Research in Diagnostic and Interventional Imaging 1 (2022) 100005

Contents lists available at ScienceDirect

Research in Diagnostic and Interventional Imaging

journal homepage: https://www.journals.elsevier.com/redii

Original article

Quantitative and qualitative evaluation of liver metastases with intraprocedural cone beam CT prior to transarterial radioembolization as a predictor of treatment response

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ARTICLE INFO

Article History:
Received 23 December 2021
Accepted 21 March 2022
Available online 5 April 2022

Keywords:
Therapeutic Embolization
Cone-beam computed tomography
Neoplasm metastasis
Diagnostic imaging

ABSTRACT

Purpose: To investigate, by quantitative and qualitative enhancement measurements, the correlation between tumor enhancement on cone beam computed tomography (CBCT) images and treatment response at 6 months in patients undergoing transarterial radioembolization (TARE) for liver metastases.
Materials and Methods: 36 patients (56% male; median age 62.5 years) with 104 metastases were retrospectively included. Quantitative and qualitative enhancement of liver metastases were evaluated on CBCT images before TARE. Quantitative analysis consisted of lesion enhancement measurements (ROI HU lesion – ROI HU relative to inferior vena cava). Qualitative analysis consisted of subjective enhancement pattern analysis (diffuse, sparse, rim-like or non-enhancing). Morphologic tumor response was evaluated according to RECIST 1.1 criteria on follow-up CT or MR imaging.
Results: At a mean follow up of 6.5 ± 3.7 months, progressive disease (PD) was found in 4 patients, partial response (PR) in 11 and stable disease (SD) in 21. Relative lesion enhancement was significantly different between these groups (-37.5±154.2 HU vs. 103.8±93.4 vs. 181±144 HU in PD vs. SD vs. PR group, respectively; $p<0.01$). ROC analysis of relative lesion enhancement to predict progressive disease showed an area under the curve of 0.86 ($p<0.01$). For qualitative lesion enhancement analysis, no difference between groups was found.
Conclusion: Quantitative enhancement measurements derived from intraprocedural contrast enhanced CBCT may identify responders to TARE in patients with liver metastases.

1. Introduction

Transarterial Radioembolization (TARE) of the liver using Yttrium-90 (Y-90) microspheres is a catheter-based tumor therapy where microspheres labeled with a radioactive tracer are being injected directly into the liver arteries. It has become an established part in treatment of primary liver tumors as well as liver metastases in patients who are not suitable for surgery [1–3].

Response to TARE is difficult to predict [4]. It can be a technically demanding and costly procedure with potential morbidising side effects such as liver failure and non-healing gastrointestinal ulcers [5]. Thus, the need evolves to appropriately select patients beforehand that are more likely to respond. This would spare them unnecessary treatments and help direct these patients to more promising therapies at an earlier stage of their disease.

The search for a reliable imaging biomarker is still ongoing. Various imaging techniques have been proposed, such as arterial perfusion calculated from time-resolved CT-perfusion studies or by calculating the arterial enhancement fraction of colorectal liver metastases based on a pre-treatment triphasic contrast enhanced CT [6]. Dynamic perfusion Magnetic Resonance Imaging, Magnetic

Abbreviations: AEF, Arterial Enhancement Fraction; ANOVA, Analysis of variance; AUC, Area under the curve; CBCT, Cone beam computed tomography; CR, Complete Response; CT, Computed Tomography; DEM, Drug Eluting Microspheres; HCC, Hepatocellular Carcinoma; HU, Hounsfield Units; MBq, Mega Becquerel; MDCT, Multidetector computed tomography; MRI, Magnetic Resonance Imaging; PBV, Parenchymal Blood Volume; PD, Progressive Disease; PR, Partial Response; RECIST, Response evaluation criteria in solid tumors; ROC, Receiver operating characteristics; ROI, Region of interest; SD, Stable Disease; SPECT, Single positron emission computed tomography; TACE, Transarterial Chemoembolization; TARE, Transarterial Radioembolization; Y-90, Yttrium-90; 3D, 3-dimensional; 99mTc-MAA, Technetium-99 labeled macroaggregates of albumin

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https://doi.org/10.1016/j.redii.2022.100005

Resonance Elastography and Intravoxel Incoherent Motion are other examples [25].

In addition to pre-interventional cross sectional imaging techniques, contrast enhanced cone beam computed tomography (CBCT) of the liver can routinely be performed during the diagnostic workup before TARE in most centers. This would make CBCT an ideal and rapid tool in predicting treatment response to TARE in an individual patient.

Therefore, the purpose of this study was to evaluate whether quantitative and/or qualitative enhancement measurements during intraprocedural CBCT correlate with treatment response in patients with hepatic metastases undergoing TARE.

2. Materials and methods

This retrospective study was approved by the local ethics committee. Written informed consent was waived.

2.1. Patient population

Between January 2010 and May 2018, a total of 365 patients were evaluated for TARE with diagnostic angiography at our institution; all these patients were screened for potential retrospective inclusion in the present study.

Inclusion criteria were as follows: patients with liver metastases from any primary tumor undergoing TARE, CBCT of the liver during the diagnostic workup and comprehensive follow up imaging (CT or MRI) at a minimum of 6 months.

2.2. Transarterial radioembolization

A commercial angiography system (Artis Zeego, Siemens, Erlangen, Germany) with a 30 × 40 cm flatpanel detector was used in all patients. After acquiring overview digital subtraction images of the coeliac trunk and the superior mesenteric artery, a microcatheter was advanced into the hepatic artery with the catheter tip either in the distal proper hepatic artery or the origin of the right or left hepatic artery, respectively. CBCT was then performed with a standard injection protocol of 36ml of a 50:50 dilution of contrast (Ultravist 370, 370 mg iodine/mL, Bayer Schering Pharma, Berlin, Germany) and Sodium chloride 0.9% at an injection rate of 2ml/s via the microcatheter. Following a delay of 10 seconds after beginning the injection of contrast, the scan started with a detector rotation rate of 7 seconds for a 270-degree rotation, making a total examination time of 17 seconds. If a stepwise right and left radioembolization was anticipated, by reviewing the cross-sectional imaging prior to the procedure, separated CBCT via both, the right and left hepatic arteries, was performed. Patients were instructed to hold their breath in expiration for the duration of the scan.

Following diagnostic angiography and CBCT, Technetium-99 labeled macroaggregates of albumin (99mTc-MAA, mean dose 180 MBq) were injected via the hepatic artery in treatment position to simulate the distribution of the Y-90-spheres. After the procedure, a single positron emission computed tomography (SPECT) was performed, showing the detailed distribution of the radiotracer and indicating potential shunting to the lung or gastrointestinal tract.

Standardized imaging post processing used a 5 mm slice thickness and an increment of 4 mm. Coronal and axial images were stored in the PACS system.

TARE was performed 2-4 weeks after planning (mean 18.2 days) using SIR-spheres (SIR-spheres, Sirtex Medical Limited, Lane Cove, Australia). Panhepatic, lobar or segmental TARE was performed based on the distribution of liver metastases. If the whole liver was affected, separate right and left lobar TARE were performed in two separate sessions. The amount of activity applied per session was calculated using the body-surface-method [8]. A mean dose of 1.33 GBq (range 0.8-1.9 GBq) of Y90 spheres was injected per treatment.

2.3. Quantitative and qualitative CBCT analysis

CBCT images of all patients were evaluated using a commercial PACS system (Agfa Impax, Agfa Healthcare, Mortsel, Belgium). In patients with multiple metastases, three target lesions were defined based on size, visibility and location. Lesions that were ≥ 1cm in diameter with good visibility in both CBCT and follow-up cross sectional imaging were defined as target lesions. In total 104 metastases were analyzed. The location of the lesions matched the treated area of the liver.

A 2D Region of Interest (ROI) was manually drawn around the lesion, avoiding the inclusion of large adjacent vessels. As this study was aiming to provide a simple, intraprocedural diagnostic tool it was decided to use 2D ROI instead of 3D ROI measurements. The largest diameter as well as the average density of the whole lesion in Hounsfield units (HU) were determined. Due to the intralesional heterogeneity of tumor enhancement, especially in large metastases, it was decided to evaluate the average lesion enhancement instead of the maximum lesion enhancement. Additionally, a ROI was placed in the inferior vena cava on the same image and the density in HU was noted (Fig. 1). Enhancement of the Vena cava was chosen for calculating the relative lesion enhancement as there were no unenhanced CBCT scans of the liver available. For quantitative lesion analysis the relative lesion enhancement was measured as follows:

$$(\text{HU lesion}) - (\text{HU inferior vena cava}) = \text{relative lesion enhancement}$$

For qualitative enhancement analysis the enhancement pattern of each target lesion was determined using previously described patterns, classifying metastasis enhancement as diffuse, non-enhancing, peripheral-nodular, rim-like or sparse (Fig. 2) [7].

2.4. Follow up and treatment evaluation

Depending on oncological follow up protocols, either contrast enhanced CT or MRI imaging was performed after TARE. The largest diameter of the lesion was measured in one plane according to the Response evaluation criteria in solid tumors (RECIST v1.1) [9]. Change in tumor size (percentage of baseline) was calculated for the sum of all lesions per patient and overall therapy response was determined as complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD), respectively.

2.5. Statistical analysis

Statistical correlation between therapy response and relative enhancement as well as correlation between overall patient survival and relative enhancement was calculated using a two-way Analysis of variance (ANOVA). Correlation between RECIST subgroups was calculated using the Bonferroni's Multiple Comparison Test. Receiver operating characteristics (ROC) curves were plotted and the area under the ROC curve (AUC) was calculated. To correspond relative lesion enhancement and patient overall survival, a bivariate Pearson correlation was performed. Relation between lesion enhancement pattern and therapy response was analyzed using the Chi-Squared test.

All statistical analyses were performed by using commercially available software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). $P < 0.05$ was considered to indicate statistical significance.

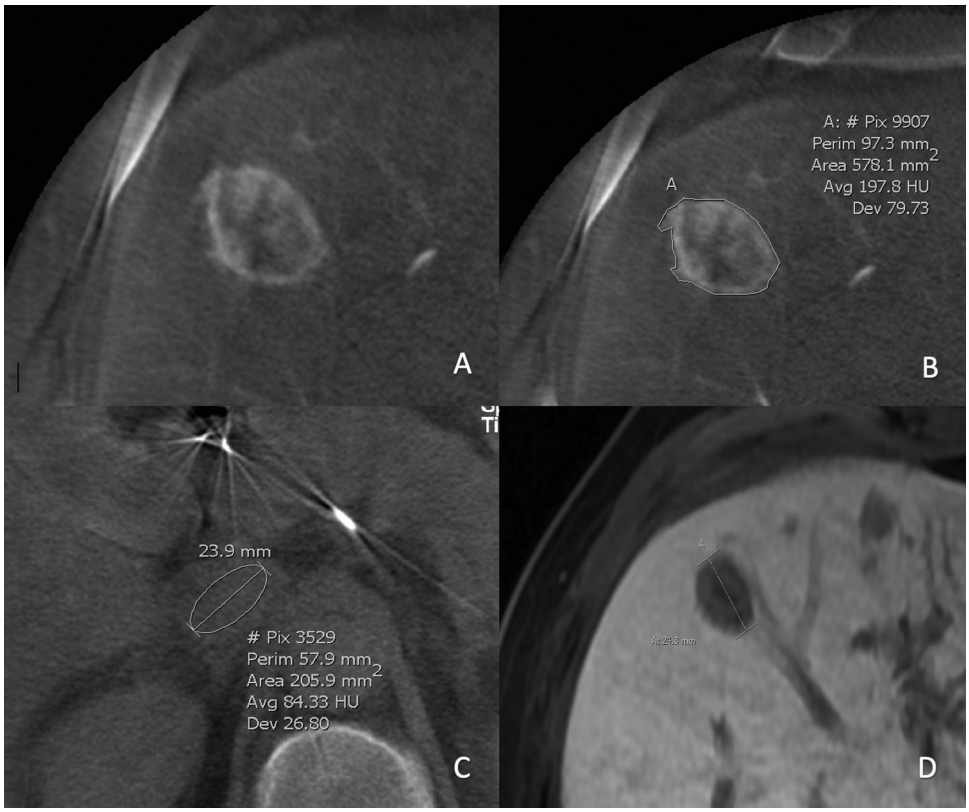

Fig. 1. Images of a 56-year-old patient with liver metastases of a neuroendocrine tumor of the small intestine. A: CBCT during diagnostic workup for TARE showing a contrast enhancing liver metastasis of the right lobe. B: A 2D ROI is manually drawn around the lesion. Lesion enhancement of 197.8 Hounsfield units (HU) is noted. C: For relative enhancement calculation, a ROI is also drawn in the inferior vena cava. This shows 84.33 HU, making a relative lesion enhancement of 113.47 HU. D: Length of the metastasis is measured on a follow up MRI scan 6 months and 20 days after TARE. For this patient, a diameter reduction of 24.45% was found for the sum of all lesions, which was classified as partial response (PR) according to the RECIST 1.1 criteria.

3. Results

3.1. Population

After exclusion of all patients not matching the inclusion criteria, 36 patients were left for further analysis. Patient inclusion flow chart is shown in Fig. 3. The patients presented with a variety of primary tumors (Table 1); tumor entities were grouped in neuroendocrine tumors (n = 8, 22.2%), gastrointestinal tract (n = 8, 22.2%), melanoma (n = 5, 13.9%), pancreas (n = 3, 8.3%), mamma (n = 3, 8.3%) and others (n = 9, 25%), respectively. “Others” included metastases originating from tumors of the kidney, prostate, testis, bronchus, tonsilles and thymus as well as metastases from hemangioendothelioma and hemangiopericytoma. 12 out of 36 patients received systemic antitumoral therapies during the follow up period.

In total 104 metastases were analyzed. The location of the lesions matched the treated area of the liver.

3.2. TARE characteristics and outcomes

TARE was performed as a panhepatic treatment in 15 (41.7%) patients. Only the right lobe was treated in 17 (47.2%) patients and only the left lobe in 4 (11.1%) patients. Follow-up imaging was performed with contrast enhanced CT in 25 patients (69%) and with MRI in 11 patients (31%). PD was found in 4 (11.1) patients, SD in 21 (58.3%) patients and PR in 11 (30.6%) patients. There was a significant difference in sum of diameters of target liver metastasis in follow-up imaging after TARE between the study groups (189.13 $\pm$ 83.24 mm vs. 90.33 $\pm$ 38.73 mm vs. 54.09 $\pm$ 23.73 mm in PD vs. SD vs. PR group respectively, p=0.001). No significant difference between the responder groups was found in terms of gender, age, number of chemotherapies before TARE, sum of diameters of target liver metastasis at baseline imaging before TARE and follow-up days (Table 1).

3.3. Quantitative image analysis

The groups differed significantly in terms of relative lesion enhancement (-37.5 $\pm$ 154.2 HU vs. 103.8 $\pm$ 93.4 HU vs 181.0 $\pm$ 144.0 HU mm in PD vs. SD vs. PR group respectively; $p < 0.001$) (Table 1). ROC analysis of relative lesion enhancement to predict progressive disease showed an AUC of 0.86 ($p = 0.001$) (Fig. 4). A relative enhancement of less than -14.70 HU was predictive for a disease progression with a sensitivity of 94% and a specificity of 65%.

3.4. Qualitative image analysis

Qualitative image analysis revealed no difference between enhancement-type and overall survival as well as between enhancement-type and therapy response (Table 1).

4. Discussion

Our study suggests that quantitative lesion enhancement analysis of pre-treatment CBCT images could predict treatment response after TARE in patients with liver metastases. A cutoff value of relative lesion enhancement of less than -14.70 HU has shown to best predict morphological disease progression following TARE according to the RECIST 1.1 criteria.

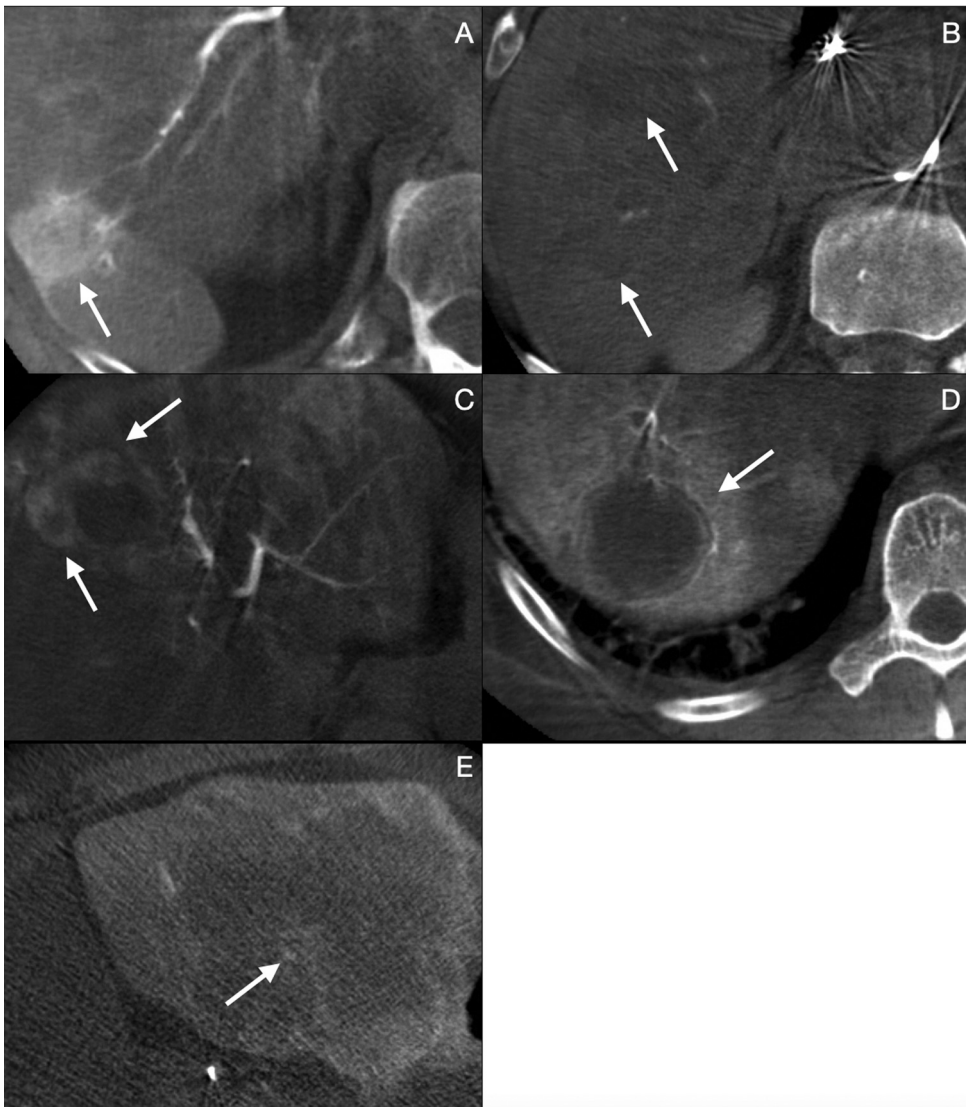

Fig. 2. Examples of the 5 qualitative enhancement patterns: diffuse (A), non-enhancing (B), peripheral-nodular (C), rim-like (D) and sparse (E).

The effectiveness of TARE in local tumor control and patient survival has been consistently demonstrated in various studies [10–12]. It remains, however, a demanding procedure requiring highly trained personnel as well as technical resources in a multidisciplinary team setting, involving diagnostic and interventional radiologists, oncologists, nuclear medicine physicians, nuclear physicists, and radiation safety physicists. In addition, high treatment costs have to be considered. Despite being tolerated well by most patients, this therapy option carries rare but potentially severe complications including liver failure, non-healing gastrointestinal ulcers and pancreatitis [5,13].

Making a statement about the potential therapeutic effect of TARE therefore is of great relevance, providing this complex therapy option to patients with the most promising outcomes. Identifying non-responders to TARE beforehand may be helpful to timely direct these patients to more promising treatments, such as extended chemotherapies. The availability of an easily obtainable, reliable imaging biomarker therefore is of great importance.

There is ample research available focusing on potential imaging biomarkers in the early postinterventional period to predict overall survival (OS) and progression free survival (PFS) [14–20,26-27]. With all these methods, however, TARE (or Transarterial Chemoembolization) has already been performed by the time when a statement can be made if the treatment was likely to be successful or not. Only few studies were actually focusing on imaging biomarkers that can be performed individually prior to therapy.

A promising technique was described by Morsbach et al who investigated the role of contrast enhanced perfusion CT as a predictor for treatment response and survival in patients with otherwise therapy refractory liver metastases [21]. All patients in this prospective trial were evaluated by dynamic contrast enhanced perfusion CT prior to treatment planning angiography and then underwent TARE within the next 24 days. Morphological treatment response was then evaluated after a mean follow up period of 112 days according to the RECIST 1.1 criteria. The pretreatment arterial perfusion differed significantly between responders and non-responders, while a cutoff arterial perfusion of 16 mL per 100 mL/min was associated with a sensitivity of 100% and a specificity of 89% for predicting therapy response. The same group could later demonstrate the superiority of this method compared to multiphase contrast enhanced CT and 99mTc-MAA SPECT [22].

Boas et al have recently demonstrated that the arterial enhancement fraction (AEF) calculated from pre-treatment contrast enhanced

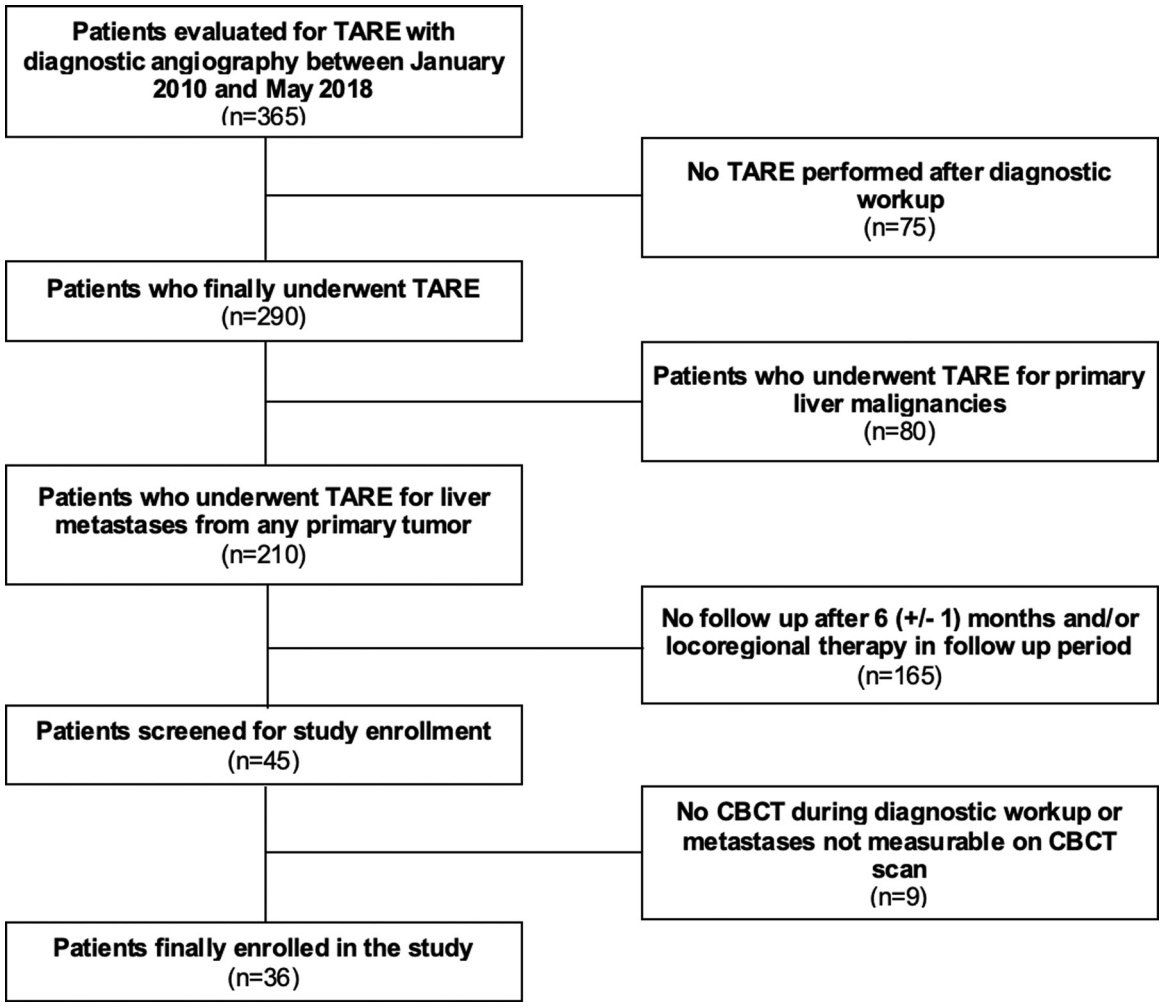

Fig. 3. Patient inclusion flow chart

CT is able to predict treatment response to TARE in patients with colorectal liver metastases [6]. The advantage of this method is that no special protocols or software are needed. The AEF, however, showed no correlation with patient survival.

These methods have in common that additional imaging protocols are needed prior to the actual diagnostic workup for patients that are potentially eligible for TARE.

Therefore, our idea was to evaluate the role of CBCT in predicting therapy response and survival for these patients, as this has become a routinely performed component during the diagnostic workup angiography before TARE. CBCT has already been found to represent a useful tool for Y90 dose calculation, periprocedural guidance, and detection of tumors [23,24].

Our hypothesis was that qualitative and quantitative assessment of metastasis enhancement during contrast enhanced CBCT, as performed by a standardized protocol at our institution, is associated with morphological treatment response following TARE. We could show that there is a significant correlation between relative lesion enhancement and morphological tumor response at 6 months. This finding is in keeping with the results of the perfusion CT studies performed by Morsbach et al [21,22] and suggests that ultimately a strong arterial tumor supply is the best predictor of treatment response whereas the enhancement pattern itself has no prognostic relevance.

This study has several limitations. First, it is a retrospective study performed in a single center with a limited number of patients. The high dropout as shown in Fig. 3 can be explained by the fact that our institution receives a high number of referrals from external hospitals for TARE, and many of these patients were then lost to follow up. Second, our cohort represents a heterogeneous group of patients with liver metastases from different underlying primary tumors. Third, all patients had received at least one prior antitumoral therapy, and to some extent received systemic antitumoral therapy during the follow up period. Hence, tumor response might not only be attributed to TARE and can bias our results. Future studies should therefore aim for a larger and more homogenous patient population, especially as the heterogeneity of our cohort does not allow any conclusions regarding patient survival.

In conclusion, according to the results of this study, quantitative relative arterial enhancement of liver metastases derived from contrast enhanced CBCT has the potential to help predicting the morphologic treatment response to TARE. This could make CBCT an easily available imaging biomarker for identifying eligible patients during the routine diagnostic workup for TARE.

Table 1
Baseline characteristics and treatment results stratified by treatment response according to RECIST 1.1

	All	PD	SD	PR	*p-value*
Total patients, n (%)	36 (100)	4 (11.1)	21 (58.3)	11 (30.6)	*0.27*
Age (years), median (min-max)	62.5 (22–80)	59 (36-74)	63 (22–80)	65 (22 – 74)	*0.63*
Male, n (%)	20 (55.6)	3 (8.3)	13 (36.1)	4 (11.1)	*0.29*
Tumor entity					
Neuroendocrine tumor, n (%)	8 (22.2)				
Gastrointestinal tract, n (%)	8 (22.2)				
Melanoma, n (%)	5 (13.9)				
Pancreas, n (%)	3 (8.3)				
Mamma, n (%)	3 (8.3)				
Others, n (%)	9 (25)				
Pre-TARE chemotherapy lines, median (min-max)	3 (0-8)	2.5 (1–5)	4 (1–8)	3 (0–8)	*0.66*
Mean of diameters of target liver metastases at baseline CT before TARE (mm), mean ±SD	32.9 ± 22.2	42.0 ± 23.1	33.5 ± 23.3	29.1 ± 19.4	*0.26*
Sum of diameters of target liver metastases at baseline CT before TARE (mm), mean ± SD	94.2 ± 32.2	104.9 ± 26.8	95.8 ± 33.6	87.3 ± 32.5	*0.62*
Sum of diameters of target liver metastases at follow-up after TARE (mm), mean ± SD	90.6 ± 54.9	189.1 ± 83.2	90.3 ± 38.7	54.1 ± 23.7	*<0.01*
Qualitative enhancement analysis					
Enhancement type					
Diffuse, n (%)	14	0	7	7	*0.19*
no enhancement, n (%)	3	0	2	1	*0.58*
rim, n (%)	12	3	7	2	*0.54*
sparse, n (%)	7	1	5	1	*0.49*
Quantitative enhancement analysis					
Relative lesion enhancement (HU), mean ± SD	113.3 ± 129.2	-37.5 ± 154.2	103.8 ± 93.4	181.0 ± 144.0	*<0.01*
Follow-up period (months), mean ± SD	6.5 ± 3.7	6.2 ± 0.9	4 ± 4.9	5.9 ± 0.6	*0.504*

CT = computed tomography; HU = Hounsfield unit; SD = Stable disease; PR = Partial response; PD = Progressive disease; TARE = Transarterial radioembolization

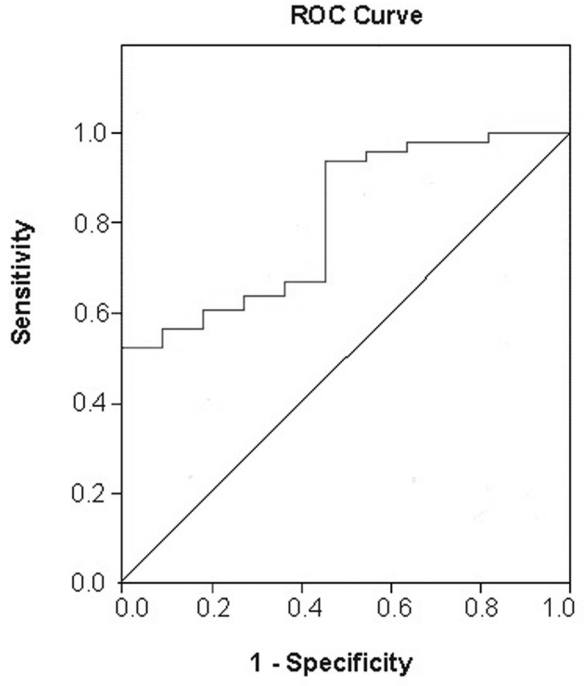

Fig. 4. ROC analysis for predictability of relative enhancement for progressive disease (AUC = 0.806, p=0.001)

Declaration of Competing Interest

The authors report no declarations of interest.

CRediT authorship contribution statement

Florian Messmer: Conceptualization, Data curation, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Juliana Zgraggen:** Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Adrian Kobe:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Lyubov Chaykovska:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Gilbert Puippe:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Caecilia S. Reiner:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Thomas Pfammatter:** Conceptualization, Investigation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

Ethics statement

This retrospective study was approved by the local Ethics Committee and conducted according to the principles of the Declaration of Helsinki. Written informed consent requirement was waived.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.redii.2022.100005.

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