Comparison of MRI-based response criteria and radiomics for the prediction of early response to transarterial radioembolization in patients with hepatocellular carcinoma

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Short title: Radiomics for early response evaluation after transarterial radioembolization

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Abbreviations

99Y = yttrium99; 99mTC-MAA = technetium-99m-labeled macroaggregates of albumin; AUC = Area under the receiver operating characteristics curve; CT = Computed tomography; EASL = European Association for the Study of the Liver; HCC = Hepatocellular carcinoma; LI-RADS = Liver Imaging Reporting and Data System; LR-TR = LI-RADS Treatment Response; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; ROC = Receiver operating characteristics; TARE = Transarterial radioembolization;

Abstract

Purpose: The purpose of this study was to evaluate the capabilities of radiomics using magnetic resonance imaging (MRI) data in the assessment of treatment response to ^{90}yttrium transarterial radioembolization (TARE) in patients with locally advanced hepatocellular carcinoma (HCC) by comparison with predictions based on European Association for the Study of the Liver (EASL) criteria.

Patients and Methods: Twenty-two patients with HCC (19 men, 3 women; mean age: 66.4 ± 9.8 [SD]; age range: 37–82 years) who underwent contrast-enhanced MRI 4 weeks ±1 before and 4 weeks ± 1 month after TARE, were enrolled in this retrospective study. Regions of interest were placed manually along the contours of the treated tumor on each axial slice of arterial and portal phase images using the ITK-SNAP post-processing software. For each MRI, the Pyradiomics Python package was used to extract 107 radiomics features on both arterial and portal phases, and resulting delta-features were computed. The Mann-Whitney U test with Bonferroni correction was used to select statistically different features between responders and non-responders (*i.e.*, those with progressive or stable disease) at 6-month follow-up, according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Finally, for each selected feature, univariable logistic regression with leave-one-

out cross validation procedure was used to perform receiver operating characteristic (ROC) curve analysis and compare radiomics parameters with MRI variables.

Results: According to mRECIST, 14 patients (14/22; 64%) were non-responders and 8 (8/22; 36%) were responders. Four radiomics parameters (long run emphasis, minor axis length, surface area, and gray level non-uniformity on arterial phase images) were the only predictors of early response. ROC curve analysis showed that long run emphasis was the best parameter for predicting early response, with 100% sensitivity (95% CI: 68–100) and 100% specificity (95% CI: 78–100). EASL morphologic criteria yielded 75% sensitivity (95% CI: 41–96%) and 93% specificity (95% CI: 69–100%).

Conclusion: Radiomics revealed significant differences between responders and non-responders, and could aid in prediction of an early treatment response following TARE in patients with HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, and its incidence has gradually increased [1]. Many patients are diagnosed with advanced-stage HCC and thus are not candidates for curative treatment. Although not included in the European Association for the Study of the Liver (EASL) recommendations, the usefulness of ^{90}yttrium (^{90}Y) transarterial radioembolization (TARE) for HCC has been reported, especially among patients with HCC associated with portal vein involvement [2, 3].

Thorough evaluation of the tumor response after TARE is essential for clinical management and prognosis. The radiologist must interpret the treatment response after TARE with caution, as 3–6 months may be necessary for responding lesions to show reductions in size and enhancement. During the first three months, patients may show necrosis and/or

peritumoral edema or inflammation, which can lead to underestimation of the treatment response or overestimation of tumor progression, thereby affecting clinical decision-making [4]. The modified Response Evaluation Criteria in Solid Tumors (mRECIST), which are based on the largest diameter of the viable enhancing tumor during the arterial phase, are currently the standard criteria to assess the radiological response in patients with HCC [5]. The EASL criteria were established in 2001 to assess the radiological response of HCC, based on the cross-product of the two largest diameters of viable target HCC lesions [6]. The mRECIST and EASL criteria are applied based on contrast-enhanced computed tomography (CT) or T1-weighted magnetic resonance imaging (MRI) findings. Although EASL and mRECIST can predict survival after transarterial chemoembolization [7-8] and TARE [9-10], no consensus regarding early imaging biomarkers for assessing the HCC tumor response and outcome after TARE has been reached.

The Liver Imaging Reporting and Data System (LI-RADS) version 2018 introduced an algorithm to standardize the reporting of treatment outcomes, regardless of the pretreatment LI-RADS category, and can be applied after any type of locoregional therapy [11]. LI-RADS treatment response (LR-TR) categories reflect the relative probability of tumor viability after locoregional therapy, and can help guide management decisions with a good interobserver agreement [12]. Similar to mRECIST, the LR-TR criteria are based on unidimensional measurements of the largest enhancing component of a treated tumor (excluding areas of nonenhancement). They also expand on the mRECIST approach by defining viable disease, and including non-evaluable, equivocal, and non-viable treatment response categories. LI-RADS has shown both high positive predictive (86–96%) and high negative predictive (81–87%) values in the assessment of the histopathologic viability of HCC treated with transarterial chemoembolization [13], but its utility for evaluating HCC treated with TARE has not been studied.

Radiomics can be used to quantitatively evaluate tumor heterogeneity by mathematically analyzing the spatial distribution and relationships of gray levels in medical images [14]. Radiomics is gradually being implemented for prognostic prediction and treatment response evaluation in patients with HCC [15]. Studies have reported that radiomics based on contrast-enhanced MRI can help predict early response of hepatic metastases to TARE [16], and of HCC to transarterial chemoembolization combined with high-intensity focused ultrasound [17]. However, the value of radiomics based on contrast-enhanced MRI for predicting an early response of HCC to TARE remains unknown.

The purpose of this study was to evaluate the capabilities of radiomics using MRI data in the assessment of treatment response to TARE in patients with locally advanced HCC by comparison with predictions based on the mRECIST, RECIST, EASL, and LR-TR criteria.

2. Patients and methods

2.1. Patient population

The data of patients with HCC who underwent TARE treatment between November 2011 and July 2020 were retrospectively reviewed. The data were obtained from the patient database of our university hospital. All patients with pre-therapeutic (4 ± 1 week before TARE) and early (4 ± 1 week after TARE) and late (3-6 months after TARE) post-therapeutic liver MRI data were included. Of the 74 patients, 22 were included in this study (Figure 1). The study protocol followed the tenets of the 1975 Declaration of Helsinki. HCC was diagnosed histologically or clinically, in accordance with the guidelines proposed by the EASL. Arterial enhancement followed by washout in the portal or equilibrium phase on dynamic CT or MRI was taken to indicate typical HCC [3].

2.2. TARE procedure

The decision to perform TARE was made at multidisciplinary liver tumor board meetings, which were held weekly and always attended by at least one certified radiologist specializing in interventional radiology. Patients first underwent a standard work-up to evaluate their eligibility for TARE, including catheter angiography for evaluation of the arterial supply to the tumor and gastrointestinal tract, as well as single-photon emission CT for assessment of extrahepatic shunting and dose calculation [18]. During catheter angiography, arterial branches from the hepatic artery to the gastrointestinal tract were embolized with coils as needed. The microcatheter tip was then placed in the appropriate position, and technetium-99m-labeled macroaggregates of albumin (^{99}mTC-MAA) were injected to measure the degree of extrahepatic shunting. The degree of shunting to the lung, and any residual shunting to the gastrointestinal tract, were assessed with ^{99}mTC-MAA single-photon emission CT. Patients eligible for TARE underwent additional catheter angiography in a second session, where ^{90}Y-microspheres (TheraSphere®; Boston Scientific Corp., n = 5, or SIR-Spheres®; Sirtex Medical Ltd., n = 17) were slowly injected with the microcatheter in the same position. ^{90}Y positron emission tomography/ CT was performed immediately after TARE to visualize the distribution of ^{90}Y activity and verify that there were no ^{90}Y microspheres in organs other than the liver.

3.3. Image acquisition

MRI data were acquired in daily practice at different radiological centers 4 ± 1 weeks before and after TARE and three to six months thereafter. The routine liver MRI protocol

included non-fat-suppressed single-shot fast spin-echo T2-weighted images in the axial and coronal plane, fat-suppressed fast spin echo images in the axial plane, T1-weighted in- and out-of-phase images in the axial plane, and dynamic contrast-enhanced T1-weighted images in the axial plane. For dynamic MRI, unenhanced, arterial phase, portal venous phase and transitional phase images were obtained before and after administration of gadoterate meglumine (Dotarem®, Guerbet).

3.4. MRI analysis

Two radiologists (G.A. and P.P. with three and four years of experience in abdominal MRI, respectively) reviewed the images at baseline, as well as at 4 weeks and 3–6 months after TARE. They assessed contrast-enhanced and subtracted images of treated lesions, in accordance with the respective guidelines for RECIST 1.1, mRECIST, EASL, and LR-TR v2018. When using the LR-TR criteria, cases with viable and equivocal responses were classified as non-responders, while those with non-viable responses were classified as responders. In all patients, the response of the "target" lesion treated with ^{90}Y was focused on.

The primary outcome was the response of the target lesion at six months, according to mRECIST. The responses were classified as follows: complete response, disappearance of intratumoral arterial hyperenhancement in the target lesion; partial response, ≥ 30% reduction in the sum of the diameters of the viable (intratumoral arterial hyperenhancement) target lesions; stable disease, insufficient shrinkage to qualify as partial response and insufficient growth to qualify as progressive disease; and progressive disease, ≥ 20% increase in the sum of the diameters of viable target lesions. Responders were patients who showed either a complete or partial response according to mRECIST, similar to the definition of an objective

response used in the literature; non-responders were those with stable or progressive disease [19].

3.5. Radiomics

Arterial phase and portal venous phase MR images (DICOM format) were obtained one month before and one month after TARE, respectively. These images were imported into the ITK-SNAP post-processing software [20]. Regions of interest were placed manually along the contours of the treated tumor on each axial slice of arterial and portal phase images by a radiologist with 4 years of experience in abdominal imaging. For all images, signal intensity was standardized based on the mean intensity of the reference region of interest (portal bifurcation) and normalized for non-uniform intensity using N4 bias correction. All slices were resampled to a common isotropic voxel size of $1 \times 1 \times 1$-mm^3. Radiomics features were extracted from the images using the PyRadiomics Python package in the standard configuration for two-dimensional extraction from MRI images [21]. In particular, no filter was applied on the images, all feature classes were computed (first-order, shape, glcm, glrlm, glszm, gldm, ngtdm), and gray levels were discretized from a 25 bin width. In total, 107 shape, first- and second- order features were computed (*e.g.*, uniformity, energy, entropy, skewness, kurtosis).

3. 6. Statistical analysis

The significantly different radiomics features between responders and non-responders, among the baseline, post-treatment and delta features, in both arterial and portal phases were

selected by using the nonparametric Mann-Whitney U test. The Bonferroni correction was used to take into account the alpha risk inflation: the obtained p-values were multiplied by the numbers of tests (2 ×107), and P <0.05 was considered statistically significant.

Then, univariate logistic regression with L1-norm penalization was used with Leave-one-out cross validation to determine the predictors of an early therapeutic response. In particular, a receiver operating characteristic (ROC) curve analysis was used to determine the test performance of significant parameters in the Mann–Whitney U test, based on the area under the curve (AUC), sensitivity and specificity values. Optimal cutoff values to distinguish between responders and non-responders were obtained using the maximum Youden index (sensitivity + specificity - 1). The sensitivities and specificities of significant radiomics features were compared to those of mRECIST, RECIST, EASL and LI-RADS criteria at one month, to determine the best predictor of an early therapeutic response.

3. Results

3.1. Patient characteristics

Twenty-two patients with HCC were included. There were 19 men and 3 women, with a mean age of 66.4 ± 9.8 (SD) years (median, 73; Q1, Q3: 66, 78; range: 37–82 years). The patients' baseline characteristics are summarized in Table 1. TARE was the first-line treatment in 6 (6/22, 28%) patients, and 16 (16/22, 72%) patients had previously undergone therapy. There were 17 patients (17/22, 77%) with advanced-stage disease, mostly in the form of portal vein thrombosis (16/22, 72%), and intermediate-stage disease (5/22, 23%) in which liver function was preserved (Child-Pugh status ≤ B7). According to mRECIST, at six months, three patients (3/22, 14%) showed a complete response and five (5/22, 23%) a partial

response. Eight patients (8/22, 36%) had stable disease and six (6/22, 28%) had progressive disease.

3.2. Prediction of treatment response

Significant radiomics features for target lesions (*i.e.*, those showing differences between responders and non-responders on arterial and portal phase MRI) are shown in Table 2. Among the 107 tested features, two second-order (glrm long run emphasis and glrm gray level non-uniformity) and two shape-based (minor axis length and surface area) parameters had statistically significant delta values in the arterial phase. None of the pre-therapeutic or portal phase parameters were predictive of the treatment response at six months.

The AUC (delta value) for long run emphasis in the arterial phase was 1, and the optimal cutoff value for distinguishing between responders and non-responders was 0.5 (sensitivity = 100%, specificity = 100%). The AUC (delta value) for minor axis length in the arterial phase was 0.92, and the optimal cutoff value was 0.11 (sensitivity = 100%, specificity = 86%). The AUC (delta value) for surface area in the arterial phase was 0.88, and the optimal cutoff value was 0.55 (sensitivity = 75%, specificity = 93%). The AUC (delta value) for gray level non-uniformity in the arterial phase was 0.86, and the optimal cutoff value was 0.55 (sensitivity = 75%, specificity = 93%). Figures 2 and 3 show the ROC curves and boxplots of the four statistically significant parameters, respectively. Table 3 lists the statistical results for the ROC analysis.

Sensitivity and specificity values at one month evaluation for mRECIST, EASL, RECIST, and LR-TR criteria, based on MRI examinations, are shown in Table 4.

4. Discussion

The aim was of this study was to evaluate the utility of radiomics analysis, based on contrast-enhanced MRI performed before and after TARE, for predicting an early treatment response among patients with HCC. Based on arterial phase images, four Radiomics features were able to reliably distinguish early responders and non-responders, with higher sensitivity and specificity compared with established MRI criteria. The best classification criteria at the one-month follow-up were EASL and mRECIST, with sensitivity and specificity of 75% and 93%, and 63% and 93%, respectively. The results of this study indicate the potential for MRI-based Radiomics Analysis to better predict an early response to TARE than morphologic imaging criteria alone. Prediction of non-response at an early stage may lead to additional therapy or application of TARE at an earlier juncture. In turn, this could prolong survival in some patients.

RECIST and LR-TR were not able to accurately predict an early treatment response, presumably because RECIST considers changes in lesion size rather than enhancement. With the LR-TR criteria, all lesions were classified as viable or equivocal at the one-month follow-up MRI, because an incomplete response at an early stage is not considered a partial response. Therefore, RECIST and LR-TR were not suitable for evaluation of the early response to TARE.

Radiomics is an emerging method for the quantification of tumor heterogeneity, through mathematical analysis of the spatial distribution and relationships of gray levels in medical images. Published studies on radiomics analysis of HCC have provided encouraging data regarding its potential utility for predicting tumor biology, molecular profiles, the post-therapy response, and outcomes [22-23]. To the best of our knowledge, this is the first study to evaluate the ability of Radiomics analysis, based on dynamic contrast-enhanced MRI, to assess the early response of patients with HCC to TARE. The signal measured on dynamic

contrast-enhanced MRI represents a combination of perfusion and permeability. It is sensitive to changes in blood flow, vascular permeability, and extracellular space. Thus, increased lesion heterogeneity on dynamic contrast-enhanced MRI could indicate heterogeneous perfusion and permeability, and may arise due to differences in necrosis, arteriovenous shunting, or neovascularization among tumors [24]. Reiner *et al.* showed that differences in arterial perfusion parameters before and after TARE were correlated with survival in patients with liver metastases [25]. However, contrary to CT perfusion findings in patients with HCC who received TARE treatment [26], the pretreatment heterogeneity parameters in arterial and portal phase images in our study were not significantly different between responders and non-responders, according to mRECIST. This could be because most of the treated lesions were infiltrative lesions with portal vein thrombosis. Moreover, the patients had previously undergone systemic or locoregional treatment, resulting in high pre-TARE heterogeneity in both responders and non-responders. Two of the four Radiomics features were three-dimensional, and the results were consistent with Tacher et al., who observed a better correlation with survival after transarterial chemoembolization in patients with HCC when using a volumetric response assessment compared with two-dimensional parameters [27].

In our population as in meta-analyses [28-29], EASL and mRECIST showed similar diagnostic performance. However, Seyal et al. reported good intraobserver agreement (kappa = 0.70), but only moderate interobserver agreement (kappa = 0.56), in the assessment of the response to TARE in patients with HCC based on mRECIST [30]. Peri-tumoral inflammation during the arterial phase, which can suggest pseudo-progression, presents the greatest difficulty with respect to assessing the early response with EASL and mRECIST. This phenomenon may also be observed after immunotherapy. Considering the increasing use of TARE and immunotherapy to treat patients with HCC, the development of new morphologic

imaging criteria for HCC that consider markers of pseudo-progression (*e.g.*, iRECIST [31]) might be necessary.

Currently, no robust and easy-to-use software for volumetric assessment of radiomics analysis and therapeutic response is available for clinical routine use. With the emergence of tools for automated and semi-automated tissue segmentation [32-33], and the standardization of radiomics features (*i.e.*, the Imaging Biomarker Standardization Initiative), radiomics may become a viable clinical tool for radiologists. This could help overcome delay required to obtain a clinically relevant imaging after TARE [34] and thus allow the patient for an early therapeutic change as TARE procedures are usually well tolerated [35].

This study had several limitations. First, the retrospective nature of the study means that caution is needed when drawing conclusions. Second, the small number of included patients restricted the analyses. The low percentage of included patients in this retrospective study can be explained by the fact that, according to most author's recommendations to evaluate the response three months after TARE treatment, only a few patients underwent an early MRI control one month after treatment in our institution. The long run emphasis parameter showed sensitivity and specificity values of 100% in ROC curve analysis, presumably due to the small patient population. To evaluate the generalization ability and risk of overfitting of the model, a larger cohort would be necessary for cross-validation, as well as an external cohort. Third, mRECIST was used for response evaluation, although these criteria are not ideal for predicting HCC viability after locoregional therapy when using a liver explant as a reference [36]. Fourth, the reproducibility of the manual contouring of each tumor was not evaluated as it was done by only one radiologist [37]. Fifth, standard protocols for MRI acquisition parameters, contrast agent administration, and radiomics analysis are needed for multicenter studies. However, this limitation reflects current clinical practice. For all images, signal intensities were standardized using the mean intensity of the reference

region of interest (portal bifurcation), and then normalized for non-uniform intensity using N4 bias correction.

In conclusion, the results of the present study suggest that radiomics analysis based on contrast-enhanced MRI data, before and after TARE, is promising in predicting an early response among patients with HCC. Larger, prospective studies are needed to validate these findings.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification.

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Disclosure of interest

The authors declare that they have no competing interest.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Declaration of Competing Interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

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Legends for figures

Figure 1. Study flow chart. HCC= Hepatocellular carcinoma; MRI = Magnetic resonance imaging; TARE = Transarterial radioembolization

Figure 2. Graph shows results of ROC curve analysis for estimating cut-off values for the four radiomics parameters.

Figure 3. Graph shows boxplots of the four significant radiomics parameters for arterial phase contrast-enhanced MRI between responders and nonresponders.

A. Long run emphasis (Δ) - glrlm

B. Minor axis length (Δ) - shape

C. Gray level non-uniformity (Δ) - glrlm

D. Surface area (Δ) – shape