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*REVIEW*

# Current status and future perspectives of radiomics in hepatocellular carcinoma

Joao Miranda, Natally Horvat, Gilton Marques Fonseca, Jose de Arimateia Batista Araujo-Filho, Maria Clara Fernandes, Charlotte Charbel, Jayasree Chakraborty, Fabricio Ferreira Coelho, Cesar Higa Nomura, Paulo Herman

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## Abstract

Given the frequent co-existence of an aggressive tumor and underlying chronic liver disease, the management of hepatocellular carcinoma (HCC) patients requires experienced multidisciplinary team discussion. Moreover, imaging plays a key role in the diagnosis, staging, restaging, and surveillance of HCC. Currently, imaging assessment of HCC entails the assessment of qualitative characteristics which are prone to inter-reader variability. Radiomics is an emerging field that extracts high-dimensional mineable quantitative features that cannot be assessed visually with the naked eye from medical imaging. The main potential applications of radiomic models in HCC are to predict histology, response to treatment, genetic signature, recurrence, and survival. Despite the encouraging results to date, there are challenges and limitations that need to be overcome before radiomics implementation in clinical practice. The purpose of this article is to review the main concepts and challenges pertaining to radiomics, and to review recent studies and potential applications of radiomics in HCC.

**Key Words:** Radiomics; Hepatocellular carcinoma; Texture analysis; Radiology

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**Core Tip:** Radiomics is an emerging field that extracts high-dimensional mineable quantitative features that cannot be assessed visually with the naked eye from medical imaging. The main potential applications of radiomic models in hepatocellular carcinoma (HCC) are to predict histology, predict response to treatment, predict genetic signature, predict recurrence, and predict survival. The purpose of this article is to review the main concepts and challenges pertaining to radiomics, and to review recent studies and potential applications of radiomics in HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide [1]. Liver cancer is especially common in Asia, where 72.5% of all new liver cancer cases worldwide are diagnosed[2]. HCC accounts for over 90% of all primary liver cancer cases[3]. The main risk factors for HCC in the West is viral hepatitis (hepatitis C virus in the West and hepatitis B virus in Asia and in developing countries) and alcohol intake. In addition, non-alcoholic steatohepatitis is becoming a common risk factor, particularly in the West[3,4]. HCC patient prognosis depends on the stage of HCC at the time of diagnosis[5]; and advanced-staged patients at the time of diagnosis have a poor prognosis [5-7].

The treatment of HCC is based on tumor burden, clinical performance of the patient, and liver function[8]. Given the frequent co-existence of an aggressive tumor and underlying chronic liver disease, the management of HCC requires experienced multidisciplinary team discussion[9]. Moreover, radiology plays a key role in the screening, diagnosis, staging, restaging, and surveillance of HCC. Currently, imaging assessment is based on qualitative characteristics, such as size and enhancement pattern, which are prone to inter-reader variability. Reliable tools that can potentially address this variability as well as deal with the vast amount of imaging data are warranted[10]. Over the last decade, radiomics has become a popular quantitative tool that can potentially address these challenges and provide information not previously available for precision decision-making[11].

Radiomics is an emerging field that extracts high-dimensional mineable quantitative features that cannot be assessed visually with the naked eye from medical imaging[12]. The main potential applications of radiomic models in HCC are to predict histology, response to treatment, genetic signature, recurrence, and survival[13]. Despite the encouraging results to date, there are several challenges and limitations that need to be overcome before the implementation of radiomics in clinical practice. The purpose of this study is to review the main concepts, challenges pertaining to radiomics and recent studies and potential applications of radiomics in HCC.

## RADIOMICS

### *Main concepts*

In the new era of precision medicine, artificial intelligence (AI) and in its various branches, such as machine learning (ML) and deep learning (DL), have provided new imaging biomarkers that can potentially provide new data that are useful for clinical decision-making. ML is related to a set of computational systems that improve with experience. DL is a subset of ML based on series of layers (trainable nonlinear operations), each of which transforms input data into a representation that facilitates pattern recognition[14].

Radiomics has recently emerged as a translational research field that proposes to discover new associations between clinical data and quantitative data extracted from medical images using conventional biostatistics or AI methods[12] and become popular, particularly in oncologic imaging. Radiomics involves mineable high-dimensional data extraction, characterizing intensity, shape, size, and/or texture from images to create big-data datasets that are then used to identify distinct sub-visual imaging

patterns[15]. Radiomics models usually use magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography (PET) images data. Fundamentally, radiomics is motivated by the observation that these imaging characteristics reflect phenotype and genotype of underlying tissue and thus can help in clinical decision making[16].

Radiomic can be subdivided into texture, size and shape, and transformed based features. The most common radiomic features is texture. It can be subdivided into first-order, second-order and higher-order statistical features. First-order features reflect the distribution of values of individual voxels without concern for spatial relationships; they are generally histogram-based, such as mean (average intensity), entropy (quantify randomness of intensity), kurtosis (flatness) and skewness (asymmetry). Second-order features reflect the statistical interrelationships between voxels with similar (or dissimilar) contrast values[12] and some of the commonly used 2$^{nd}$ order features are: Grey level co-occurrence matrix, grey level run length matrix, and grey level size zone matrix features. Taking into account the repetitive patterns in radiological images, higher-order statistical methods use sophisticated filter grids on the images - such as Minkowski functionals (to evaluate voxels whose intensity is above a determined threshold), Wavelet and Laplacian transforms (to identify coarse texture patterns) and fractal analysis (to assess the irregularity of a surface)[12]. In practice, standard libraries with predefined feature configurations and validated reference values (such as PyRadiomics) are frequently used to increase the reproducibility of radiomic models.

### Workflow

Radiomic analysis is a multistep process involving the processing of medical images to generate different features from segmented images. The typical radiomics workflow can be summarized in the following steps (Figure 1):

**Image acquisition and preprocessing:** Standardized imaging protocols should be used to avoid reproducibility issues related to noise and confounding. However, standardized imaging protocols also decrease the generalizability of the results. Once a patient dataset has been identified, images should be anonymized as well as exported as Digital Imaging and Communication in Medicine files[17]. De-noising and motion correction steps may be needed.

**Segmentation:** Segmentation involves the delineation of region of interests (ROIs) on the tumor or peritumoral zones. ROIs can be delineated manually, semiautomatically, or automatically (using ML tools) in either two-dimensional (2D) or three-dimensional (3D) views (Figure 2). Whenever possible, segmentations should be checked by a radiologist to ensure accuracy.

**Feature extraction, feature selection and model building:** A wide range of statistical models are commonly used to choose a subset of optimal features that correlate with the predenid outcome[15]. Many of the extracted features are in fact redundant and supervised or unsupervised approaches can be applied to achieve dimension reduction. ML and DL techniques are emerging as useful tools to achieve more accurate feature selection[18,19]. The features should be selected only based on the training data to avoid bias.

Of note, the number of extracted features is commonly larger than the study sample, which can contribute to overfitting of the model and to overoptimistic results. Some strategies can be done, for example, select the features in such a way to maintain the ratio or regularization methods are used to minimize the complexity of the respective models[20]. Once the optimal features are identified, a statistical model can be proposed to predict a specific clinical question using different classifiers such as generalized linear models, random forests, support vector machines, or neural networks[20,21].

**Validation:** Validation is essential to estimate model performance and can be done using subsets of the original training dataset (*i.e.*, cross-validation) or using a separate hold-out dataset containing either internal or external data[17].

### Main challenges

To date, radiomic models reproducibility is often poor, due to insufficient reporting or limited open-source code and data, which undermines external validation and increases the subsequent risk of false-positive results[22]. Further, researchers often face great difficulty in acquiring unbiased and homogeneous datasets across multiple institutions, thus hampering multi-institutional collaborations involving large multi-institutional datasets for the training and validation of radiomic models[14]. For successful multi-institutional cooperation for building large multi-institutional datasets for radiomic models training and validation, radiomics workflow standardization, clear reporting of study methodology, and data sharing across different institutions are needed[17]. Additionally, an effective means to interpret the vast and varied data derived from radiomics analysis is another key obstacle to the clinical implementation of radiomic models. Therefore, a balanced interpretation of results and an increased focus on interpretable models are essential to their successful integration into clinical practice [23]. Finally, manual segmentation is a time-consuming process and one of the most common limitations that should be managed with automatic or semiautomatic strategies before widespread use of radiomics tools.

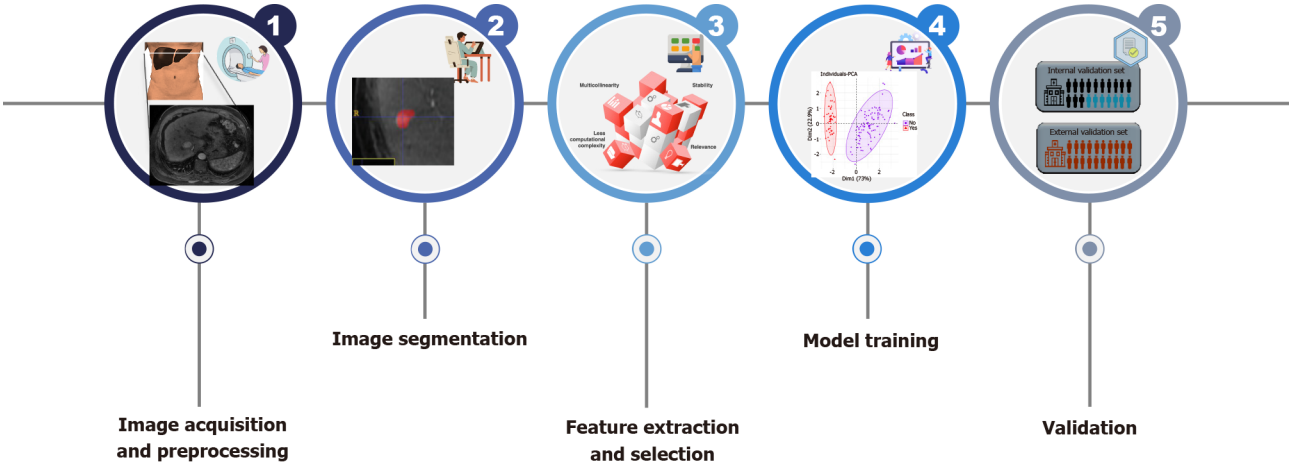


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**Figure 1 Illustration summarizing radiomics workflow.**

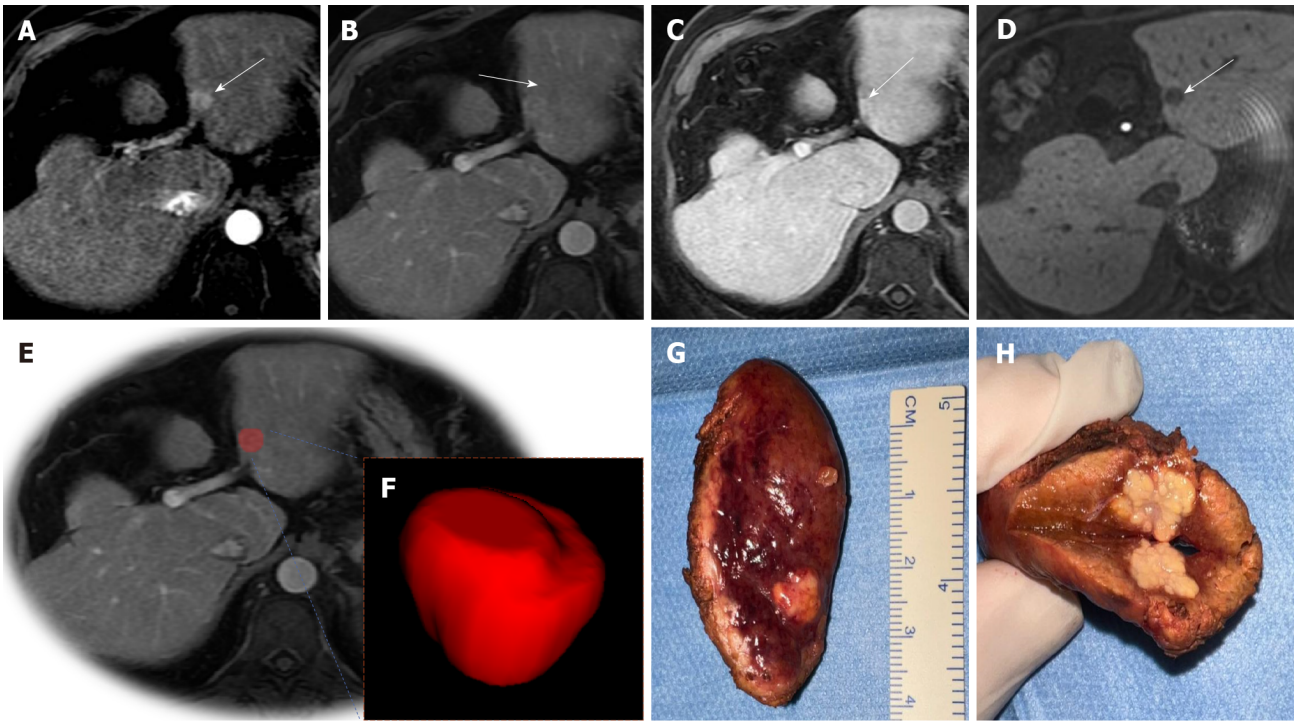


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**Figure 2 Illustration of hepatocellular carcinoma segmentation.** 72-year-old man with cirrhosis had a new liver lesion on computed tomography, indeterminate. Gadoxetic acid-enhanced T1-weighted images show a 1.3 cm (arrows) lesion. A: With arterial phase hyperenhancement; B: Questionable washout appearance on portal venous; C: Delayed phases; D: Hypointensity on during hepatobiliary phase (20 min); E and F: A tumor bed segmentation was exemplified, the portal venous phase (E) was used to manually segment the volume of interest (F); G and H: Note the gross findings after surgery. Histology confirmed hepatocellular carcinoma.

## APPLICATIONS OF RADIOMICS IN HCC

### *Prediction of HCC histology*

Table 1 summarizes the studies in the literature to date that have evaluated the use of radiomics to preoperatively predict HCC histology.

**Distinguishing between HCC and other malignant or benign lesions:** The distinction between HCC and other primary hepatobiliary malignancies can be challenging on imaging, because of the overlap of some features, especially for combined tumors[24]. In light of this, many studies have investigated radiomics performance in differentiating HCC from other malignant and benign hepatic lesions. For instance, Liu *et al*[24] studied the use of MRI- and CT-based radiomics to differentiate between HCC,

**Table 1 Summary of the studies that evaluated radiomics to preoperatively predict hepatocellular cholangiocarcinoma histology**

| Ref. | Country | *n* | Imaging modality | Endpoint | Segmentation | ROI/VOI | No. of readers | Main results | Validation |
|---|---|---|---|---|---|---|---|---|---|
| Wang *et al* [92], 2022 | China | 196 | MRI | cHCC-CC *vs* HCC | Manual, intratumoral | ROI | 1 | AUC (delayed phase MRI): 0.91 | None |
| Liu *et al* [24], 2021 | Canada | 85 | MRI and CT | cHCC-CC *vs* HCC *vs* CC | Manual, intratumoral | ROI | 2 | AUC (MRI): 0.77-0.81. AUC (CT): 0.71-0.81 | Cross-validation |
| Lewis *et al* [25], 2019 | United States | 63 | MRI | cHCC-CC *vs* HCC *vs* CC | Manual, intratumoral | VOI | 2 | AUC (LI-RADS and male gender): 0.90 | None |
| Nie *et al* [27], 2020 | China | 156 | CT | HCC *vs* FNH | Manual, intratumoral | ROI | 2 | AUC (radiomics): 0.96 training, 0.87 validation. AUC (radiomics + clinical factors): 0.98 training, 0.92 validation | None |
| Wu *et al* [28], 2019 | China | 369 | MRI | HCC *vs* hemangioma | Manual, intratumoral | ROI | 2 | AUC: 0.86 training, 0.89 testing | None |
| Mokrane *et al*[29], 2020 | United States | 178 | CT | HCC diagnosis | Manual, intratumoral | VOI | 2 | AUC: 0.70 training, 0.66 validation | External |
| Brancato *et al*[34], 2022 | Italy | 38 | MRI | Tumor grade | Manual, intratumoral | VOI | 1 | AUC: 0.89 | None |
| Gao *et al* [93], 2018 | China | Training: 125. Validation: 45 | MRI | Tumor grade | Manual, intratumoral | N/A | N/A | AUC: 0.83 training, 0.74 validation | None |
| Wu *et al* [30], 2019 | China | Training: 125. Validation: 45 | MRI | Tumor grade | Manual, intratumoral | ROI | 1 | AUC: 0.83 training, 0.74 validation | Internal |
| Zhou *et al* [94], 2017 | China | 46 | MRI | Tumor grade | Manual, intratumoral | ROI | 1 | AUC: 0.83-0.92 | None |
| Mao *et al* [31], 2022 | China | Training: 85. Validation: 37 | MRI | Tumor grade | Manual, intratumoral | ROI | 2 | AUC: 0.97 training, 0.94 validation | Internal |
| Chen *et al* [33], 2021 | China | Training: 112. Validation: 49 | CT | Tumor grade | Manual, intratumoral | VOI | 2 | AUC: 0.90 training, 0.94 validation | Internal |
| Yang *et al* [95], 2019 | China | Training: 146. Validation: 62 | Gadoxetic acid-enhanced MRI | MVI | Manual, intratumoral | ROI | 2 (consensus) | AUC: 0.94 training, 0.86 validation | Internal |
| Xu *et al* [39], 2019 | China | 495 | CT | MVI | Semi-automatic, intratumoral and peritumoral | VOI | 3 | AUC: 0.91 training, 0.89 validation | Internal |
| Feng *et al* [40], 2019 | China | 160 | Gadoxetic acid-enhanced MRI | MVI | Manual, intratumoral and peritumoral | VOI | 3 | AUC: 0.85 training, 0.83 validation | Internal |
| Zheng *et al*[41], 2017 | United States | 120 | CT | MVI | Semi-automatic | ROI | 1 | AUC: 0.80 | None |
| Bakr *et al* [96], 2017 | United States | 28 | CT | MVI | Manual, intratumoral | ROI | 4 | AUC: 0.76 | None |
| Ma *et al* [97], 2019 | China | 157 | CT | MVI | Manual, intratumoral | VOI | 1 | AUC (portal venous phase CT): 0.79 | Cross-validation |

AUC: Area under the curve; cHCC-CC: Combined hepatocellular cholangiocarcinoma; CT: Computed tomography; FNH: Focal nodular hyperplasia; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; MVI: Microvascular invasion; ROI: Region of interest; VOI: Volume of interest.

cholangiocarcinoma, and combined HCC-cholangiocarcinoma. Using MRI, radiomic features derived from contrast-enhanced phases demonstrated excellent performance to differentiate HCC from non-HCC [area under the curve (AUC) ≥ 0.79], with the highest AUC obtained from the arterial phase (AUC of 0.81); meanwhile, using CT, radiomic features derived from the pre-contrast and portal venous phase yielded AUC values of 0.81 and 0.71, respectively. In another study, Lewis *et al*[25] found that the combination of the apparent diffusion coefficient 5$^{th}$ percentile radiomic feature with Liver Imaging Reporting and Data System classification and male gender achieved an accuracy of 80%-81.5% in distinguishing HCC from intrahepatic cholangiocarcinoma (ICC) and combined HCC-ICC, and outperformed either measure alone. Other studies showed that radiomics is helpful to distinguish between HCC and benign tumors in non-cirrhotic livers, *e.g.*, from hepatocellular adenoma (AUC of 0.96 in the training set and 0.94 in the test set)[26], from focal nodular hyperplasia (AUC of 0.979 in the training set and 0.917 in the test set)[27], and from hemangioma (AUC: 0.86 in the training set and 0.89 in the test set)[28]. Mokrane *et al*[29] validated a radiomics signature to diagnose HCC in patients with cirrhosis and increased radiologists' confidence.

**Prediction of histologic grade:** Histologic grade is an important prognostic factor in patients with HCC and is only available preoperatively in patients who undergo biopsy. Therefore, studies have aimed to identify non-invasive imaging features such as radiomic features that could potentially predict the tumor grade. Wu *et al*[30] found that MRI-based radiomics can successfully categorize low-grade and high-grade HCC, with the radiomic model outperforming the clinical model (AUC 0.742 for the combined T1-weighted and T2-weighted MRI-based radiomic model *vs* AUC 0.6 for the clinical one) and the combined radiomic and clinical model (AUC 0.8) outperforming both models alone. Mao *et al*[31] also investigated MRI-based radiomic features, with Gd-EOB-DTPA contrast administered for the MRI exams, finding that the artificial neural network combining radiomic features from the contrast-enhanced arterial phase and hepatobiliary phase yielded the highest AUC of 0.944. Moreover, they found that the artificial neural network models were superior to the logistic regression models. In other studies, CT-based radiomics has been found to have high performance in distinguishing between low- and high-grade tumors[32-34]; for instance, Chen *et al*[33] found an AUC of 0.937 for a ML-based radiomics model based on the CT portal phase.

**Prediction of microvascular invasion:** Microvascular invasion (MVI) is found in about 15%-57% of patients with HCC who undergo surgery[35,36] and is associated with higher rates of recurrence and shorter survival after surgery[37]. Although imaging can be used to diagnose macrovascular invasion (or tumor in vein), preoperative imaging identification of MVI is difficult. Studies have evaluated the performance of radiomics as a tool to predict MVI, with most predictive models combining radiomics and clinical biomarkers[38]. For instance, Xu *et al*[39] proposed a model combining CT-based radiomic features with radiologic and clinical parameters; the model was not only an independent predictor of histologic MVI (AUC of 0.909 in the training/validation set and 0.889 in the test set) but was also an independent predictor of worse prognosis (disease-specific recurrence and disease-specific mortality). Of note, the radiomics-only model did not add significant value to radiologist scores alone. Since MVI occurs primarily at the tumor periphery (approximately 85% of MVI is located within one centimeter from the tumor margin), studies have investigated radiomic features derived from the peritumoral tissue. For instance, Feng *et al*[40] demonstrated that a model combining intratumoral and peritumoral radiomic features was superior in predicting MVI using Gd-EOB-DTPA-enhanced MRI compared to the model containing only intratumoral radiomics features. Additionally, Zheng *et al*[41] demonstrated that peritumoral textural features had an AUC of 0.80 and a multivariate model combining alfa-fetoprotein, tumor size, hepatitis status and quantitative features achieved an AUC of 0.88.

### *Prediction of HCC genetic expression*

Compared to the prediction of histology, fewer researches in the literature have evaluated the use of radiomics to predict genetic expression in patients with HCC (Table 2). Overall, studies on the use of radiomics to predict genetic expression have focused on using radiomics to predict Ki67 expression as well as cytokeratin 19 (CK19), P53, and phosphatidylinositol-3 kinase (PI3K) status. Of note, in 2007, Segal *et al*[42] investigated for the first time the correlation between HCC genetic expression and CT imaging traits, finding 32 CT imaging traits that were correlated with the expression levels of 116 genetic markers.

**Ki67 expression:** High Ki-67 expression in HCC patients is associated with fast progression and poor prognosis[43]. To determine if radiomics can be useful to predict Ki67 expression, Wu *et al*[44] developed and validated a radiomic nomogram based on the combination of CT-based radiomic features and clinical factors. Using Gd-EOB-DTPA-enhanced MRI, Li *et al*[45] found that texture analysis of the hepatobiliary phase, arterial phase, and portal vein phase were helpful for predicting Ki67 expression. In their study, a single slice with the largest proportion of the lesion was delineated, and the predictive performance of models were compared by misclassification rate. In another study by Fan *et al*[46] using Gd-EOB-DTPA-enhanced MRI, the authors delineated the whole lesion, and the predictive performance of different models were compared using the receiver operating curve, calibration curve,

**Table 2 Summary of the studies that evaluated radiomics models to predict genetic profile in patients with hepatocellular cholangiocarcinoma**

| Ref. | Country | *n* | Imaging modality | Endpoint | Segmentation | ROI/VOI | No. of readers | Main results | Validation |
|---|---|---|---|---|---|---|---|---|---|
| Xia *et al* [98], 2018 | China | 38 | CT | Association with gene expression profile | Manual, intratumoral | ROI | 1 | Individual textural features predicted gene modules | No |
| Wu *et al*[44], 2022 | China | Training: 120. Validation: 52 | CT | Ki-67 expression | Manual, intratumoral | VOI | 2 | AUC: 0.85 (training), 0.74 (validation) | Internal |
| Li *et al* [45], 2019 | China | 83 | MRI | Ki-67 expression | Manual, intratumoral | ROI | 2 | Some features were associated, no model | No |
| Ye *et al* [47], 2019 | China | 89 | MRI | Ki-67 expression | Manual, intratumoral | VOI | 2 | C-index: 0.878 | No |
| Fan *et al*[46], 2021 | China | Training: 103. Validation: 48 | MRI | Ki-67 expression | Manual, intratumoral | VOI | 2 | AUC: 0.88 (training), 0.80 (validation) | Internal |
| Hu *et al* [48], 2022 | China | Training: 87. Validation: 21 | MRI | Ki-67 expression | Manual, intratumoral | ROI | 1 | AUC: 0.90 (training), 0.83 (validation) | Internal |
| Wang *et al* [50], 2019 | China | 78 | MRI | CK19 positivity | Manual, intra- and peritumoral | ROI | 1 | AUC: 0.76 | No |
| Chen *et al*[51], 2021 | China | Training: 102. Validation: 19 | MRI | CK19 positivity | Manual, intratumoral | ROI | 2 | AUC: 0.82 (training), 0.78 (external validation) | Internal and external |
| Yang *et al*[52], 2021 | China (multicenter) | Training: 143. Validation: 75 | MRI | CK19 positivity | Manual, intratumoral | ROI | 2 | AUC: 0.85 (training), 0.79 (external validation) | Internal and external |
| Wu *et al*[55], 2019 | China | 63 | CT | P53 mutation status | Manual, intratumoral | ROI | 2 | AUC: 0.62-0.79 | No |
| Li *et al* [99], 2022 | China | 92 | MRI | Gene signatures associated with disease recurrence | Manual, intratumoral | ROI | 2 | MRI radiomics features could help quantify GOLM1, SETD7, and RND1 expression levels | Internal |
| Liao *et al*[56], 2022 | China | Training: 86. Validation: 46 | CT | Somatic mutations of the PI3K signaling pathway | Manual, intratumoral and peritumoral | VOI | 2 | AUC: 0.74 (training), 0.73 (external validation) | Internal and external |
| Che *et al*[60], 2022 | China | Training: 69. Validation: 30 | CT | β-arrestin1 phosphorylation | Manual, intratumoral | ROI | 1 | AUC: 0.89 (training), 0.74 (validation) | Internal |

AUC: Area under the curve; CT: Computed tomography; MRI: Magnetic resonance imaging; ROI: Region of interest; VOI: Volume of interest; CK19: Cytokeratin 19; PI3K: P53, and phosphatidylinositol-3 kinase.

and decision cure analysis. The optimal model combining the arterial phase radiomic score and serum alpha-fetoprotein (AFP) levels showed high AUCs (AUC of 0.922 and 0.863 in the training and validation cohorts, respectively) for the preoperative Ki-67 expression prediction. In yet another study using Gd-EOB-DTPA-enhanced MRI, Ye *et al*[47] showed that the nomogram combining the texture signature (using the segmentation of the whole lesion) and clinical factors demonstrated a high discrimination ability (C-index of 0.936) for predicting Ki-67 group (high *vs* low). Finally, Hu *et al*[48] explored the added value of viscoelasticity measured by magnetic resonance elastography to predict Ki-67 expression, showing that shear wave speed and phase angle significantly improved the performance of the radiomic model.

**CK19 expression:** CK19 expression is associated with aggressive tumor behavior, resistance to therapy, and poor outcomes including worse overall survival and recurrence[49]. To date, three studies have focused on developing radiomic models to predict CK19 expression[50-52], all using MRI. Wang *et al*[50] showed that their texture model independently predicted CK19-positive HCC cases and improved the diagnostic performance of AFP level ≥ 400 ng/mL and arterial rim enhancement. The two remaining studies developed a radiomics model based on Gd-EOB-DTPA-enhanced MRI, with external validation AUC varying from 0.78-0.79; of note, one of the studies was a multicenter study with over 250 patients [51,52].

**P53, PI3K, and other genetic expression:** P53 can be used as a tumor biomarker, since it plays an important role in the pathogenesis of HCC[53]. P53 mutation has also been suggested as a feasible target for antitumor therapy[54]. Wu *et al*[55] demonstrated a direct relationship between P53 mutations in patients with HCC and the gray-level co-occurrence matrix on CT. PI3K signaling is a key pathway regulating HCC aggressiveness and is associated with response to sorafenib. Liao *et al*[56] developed a CT-based radiomics model that yielded an AUC of 0.73 in the external validation set for prediction of PI3K status.

The phosphorylation status of β-arrestin1 is associated with sorafenib resistance[57-59]. Che *et al*[60] developed a model combining a CT-based radiomics score with clinico-radiological risk factors which yielded an AUC of 0.898 in predicting β-arrestin1 phosphorylation, and the predicted β-arrestin1 phosphorylation was in turn significantly associated with overall survival in both the training and validation cohorts ($P < 0.05$).

### *Prediction of recurrence, treatment response, and liver failure*

Tumor recurrence, liver failure and treatment response rates are major concerns during HCC treatment. Radiomics has emerged as a promising tool to predict recurrence and treatment response beyond the current predictive criteria[61,62]. Table 3 summarizes the studies to date that have evaluated the use of radiomic models to predict recurrence and treatment response. Most of these studies were single-center studies performed in China, with only a few studies incorporating external validation[63,64]. Segmentation strategies were predominantly manual strategies, including manual segmentation of the tumor region or area of interest, with only a few studies involving the segmentation of the peritumoral liver parenchyma[63,65-67]. Overall, the radiomic models yielded an AUC between 0.59 and 0.94 (see Table 3).

Of the studies evaluating the use of radiomics to predict recurrence, most involved the prediction of recurrence after surgical resection on CT or MRI, demonstrating a validation AUC between 0.59 and 0.84 (Table 3). Zhou *et al*[68] demonstrated that combining the radiomic signature with conventional preoperative variables significantly improved clinical model accuracy in early recurrence prediction (AUC of 0.84). Ji *et al*[64] developed and externally validated a radiomic model with better prognostic ability (C index ≥ 0.77, AUC of 0.78), lower prediction error (Brier score ≤ 0.14), and better clinical use compared with other staging systems and models. A few other studies evaluating the use of radiomics to predict recurrence involved the prediction of recurrence after liver transplant[69], transarterial chemoembolization (TACE)[67,70], and radiofrequency ablation (RFA)[71], demonstrating a validation AUC between 0.71 and 0.82.

Of the studies evaluating the use of radiomics to predict treatment response, a few involved the prediction of treatment response post-TACE[63,72,73]. In Canada, Ivanics *et al*[73] developed a CT-based radiomic model and achieved an AUC of 0.87 on the internal validation set. A large multi-center Chinese study by Chen *et al*[63] evaluating treatment response after TACE performed semi-automatic segmentation of the tumor and of the peritumoral region on contrast-enhanced CT in 585 patients, and the validation AUC was 0.90. One small study by Horvat *et al*[74] assessed treatment response after RFA using tumor 3D volumes of interest on MRI, yielding an AUC of 0.76 for the radiomics model, although the model lacked validation. Finally, two studies from China evaluated the use of radiomics to predict liver failure after surgical resection[75,76].

### *Prediction of survival*

Table 4 summarizes the studies to date that have evaluated the use of radiomics to predict survival in patients with HCC. Four studies evaluated the use of CT-based radiomics to predict survival after hepatic resection, demonstrating an AUC between 0.71 and 0.81, with two of the four studies performing internal validation[39,77-79]. A few other studies evaluated the use of radiomics to predict survival after TACE[80], TARE[81], and RFA[82], all without validation.

Of the studies that involved the prediction of survival after hepatic resection, Xu *et al*[39] had the largest sample size. In their study, a risk model integrating clinico-radiological factors and a high CT-based radiomic score was independently associated with long-term mortality and disease-specific recurrence. Kim *et al*[80] evaluated the use of CT-based radiomics in survival prediction in patients after TACE. They demonstrated a combined model integrating radiomic features and clinical data (HCC size, Child-Pugh score and AFP) outperformed the clinical sore model or the radiomic score model. Petukhova-Greenstein *et al*[82] found that a higher MRI-based radiomic signature based on nodular and

**Table 3 Summary of the studies that assessed radiomics to predict recurrence and treatment response in patient with hepatocellular cholangiocarcinoma who underwent surgery, liver transplantation or locoregional treatment**

| Ref. | Country | *n* | Imaging modality | Endpoint | Treatment type | Segmentation | ROI/VOI | No. of readers | Main results | Validation |
|---|---|---|---|---|---|---|---|---|---|---|
| Hui *et al* [100], 2018 | Singapore | 50 | MRI | Recurrence | Hepatic resection | Manual, intratumoral | ROI | 3 | AUC: 0.78-0.84 | None |
| Kim *et al* [65], 2019 | South Korea | Training: 128. Validation: 39 | MRI | Recurrence | Hepatic resection | Semiautomatic, intra- and peritumoral | VOI | 2 | C-index: 0.716 | Internal |
| Zhao *et al*[101], 2021 | China | Training: 78. Validation: 35 | MRI | Recurrence | Hepatic resection | Manual, intratumoral | VOI | 2 | AUC: 0.83 (training), 0.77 (validation) | Internal |
| Zhou *et al*[68], 2017 | China | 215 | CT | Recurrence | Hepatic resection | Manual, intratumoral | ROI | 2 | AUC: 0.84 (combined model) | None |
| Ji *et al* [64], 2020 | China | Internal: 177. External: 118 | CT | Recurrence | Hepatic resection | Manual, intratumoral | VOI | 1 | AUC: 0.77 (internal), 0.78 (external) | External |
| Guo *et al* [69], 2019 | China | Training: 93. Validation: 40 | CT | Recurrence | Liver transplant | Semiautomatic, intratumoral | ROI | 1 | AUC: 0.79 (training), 0.79 (validation) | Internal |
| Shan *et al*[66], 2019 | China | Training: 109. Validation: 47 | CT | Recurrence | Hepatic resection or ablation | Manual, intra- and peritumoral | ROI | 2 | AUC: 0.80 (training), 0.79 (validation) | Internal |
| Zheng *et al*[79], 2018 | China | Training: 212. Validation: 107 | CT | Recurrence and survival | Hepatic resection | Manual, intratumoral | ROI | 2 | AUC: 0.64 (training), 0.59 (validation) | Internal |
| Song *et al*[67], 2020 | China | Training: 110. Validation: 74 | MRI | Recurrence | TACE | Semiautomatic, intra- and peritumoral | VOI | 2 | C-index: 0.82 | Internal |
| Lv *et al* [71], 2021 | China | Training: 40. Validation: 18 | MRI | Recurrence | RFA | Semiautomatic, intratumoral | VOI | 2 | AUC: 0.94 (training), 0.82 (validation) | Internal |
| Sun *et al* [70], 2020 | China | Training: 67. Validation: 17 | MRI | Recurrence | TACE | Manual (intratumoral) | VOI | 2 | AUC: 0.71-0.79 | Internal |
| Cai *et al* [75], 2019 | China | Training: 80. Validation: 32 | CT | Liver failure | Hepatic resection | Semiautomatic, intratumoral | ROI | 2 | AUC: 0.82 (training), 0.76 (validation) | Internal |
| Zhu *et al* [76], 2020 | China | 101 | MRI | Liver failure | Hepatic resection | Manual, entire liver | ROI | 2 | AUC: 0.81-0.89 | None |
| Ivanics *et al*[73], 2021 | Canada | 88 | CT | Treatment response | TACE | Manual, intratumoral | VOI | 1 | AUC: 0.70-0.87 | None |
| Kong *et al*[72], 2021 | China | Training: 69. Validation: 30 | MRI | Treatment response | TACE | Manual, intratumoral | VOI | 2 | AUC: 0.81 (training), 0.87 (validation) | Internal |
| Chen *et al*[63], 2021 | China | Training: 355. Internal: 118. External: 122 | CT | Treatment response | TACE | Semiautomatic, intra- and peritumoral | ROI | 2 | AUC: 0.94 (internal), 0.90 (external) | Internal and external |
| Horvat *et al*[74], 2021 | Brazil | 34 | MRI | Treatment response | RFA | Manual, intratumoral | VOI | 1 | AUC: 0.76 | None |

AUC: Area under the curve; CT: Computed tomography; MRI: Magnetic resonance imaging; RFA: Radiofrequency ablation; ROI: Region of interest; TACE: Transarterial chemoembolization; VOI: Volume of interest.

perinodular radiomic features predicted poorer survival after RFA. A study evaluated the survival prediction after TARE, using 18-fuoro-deoxyglucose PET-based radiomics[81]. They observed that whole-liver radiomics textural features were an independent negative predictor of survival.

**Table 4 Summary of the studies that evaluated radiomics to predict survival in patients with hepatocellular cholangiocarcinoma**

| Ref. | Country | *n* | Imaging modality | Endpoint | Treatment type | Segmentation | ROI/VOI | No. of readers | Main results | Validation |
|---|---|---|---|---|---|---|---|---|---|---|
| Kiryu *et al* [77], 2017 | Japan | 122 | CT | Survival | Hepatic resection | Manual, intra- and peritumoral | ROI | 1 | OS and DFS were significantly different between 2 rad score groups | None |
| Xu *et al*[39], 2019 | China | Training: 350. Validation: 145 | CT | Survival | Hepatic resection | Semiautomatic, intratumoral | VOI | 3 | AUC: 0.91 (training), 0.81 (validation) | Internal |
| Akai *et al* [78], 2018 | Japan | 127 | CT | Survival | Hepatic resection | Manual, intrat-umoral | ROI | 1 | OS and DFS were significantly different between 2 rad score groups | None |
| Kim *et al* [80], 2018 | South Korea | 88 | CT | Survival | TACE | Manual, intrat-umoral | ROI | 1 | Combined clinical and radiomics score was a better predictor of survival | None |
| Blanc-Durand *et al* [81], 2018 | Switzerland | 47 | $^{18}$F-FDG PET-CT | Survival | TARE | Semiautomatic, whole liver | VOI | N/A | PFS-Rad Score and OS-Rad Score were independent negative predictors | None |
| Petukhova-Greenstein *et al*[82], 2022 | United States | 65 | MRI | Survival | RFA | Semiautomatic, intra- and peritumoral | VOI | 2 | OS was significantly different between 2 rad score groups | None |
| Zheng *et al* [79], 2018 | China | Training: 212. Validation: 107 | CT | Survival | Hepatic resection | Manual, intrat-umoral | ROI | 2 | AUC: 0.71 (training and validation) | Internal |

AUC: Area under the curve; CT: Computed tomography; DFS: Disease-fee survival; MRI: Magnetic resonance imaging; OS: Overall survival; PFS: Progression-free survival; RFA: Radiofrequency ablation; ROI: Region of interest; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; VOI: Volume of interest; PET: Positron emission tomography.

Furthermore, radiomic scoring system did not differ after stratification by tumor size and Barcelona Clinic Liver Cancer staging.

### *Other applications of radiomics in HCC*

Immunotherapy represents a paradigm shift in the management of patients with advanced HCC. Preoperatively assessing the immune status can assist the multidisciplinary team to identify which patients are suitable for immunotherapy, potentially improving treatment efficiency and overall survival rate. A few studies have evaluated the use of radiomics to predict programmed cell death ligand 1 (PD-L1) expression[83], CD8+ T cell infiltration[84], immunoscore[85,86], and anti-PD-1 treatment efficacy[87] in patients with HCC, with none of them performing external validation. Tian *et al*[83] were the first group to explore the efficacy of MRI-based radiomics to predict PD-L1 status. They proposed a model integrating radiomic and DL features for the quick and accurate assessment of PD-L1 expression levels in HCC patients before immune checkpoint inhibitor therapy which yielded an AUC of 0.897. Chen *et al*[85] demonstrated in 207 patients that radiomic features including those from the peritumoural region were associated with a validated "immunoscore". This score characterizes the tumor infiltrating lymphocyte population and theoretically reflects the immune phenotype of the tumor microenvironment.

## RADIOMICS REPRODUCIBILITY IN HCC

Reproducibility refers to variations of the same patient across different imaging scenarios (*e.g.*, scanner or imaging parameters), while repeatability refers to variations of the same patient using the same imaging protocol. Table 5 summarizes the 13 studies to date that have studied the reproducibility of radiomics in HCC patients. Most of these studies were conducted in China (8/13; 62%). Seven were performed using CT (54%), 5 using MRI (38%), and 1 using both CT scan and MRI (8%). Different software programs were used for segmentation and feature extraction. Most studies adopted manual segmentation (11/13; 85%), and most evaluated first- and second-order features, with a few including shape and higher-order features. In addition to intra and inter-reader reproducibility, some also assessed the repeatability of radiomic features obtained through two separate exams from the same scanner, different scanners from different vendors and centers, 3D *vs* 2D segmentation, different contrast imaging phases, injection rates and pixel resolutions on contrast-enhanced CT, and different *b*-values on diffusion-weighted imaging on MRI.

Of note, one study showed that intra-reader tumoral and peritumoral reproducibility were greatest in MRI[88]. Another study showed that for test-retest (same MRI system, 2 different MRI exams), the intraclass correlation coefficient varied from 0.53-0.99 and the inter-platform reproducibility (MRI systems from 2 different vendors) varied from 0.58-0.99[89]. Regarding different contrast phases, Ibrahim *et al*[90] showed that 25% of extracted features had a concordance correlation coefficient (CCC) > 0.9 across arterial and portal venous phases. Perrin *et al*[91] demonstrated that the number of reproducible features decreased with variations in contrast injection rate, pixel resolution, and scanner model.

## FUTURE DIRECTIONS OF RADIOMICS IN HCC

Despite the increasing and encouraging results in the literature concerning radiomics in patients with HCC, there are challenges and limitations to be overcome before its clinical implementation, particularly related to reproducibility and repeatability, lesion segmentation, model overfitting, multidisciplinary acceptance, and multi-modal data integration[23].

Patient selection, imaging data, segmentation strategy, image processing, feature selection, and computational processing are some factors that may affect the reproducibility and repeatability. Transparent patient accrual, data normalization, standard image manipulation, and feature extraction data are some strategies that may improve these challenges. Additionally, multi-center studies are recommended to increase reproducibility of the results.

Overfitting occurs when the model performs better in the training set with limited generalization of the results. The main factors contributing to overfitting are the number of included features being higher than the number of events and overoptimistic feature selection. Multiple strategies can be implemented to decrease overfitting, such as increasing the number of patients and events, using regularization methods, and including external validation cohorts. Multidisciplinary acceptance may improve with clear methods and a close relationship between radiologists, surgeons, oncologists, statistician, and data scientists to improve the interpretability of the results and to make way for clinical translation.

Multi-omics data integration is an additional step to improve the clinical acceptance of radiomics. Radiomics requires a multistep workflow process using different software and expertise; technological investments to create integrated and user-friendly tools are necessary to facilitate its widespread use in clinical practice. Finally, segmentation is a time-consuming process, susceptible to intra and inter-observer variability. Automatic and semi-automatic segmentations are required, particularly using DL strategies to facilitate this crucial step.

Additionally, some heterogeneity related to patients with HCC should be take into consideration. Since pathological confirmation is not always performed, the definition of clear and reproducible endpoints, like the LI-RADS criteria, are relevant strategies. Combined data integrating imaging and clinical variables are important to address the issue that patients with HCC are also dealing with systemic consequences related to cirrhosis.

## CONCLUSION

Radiomics is an evolving computer-assisted tool with the potential to improve the multidisciplinary management of patients with HCC and to provide personalized treatment optimizing the available resources. Multiple studies have evaluated the use of radiomics in HCC with promising applications, including the prediction of pre-surgical histology, genetic signature, recurrence, and treatment response, as well as survival rates. Although promising, several challenges need to be overcome before radiomics can achieve clinical translation, including workflow optimization, model validation in multi-center studies, and the development of integrated models to facilitate clinical use and acceptance.

**Table 5 Summary of the studies that assessed reproducibility of hepatocellular cholangiocarcinoma textural features**

| Ref. | Country | *n* | Imaging modality | Segmentation | Segmentation software | ROI/VOI | No. of readers | Intra-reader reproducibility | Inter-reader reproducibility | Other reproducibility |
|---|---|---|---|---|---|---|---|---|---|---|
| Duan *et al* [88], 2022 | China | 19 | CT, MRI | Manual, intra- and peritumoral | 3D-Slicer | ROI | 2 (1 radiologist and 1 radiation oncologist) | Features with ICC ≥ 0.75 in both tumoral and peritumoral tissue greatest in MR | Features with ICC ≥ 0.75 in both tumoral and peritumoral tissue greatest in MR | N/A |
| Zhang *et al* [102], 2022 | China | 90 (31 HCC) | MRI | Manual, intratumoral | ITK-SNAP | ROI and VOI | 2 radiologists | N/A | ICC > 0.8 used | N/A |
| Carbonell *et al*[89], 2022 | United States | 55 (16 HCC) | MRI | Manual, intratumoral and liver parenchyma | Olea sphere 3.0, Olea Medical | ROI for normal liver, VOI for HCC | 2 radiologists | N/A | CCC: 0.80-0.99 | For test-retest (same MRI system, 2 different MRI exams): ICC: 0.53-0.99; and in liver parenchyma: ICC: 0.53-0.73. For inter-platform reproducibility (MRI systems from 2 different vendors): CCC: 0.58-0.99 |
| Park *et al* [103], 2022 | South Korea | 249 | CT | Manual followed by automatic segmentation, intratumoral | MEDIP PRO | ROI and VOI | 1 radiologist | For VOI: Manual: ICC 0.594-0.998 for FO, 0.764-0.997 for shape, and 0.190-0.926 for SO; DL-AS: ICC > 0.75 for all. For ROI: Manual: 0.698-0.997 for FO, 0.556-0.997 for shape, and 0.341-0.935 for SO; DL-AS ICC > 0.75 for all | N/A | |
| Haniff *et al* [104], 2021 | Malaysia | 30 | MRI | Manual and semi-automatic, intratumoral | 3D-Slicer | VOI | Manual: 4 readers. Semi-automatic: 2 readers | N/A | Manual segmentation: ICC 0.897. Semi-automatic segmentation: ICC 0.952 | NA |
| Ibrahim *et al*[90], 2021 | Germany | 61 patients, 104 lesions | CT | Manual, intratumoral | MIM software | ROI | 1 nonradiologist revised by radiologist | N/A | N/A | Across different contrast imaging phases: 25% of extracted features had CCC > 0.9 across arterial and portal venous phases |
| Hu *et al* [105], 2021 | China | 30 | CT | Manual, intratumoral | MaZda software | ROI | 2 radiologists | ICC > 0.7 | ICC > 0.7 | N/A |
| Mao *et al* [32], 2020 | China | 30 | CT | Manual, intratumoral | ITK-SNAP | ROI | 2 radiologists | N/A | ICC ≥ 0.8 | N/A |
| Hu *et al* [106], 2020 | China | 50 | CT | Semi-automatic, peritumoral | Not mentioned | ROI | 2 radiologists | N/A | ICC > 0.6 | N/A |
| Qiu *et al* [107], 2019 | China | 26 | CT | Manual and semi-automatic, intratumoral | GrowCut and GraphCut | ROI | Manual: 5 radiation oncologists. Semi-automatic: 2 radiation oncologists | N/A | ICC ≥ 0.75 in 69% of features extracted from manual segmentation, 73% from GraphCut, and 79% from GrowCut | Across different centers: Poor reproducibility of CT-based peritumoral-radiomics model |
| Zhang *et al* [108], 2019 | China | 46 (34 HCC) | MRI | Manual, intratumoral | MIM software | VOI | 1 radiologist | N/A | N/A | Across different *b*-values: radiomic features extracted from *b* = 0, 20, 50, |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 100, 200 s/mm$^2$ and $b$ = 1000 s/mm$^2$ and nearby $b$-values DWIs showed a high reproducibility (ICC ≥ 0.8) |
| Feng *et al* [40], 2019 | China | 160 (110) | MRI | Manual, intra- and peritumoral | ITK-SNAP | VOI | 3 radiologists | 85% ICC ≥ 0.8 | 82% ICC ≥ 0.8 | N/A |
| Perrin *et al* [91], 2018 | United States | 38 (6 HCC) | CT | Semi-automatic, intratumoral and liver parenchyma | Scout Liver | VOI | 1 research fellow under supervision of radiologist | N/A | N/A | Across different contrast injection rates, pixel resolutions, and scanner models: Number of reproducible radiomic features (CCC > 0.9) decreased with variations in contrast injection rate, pixel resolution, and scanner model |

CT: Computed tomography; MRI: Magnetic resonance imaging; ROI: Region of interest; VOI: Volume of interest; TACE: Transarterial chemoembolization; ICC: Intraclass correlation coefficient; DWI: Diffusion-weighted imaging; CCC: Concordance correlation coefficient; HCC: Hepatocellular carcinoma; N/A: Not applicable; FO: First order; SO: Second order; DL-AS: Deep learning-based auto-segmentation.

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