-0.233; 0.417)	36	0.55
KI67, correlation (IC95)		-0.00246 (-0.340; 0.33)	34	0.99
Number of TACE, correlation (IC95)		-0.263 (-0.541; 0.0667)	37	0.12
Number of prior treatment, correlation (IC95)		_	35	0.22
AP (UI/l), correlation (IC95)		_	24	0.85
5HIA (µmol/24 hours) , correlation (IC95)		_	27	0.17

4.2. Radiologic response: mRECIST

At the end of the TACE cycle, 23 patients (62%) presented with PR, 10 (27%) with SD, and four (11%) with PD. The only significant predictor of radiologic response was VAE ($p<0.05$) (Table 3) (Figure 3).

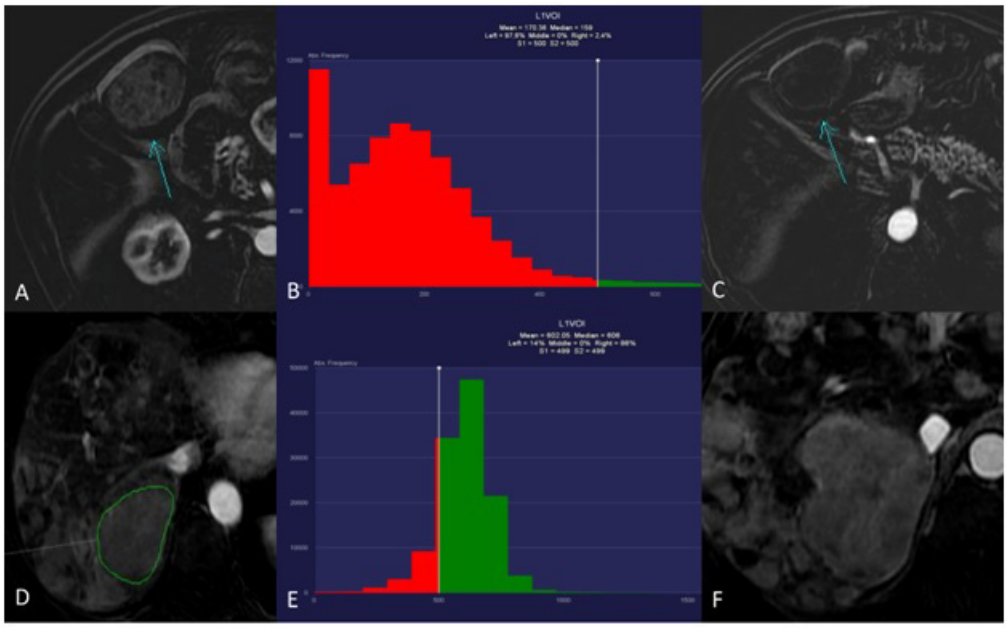

Figure 3: Examples from two patients with hepatic metastases from neuroendocrine tumors. The first patient (upper images A, B, C) had a segment IV metastasis from an intestinal neuroendocrine tumor (Ki67 2%, grade 2). The volumetric arterial enhancement was lower than 500, and the second patient (lower images D, E, F) had a segment VI metastasis from an intestinal neuroendocrine tumor (Ki67: 5%, grade 2). The median volumetric arterial enhancement greater than 500. A and D: Subtracted arterial MRI sequence enhancement images. B and E: Histograms allowing a mapping of the lesion enhancement, for the first patient (B), 98% enhancement below the threshold of 500 (red), and for the second patient (E), 86% enhancement above 500 (green). C and F: Subtracted arterial MRI sequence one month after TACE showing for the first patient (C), an almost complete devascularization of the treated lesion (blue arrow), whereas for the second patient (F), there is a poor response with progression of the treated lesion.

4.3. LPFS

Median LPFS was 13 months (IC 95: 8; 16). Local progression occurred in 31 patients during the follow-up (84%), 17/18 (94%) in a group with a VAE over 500ms, and 22 (100%) in a group with Ki-67 index over 3%. In univariate analysis, significant predictors of local recurrence were AP (p=0.035), Ki-67 index (p=0.014), and VAE (p<0.01) (Table 4), (Figure 4). In multivariate analysis, adjusting for Ki-67 index threshold of 3%, there was a statistically significant relationship between progression and a VAE over 500ms (p<0.01). Progression was also significantly related to Ki-67 index >3%. Multivariate analysis of LPFS was unable to incorporate AP because too much data was missing.

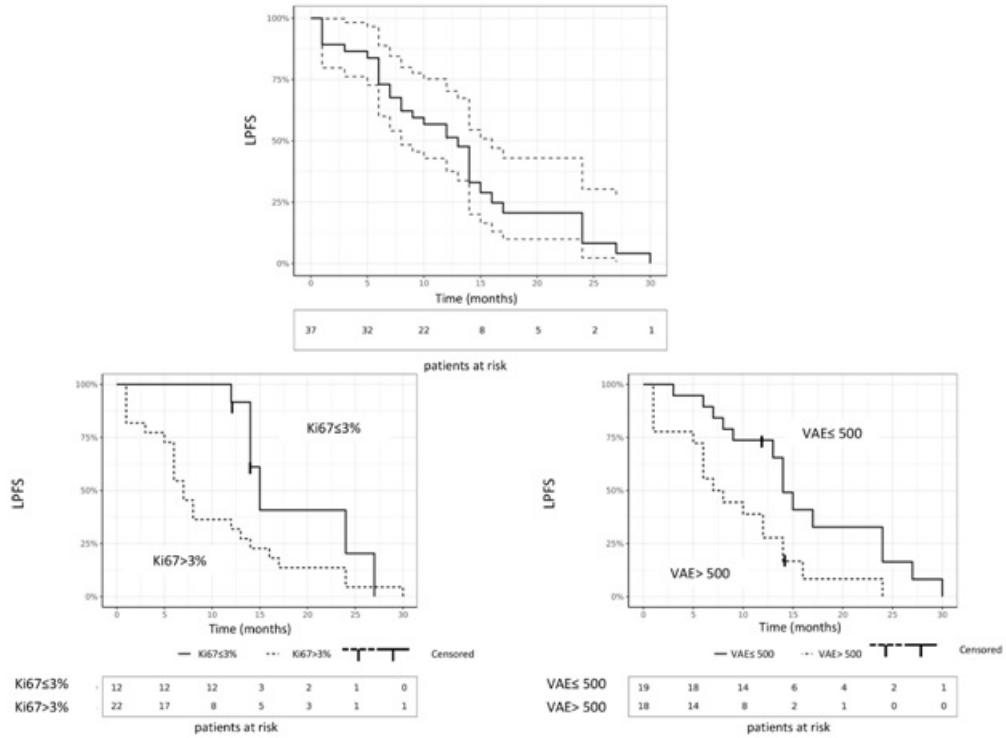

Figure 4: The upper graph represents the local tumor control curve of liver metastases from NETs after TACE for all patients (dotted lines represents the 95% confidence interval). On the lower left graph, local tumor control curves are stratified by baseline VAE. *VAE* Volumetric arterial enhancement

Table 3: Univariate analysis of clinicopathologic and treatment-related factors affecting radiologic response. PR: partial response, SD: stable disease, PD: progressive disease. *VAE* volumetric arterial enhancement, *TACE* Trans arterial chemo embolization, *AP* alkaline phosphatase, *5HIA* 5-Hydroxyindoleacetic acid

		PR (n = 23)	SD (n = 10)	PD (n = 4)	p
Age, mean (±SD)		67.0 (±9.29)	63.8 (±13.0)	62.8 (±7.80)	0.63
Sex n (%)	**F**	13 (57%)	3 (30%)	3 (75%)	0.23
	M	10 (43%)	7 (70%)	1 (25%)	-
Primary tumor n (%)	**GI**	13 (57%)	6 (60%)	2 (50%)	0.21
	Pancreatic	3 (13%)	2 (20%)	2 (50%)	-
	Lung	6 (26%)	0 (0%)	0 (0%)	-
	Unknown	1 (4.3%)	2 (20%)	0 (0%)	-
Grade, n (%)	**1**	6 (29%)	0 (0%)	0 (0%)	0.19
	2	14 (67%)	7 (78%)	4 (100%)	-
	3	1 (4.8%)	2 (22%)	0 (0%)	-
Extra hepatic disease	**No**	8 (35%)	6 (60%)	1 (25%)	0.46
	Yes	15 (65%)	4 (40%)	3 (75%)	-
Time diagnostic/TACE (months), mean (±SD)		30.2 (±27.9)	26.5 (±19.8)	21.8 (±15.2)	0.94
Number of TACE, mean (±SD)		1.48 (±0.665)	1.50 (±0.527)	1.25 (±0.500)	0.73
Surgery of primary tumor n (%)	**No**	11 (48%)	5 (50%)	3 (75%)	0.71
	Yes	12 (52%)	5 (50%)	1 (25%)	-
Liver burden n (%)	**≤25%**	18 (78%)	5 (50%)	2 (50%)	0.24
	>25%,≤50%	1 (4.3%)	2 (20%)	1 (25%)	-
	>50%	4 (17%)	3 (30%)	1 (25%)	-
Number of prior treatment, mean (±SD)		0.783 (±0.6)	1.00 (±0)	1.75 (±0.957)	**0.0503**
AP (UI/l), mean (±SD)		101 (±36.5)	132 (±82.6)	146 (±91.1)	0.73
5HIA (µmol/24 hours), mean (±SD)		178 (±216)	261 (±249)	87.0 (±67.9)	0.63
Chromogranine (mg/l), mean (±SD)		699 (±812)	2760 (±5510)	5591 (±10)	0.75
KI-67 index (%), mean (±SD)		7,6 (±0.07)	14 (±11.4)	14,5 (±12)	**0.35**
Baseline VAE, mean (±SD)		415 (±334)	514 (±419)	1234 (±517)	**0.023**
PET FDG n (%)	**Negative**	4 (27%)	2 (40%)	1 (25%)	0.83
	Positive	11 (73%)	3 (60%)	3 (75%)	-

5. Discussion

Patients with liver metastases presenting with the most elevated VAEs could have a poorer radiological response to TACE and poorer oncologic outcomes. Clinical prediction of response to therapeutics used in treating NETs is currently based on tumor cell differentiation and Ki-67 index [10], but some pathological studies have investigated the relationship between angiogenesis and tumor progression in NETs. Okubo and al. [11] have provided evidence on the relationship between tumor progression and angiogenesis in hindgut NET cases by calculating microvascular density. They did not identify a significant correlation between Ki-67 index and the maximum tumor size. Pinato and al. [12] had demonstrated that the prognostic power of selected biomarkers of hypoxia and angiogenesis (SSTR-2 and HIF-1α) in series of gastroenteropancreatic-NETs was correlated with survival and were independent from tumor staging or grading. Gadolinium-induced signal intensity increase in T1 weighted images depends not only on the contrast deposition in the lesion but also depends on vessel permeability, contrast diffusion rate, composition of interstitium and vessel density. Tumoral angiogenesis is known to affect all of these parameters. Further studies seem to be needed to determine if there is a correlation between angiogenesis and measured VAE. Our findings on the predictive value of tumor enhancement are consistent with those found in the literature about other treatments of liver metastases from NETs as radiolabeled octreotide therapy [13], everolimus [14] and even surgery [15]. As did Hamilton et al. [16], we found that Ki-67 index was a predictive factor of recurrence. This study had several limitations. First, it was a retrospective study; therefore, inherent selection bias was unavoidable. Second, because of the rarity of NETs, only a small number of patients could be included in the study. As a consequence, multivariate approaches were not performed in all analyses and some characteristics such as AP rate could therefore not be used. However, other studies have already demonstrated the value of AP as a prognostic factor in patients with NELM before TACE [17]. Transcatheter arterial procedures such as intra-arterial chemotherapy, transarterial embolization, transarterial chemoembolization and selective internal radiation therapy have been shown to be indicated for tumors with preferential vascularization from the hepatic artery and a smaller percentage from the portal veins. VAE measurement could be an intrinsic confounding factor in predicting response to this type of treatments. Despite sometimes extensive metastatic tumor spread small intestinal tumors are usually low proliferative whereas rare colonic origin have a much worse prognosis. The important number of aggressive, grade 2, small intestinal tumors might reflect the severity of disease in this patient population. As a consequence, there was probably a bias in the selection of patients in the sense that the treated patients may have a worse prognosis. This may have had an effect on the study of the predictive value of the VAE, since an over-representation of patients with a poor prognosis and high VAE may have been responsible for an overestimation of the effect of the VAE on the prognosis. We did not dissociate the subtypes of GI NETs for reasons of simplification but it could have been judicious considering the difference of prognosis. In addition, although inter-individual variability was assessed, intra-individual variability could not have been studied. Then, even if somatostatin receptors based imaging is a cornerstone in the diagnosis and follow-up of NET patients, only a small portion of these images could not retrieved, not enough to be detailed in this study. Last, in our study, patients did not undergo long-term follow-up. Prospective multicenter studies are therefore necessary. In conclusion, VAE on baseline MRI before TACE could be predictive of radiologic response and could be related to oncologic outcomes in patients with liver metastases from NETs.

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