Can response in patients with HCC after transarterial embolization be predicted by Radiomics on gadoxetate disodium MRI? A two-step selection procedure for a prediction model.

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Introduction
Hepatocellular carcinoma (HCC) accounts for about 90% of all primary liver malignancy in cirrhotic patients. In patients with localized HCC, accurate prediction of response to treatment with transarterial embolization (TAE) is crucial for treatment planning. Nevertheless, response to TAE can be heterogeneous according to pre-treatment tumors and patients' characteristics. Additionally, some studies evaluated pre-treatment qualitative imaging features of HCC on magnetic resonance imaging (MRI) to predict tumor response [1,2]. Qualitative imaging features may be affected by subjective interpretation, readers experience, and different definition among HCC guidelines. Therefore, reliable prediction of response on pre-treatment MRI remains an unsolved challenge in clinical practice.
Radiomics is as emerging as a promising tool providing many quantitative features from radiological images. Radiomics features can be combined with clinical and imaging data to construct predictive models for lesion characterization, prediction of treatment response, and patients' prognosis [3]. Initial studies have explored the potential of radiomics and texture analysis for the prediction of treatment response and prognosis of localized HCC patients after TAE on pre-treatment contrast-enhanced CT [4,5] and MRI with extracellular contrast agents [6] with high performances. None of these studies have investigated the accuracy of radiomics on gadoxetate disodium as MRI contrast agent in combination with both clinical and semantic imaging features. We hypothesize that radiomics may provide an added value for the prediction of treatment response by quantifying lesions heterogeneity related to tumor aggressiveness that cannot be perceptible by the radiologist eyes.

Aims
The aim of this study was to explore the potential of radiomics on gadoxetate disodium-enhanced MRI in comparison with clinical variables and qualitative imaging features for the prediction of hepatocellular carcinoma response after transarterial embolization.

Methods
The study population consisted of 51 patients (37 males, 14 females, median age 73 years, range 44-85 years) with unifocal HCC treated with TAE and available pretreatment gadoxetate disodium MRI. Patient-related clinical and laboratory variables were collected using the electronic data repository systems, including age at the time of treatment, sex, laboratory and tumor markers, history of ascites or varices, and Child-Pugh score. 854 radiomics features, categorized into three main categories (i.e. intensity, shape, and texture radiomics features) were analyzed. Six different radiomics models were constructed for the prediction of complete response and objective response in each analyzed phase (PVP, 3′ TP, and HBP). Each model was fitted on the combined dataset of 12 clinical variables, 19 LI-RADS qualitative imaging features, and 854 radiomics features. A two-step model selection and fitting procedure was performed. In the first step, a logistic model with elastic net penalty [7,8] and a high alpha-parameter (i.e. close to the lasso solution) was used to select the variables, while the tuning parameters were chosen by 5-fold cross-validation. Then, a new logistic model with ridge penalty was fitted on the ground of the selected variables to take into account for the correlation. All models were fitted on a training set, and validated on a test set, according to 80-20% random split of the original dataset.

Results
Table 1 reports some prediction accuracy measures in six test sets (the two responses, complete and objective, in each of the three phases of the gadoxetate disodium contrast agent administration for MRI), using the proposed two-step procedure.

Table 1: Performance of the two-step procedure for the prediction, on the test set, of complete response and objective response after TAE, on three phases of the gadoxetate disodium contrast agent administration for MRI.

	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUROC (95% CI)	p value
	Prediction of complete response				
PVP	87.5	33.3	72.7	0.667 (0.251-1.000)	0.431
3′ TP	75.0	33.3	63.6	0.750 (0.429-1.000)	0.127
HBP	100.0	100.0	100	1.000 (1.000-1.000)	<0.001
	Prediction of objective response				
PVP	100	40	72.7	0.733 (0.405-1.000)	0.163
3′ TP	40.0	66.7	54.5	0.667 (0.305- 1.000)	0.367
HBP	20.0	100.0	63.6	0.600 (0.1936-1.000)	0.630

Abbreviations: PVP: Portal Venous Phase; 3′ TP: 3 minutes Transitional Phase; HBP: Hepatobiliary Phase.

Conclusions
The prediction accuracy of HCC response predictions after TAE using Radiomics on gadoxetate disodium MRI, in conjunctions with clinical variables and qualitative imaging features, resulted to be moderate on 5 out six of the test sets. Predictions on the complete response in hepatobiliary phase resulted to be highly accurate. As expected, a very high prediction accuracy was instead obtained in all phases and responses on the six training sets. Before using the proposed procedure of analysis, several supervised machine learning techniques such as classification trees, bagging, random forests, boosting, support vector classifiers [9] were employed, but with poorer prediction accuracy than the proposed procedure.

Main References
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