CLINICAL STUDY

Predicting Treatment Response to Intra-arterial Therapies for Hepatocellular Carcinoma with the Use of Supervised Machine Learning—An Artificial Intelligence Concept

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ABSTRACT

Purpose: To use magnetic resonance (MR) imaging and clinical patient data to create an artificial intelligence (AI) framework for the prediction of therapeutic outcomes of transarterial chemoembolization by applying machine learning (ML) techniques.

Materials and Methods: This study included 36 patients with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization. The cohort (age 62 ± 8.9 years; 31 men; 13 white; 24 Eastern Cooperative Oncology Group performance status 0, 10 status 1, 2 status 2; 31 Child-Pugh stage A, 4 stage B, 1 stage C; 1 Barcelona Clinic Liver Cancer stage 0, 12 stage A, 10 stage B, 13 stage C; tumor size 5.2 ± 3.0 cm; number of tumors 2.6 ± 1.1; and 30 conventional transarterial chemoembolization, 6 with drug-eluting embolic agents). MR imaging was obtained before and 1 month after transarterial chemoembolization. Image-based tumor response to transarterial chemoembolization was assessed with the use of the 3D quantitative European Association for the Study of the Liver (qEASL) criterion. Clinical information, baseline imaging, and therapeutic features were used to train logistic regression (LR) and random forest (RF) models to predict patients as treatment responders or nonresponders under the qEASL response criterion. The performance of each model was validated using leave-one-out cross-validation.

Results: Both LR and RF models predicted transarterial chemoembolization treatment response with an overall accuracy of 78% (sensitivity 62.5%, specificity 82.1%, positive predictive value 50.0%, negative predictive value 88.5%). The strongest predictors of treatment response included a clinical variable (presence of cirrhosis) and an imaging variable (relative tumor signal intensity >27.0).

Conclusions: Transarterial chemoembolization outcomes in patients with HCC may be predicted pre-procedurally by combining clinical patient data and baseline MR imaging with the use of AI and ML techniques.

ABBREVIATIONS

AI = Artificial Intelligence, HCC = hepatocellular carcinoma, ML = machine learning, qEASL = quantitative European Association for the Study of the Liver

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Transarterial chemoembolization is a well established primary therapy for patients with unresectable hepatocellular carcinoma (HCC) (1,2). Radiologic response criteria are used to quantify transarterial chemoembolization efficacy based on post-treatment contrast-enhanced magnetic resonance (MR) or computerized tomography (CT) imaging. Conventional criteria used to assess radiologic response after transarterial chemoembolization are measured on 2-dimensional axial slices, based on diameter changes in target tumors or visually estimated changes in image enhancement (3–6). The quantitative European Association for the Study of the Liver (qEASL) response criterion measures the degree of change in 3-dimensional (3D) enhancing tumor volume and has been demonstrated to be superior to all other response criteria in both reproducibility and ability to predict overall survival sooner (7).

Although these improvements in radiologic response measures have advanced the assessment of patients after treatment, it remains clinically challenging to predict which patients will respond to transarterial chemoembolization before treatment; no single pre-treatment clinical or imaging feature is predictive of response. An accurate method for predicting a patient's likelihood of response could reduce unnecessary interventions, lower health care costs, and minimize patient harm. It is worthwhile, therefore, to investigate how pre-treatment patient characteristics influence treatment efficacy as measured by post-treatment response.

The challenge of applying pre-treatment imaging and clinical traits to predict post-treatment response can be solved with the use of machine learning (ML), an application of artificial intelligence (AI) that self-improves by learning from data (8). Predicting response to treatment can be conceptualized as a classification problem, in which an ML model sorts patients into categories of treatment responders or nonresponders with the use of information gathered before treatment. Classification is accomplished through supervised ML, a technique that requires outcome-labeled training data. Trained models can be applied to new cases that they have not previously encountered (9). For example, patient baseline imaging and clinical data, treatment characteristics, and treatment outcomes can be applied from a retrospective patient cohort to teach a model to learn the relationships between these variables and treatment outcomes. The model predicts treatment response in new patients pre-procedurally, provided that planned treatment characteristics are specified. The purpose of the present study was to use MR imaging and clinical patient data to create an AI framework for the prediction of therapeutic outcomes of transarterial chemoembolization in HCC by applying ML techniques.

MATERIALS AND METHODS

Patient Cohort

This was a Health Insurance Portability and Accountability Act–compliant, single-institution, Institutional Review Board–approved retrospective analysis of prospectively collected data. Requirement for informed consent was waived. A cohort of 36 patients with HCC treated by conventional transarterial chemoembolization with ethiodized oil or transarterial chemoembolization with drug-eluting embolic agents from 2012 to 2015 was selected for analysis; only transarterial chemoembolization-naïve patients were included in the study. The patient cohort consisted of individuals who had noninfiltrative tumors with well-delineated capsules and other classic diagnostic imaging features of HCC according to the Liver Imaging and Reporting System. Only patients with follow-up imaging 1 month after transarterial chemoembolization as well as complete clinical and imaging data were included. The patients were not consecutive chronologically. In patients where multiple tumors were treated in the initial transarterial chemoembolization procedure, all target tumors were included in the qEASL response analysis. Patients with HCC treated with concomitant sorafenib received it continuously, starting 1 week before the initial transarterial chemoembolization and continued in 6-week cycles without interruptions. Clinical and demographic information and treatment characteristics used to train the learning models are reported in **Table 1**.

Transarterial chemoembolization Technique

After a multidisciplinary tumor board identified transarterial chemoembolization as an appropriate treatment for each patient, transarterial chemoembolization was performed by a single interventional radiologist with 20 years of experience. Under the guidance of intraprocedural imaging, selective or superselective embolization was performed with the use of a solution containing 50 mg doxorubicin and 10 mg mitomycin C in a 1:1 mixture with ethiodized oil (Lipiodol; Laboratoire Guerbet, Aulnay-sous-Bois, France). Microspheres with a diameter of 300–500 μm were used to embolize more proximal vessels (Embosphere; Merit Medical Systems, South Jordan, Utah). In patients receiving transarterial chemoembolization with drug-eluting embolic agents, LC Beads (BTG, Farnham, United Kingdom) with a diameter of 100–300 μm were loaded with 100 mg doxorubicin hydrochloride (25 mg/mL). Doxorubicin-eluting embolic agents were mixed with an equal volume of nonionic contrast material (Oxilan, 300 mg iodine/mL; Guerbet, Bloomington, Indiana) before intra-arterial administration. The transarterial chemoembolization end point was significant flow reduction while avoiding stasis; contrast column in the feeding vessel was aimed to be cleared with 5 heart beats. Selectivity of embolization was achieved in all patients. The cohort had a 30-day procedure-related mortality of 0% and no technical periprocedural complications were observed (arterial dissections, bleeding, or infections). No grade 3/4 adverse events were observed in this patient cohort. Nausea and right upper quadrant pain were the most frequently encountered toxicities (grade 1/2 with 40% and 37%, respectively).