New Advances in Radiomics of Liver Imaging

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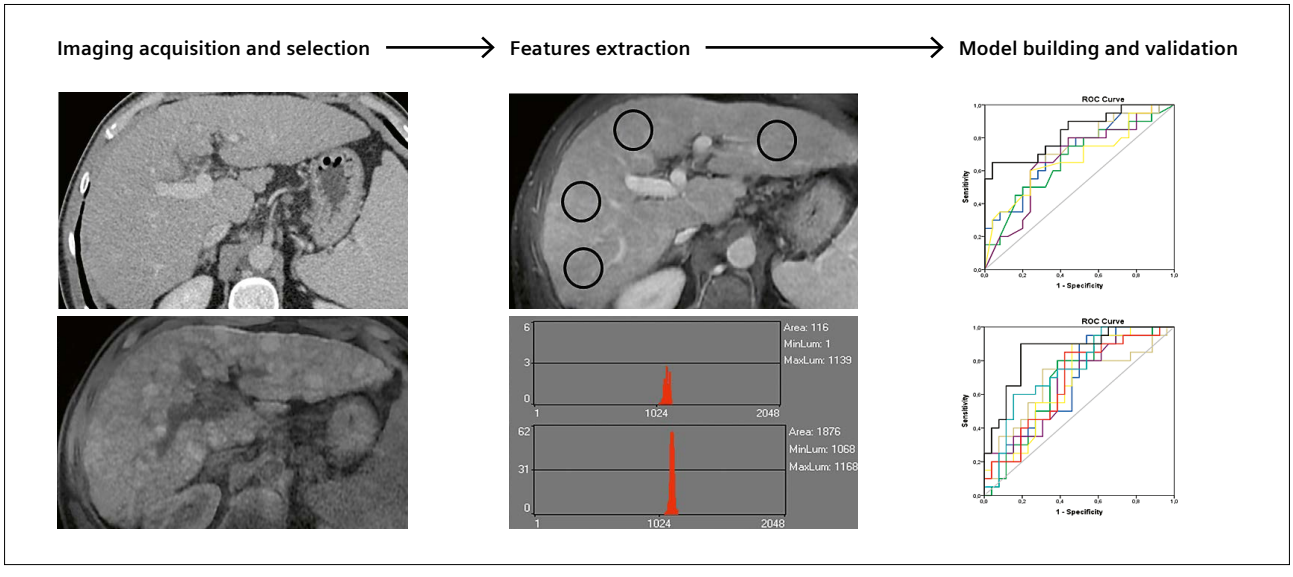
Introduction

Interpretation of liver imaging studies remains challenging in clinical practice due to the complex presentation of chronic liver disease and the presence of multiple focal liver lesions arising in normal and cirrhotic liver with overlap in imaging appearance. Radiomics is currently emerging as a new promising tool for quantitative analysis of liver imaging studies that could potentially increase diagnostic accuracy in the assessment of focal liver lesions, predict treatment response and prognosis after loco-regional or systemic therapies, and stratify the risk of advanced fibrosis and cirrhosis in patients with chronic liver disease [1].

Radiomics allows to extract a large amount of mathematical data through the analysis of the distribution and relationships of pixel densities/intensities within a defined region of interest, providing additional quantitative information from medical images that cannot be evaluated by human eyes [2]. These large amounts of quantitative data can be combined with patients' clinical characteristics, laboratory markers, histopathological parameters, or genetic data in order to provide predictive models that will help guide physicians to the most appropriate form of management [3]. Radiomics can be applied to any type of imaging study, including ultrasound, CT, MRI, and PET/CT, but most liver studies are currently based on CT or MRI examinations [4]. Although multiple experimental studies have shown promising results from radiomics, with excellent performance for diagnostic, prognostic, and predictive applications in liver imaging, there are several challenges for the adoption of radiomics in clinical practice. Differences in image acquisition, features extraction, and radiomics software pose challenges for the repeatability or application of radiomics models in large populations [3].

In this paper, we aim to discuss the basis of the radiomics workflow and review the new advances and current applications of radiomics in liver imaging, with an emphasis on the current knowledge about radiomics applications in the field of chronic liver disease and focal liver lesions.



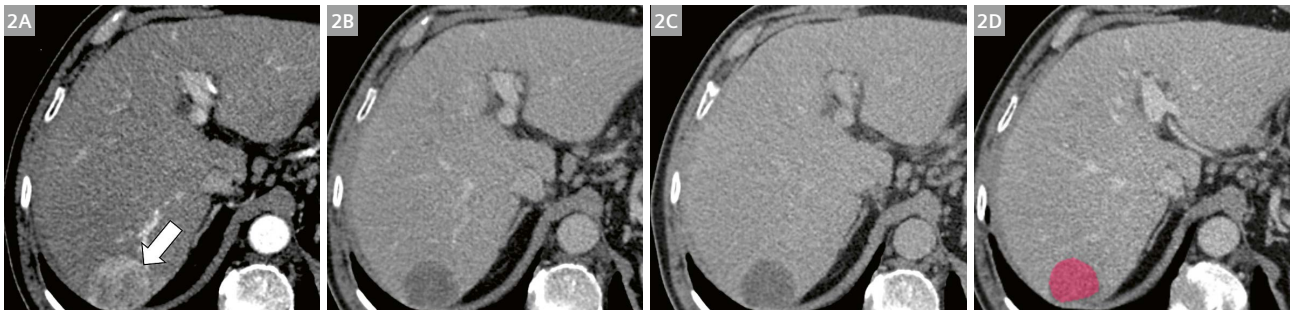
1 Schematic of radiomics workflow.

The radiomics workflow

Radiomics analysis is based on a multistep process that includes image acquisition, lesion segmentation, features extraction, features selection and reduction, predictive model building, final validation, and clinical interpretation of the results (Fig. 1) [4–7]. Acquisition of radiological imaging studies is one of the most important steps for radiomics, since scanning and technical parameters are known to influence the reproducibility of radiomics features. In particular, the reconstruction algorithm and slice thickness have an impact on the reproducibility of radiomics features on contrast-enhanced CT images [8–10]. Differences in acquisition protocols complicate the retrospective evaluation of CT or MRI studies acquired with different scanners [11]. It is also important to select the optimal phase/sequence for image analysis. Pre-contrast images are not affected by the contrast administration, but the segmentation may be not feasible if the lesion cannot be distinguished from the background hepatic parenchyma. However, pre-contrast images may provide more reliable assessment of the liver parenchyma in patients with chronic liver disease. Contrast-enhanced images may provide better lesion visualization, but the type, timing, and amount of contrast agent can be additional confounding factors, especially for images acquired in the arterial phase.

Segmentation can be performed manually by experienced radiologists using semi-automatic, or automatic software [11]. Manual segmentation is currently the gold standard in most radiomics studies, but it is often time consuming and is prone to intra- and inter-reader variability [4, 6, 12]. Semi-automatic or automatic software can provide more rapid and reproducible results, but they are prone to errors in cases of imaging artifacts, or unexpected liver anatomy or lesions. When analyzing focal liver lesions, the segmentation is usually performed by drawing an ROI within the tumor margins (Fig. 2). The ROI can be positioned on a single slice (2D ROI) on the largest tumor cross section, or it can include the whole lesion (3D ROI) [7]. When assessing diffuse liver disease, the segmentation can be performed using a single ROI with fixed diameters positioned on a specific hepatic segment (usually in the right lobe) in a single slice and not including large hepatic vessels or focal live lesions; using multiple ROIs with fixed diameters on different hepatic segments or different levels; or using ROIs that include the whole liver parenchyma or specific segments, usually at the level of the porta hepatis. Although 3D and whole-liver segmentations can capture more tissue heterogeneity, the clinical advantage remains debatable, since studies have demonstrated that single-slice analysis is often sufficient for the evaluation of chronic liver disease and focal lesions, and more practical for the radiological workflow.

Several in-house or commercially available radiomics research software programs allow users to extract a large number of radiomics features. Radiomics features are usually classified as first-, second-, or third-order features [4]. First-order features are obtained from the analysis of the gray-level histogram within a defined ROI, without considering spatial relationships between pixels. The most common histogram-based features include mean (average of the pixels within the ROI), standard deviation (dispersion from the mean), skewness (asymmetry of the histogram), kurtosis (peakedness/flatness of the histogram), and entropy (image irregularity or complexity) [5]. Second-order texture features consider the spatial relationship between pixels and most commonly include the gray-level co-occurrence matrix (GLCM), which quantifies the arrangements of pairs of pixels with the same values in a specific direction, and the gray-level run length matrix (GLRLM), which quantifies consecutive pixels with the same intensity in a specific direction. Third-order or higher order features evaluate spatial relationships between three or more pixels using statistical methods after applying filters or mathematical transforms. These features include fractal analysis, wavelet transforms, and Laplacian transforms of Gaussian-filtered images. Due to the large number of extracted parameters, a features reduction should be performed in order to exclude features that are not reproducible or redundant, and to avoid overfitting problems [8].



2 A 76-year-old man with hepatitis C-related cirrhosis and hepatocellular carcinoma: Contrast-enhanced CT imaging shows a 4 cm liver lesion with arterial phase hyperenhancement (**2A**, arrow), and washout in portal venous **(2B)** and delayed **(2C)** phases. Example of lesion segmentation was performed on portal venous phase **(2D)**.

Final radiomics models should be tailored to validate the accuracy of uncorrelated features according to the specific outcome. The choice of statistical methods depends on multiple factors, such as evaluation of primary outcome, number of features, and number of analyzed lesions. Validation in an independent or external patient cohort is necessary in order to test the real performance of radiomics [12].

Radiomics in chronic liver disease

Chronic liver disease covers a wide spectrum of liver pathologies, the incidence of which has been increasing in recent years. The most common etiologies of chronic liver disease include chronic viral hepatitis (primarily hepatitis B and C), alcoholic hepatitis, and nonalcoholic fatty liver disease (NAFLD). These may evolve into advanced fibrosis and cirrhosis, with possible complications such as portal hypertension, decompensated hepatic failure, and development of hepatocellular carcinoma. In particular, the presence of significant and advanced fibrosis has been reported as an independent predictor of mortality caused by chronic liver disease [13].

Although liver biopsy is considered the reference standard for the diagnosis and staging of fibrosis in patients with chronic liver disease, it has known complications such as pain, hemorrhage, and infections. It is also prone to sampling errors due to the heterogeneous distribution of fibrosis in the hepatic parenchyma, and to inter- and intra-reader variability. Several imaging-based noninvasive methods have been developed for assessing hepatic fibrosis in patients with chronic liver disease. They include shear wave elastography, MR elastography, diffusion-weighted imaging, and liver surface nodularity [14]. Recently, radiomics has been applied to liver imaging for the noninvasive assessment of hepatic fibrosis, with several studies reporting a fair-to-good diagnostic performance for the detection of advanced fibrosis or cirrhosis [15–23]. Most of these studies applied radiomics on CT or MR imaging, using pre-contrast or portal venous phase images. Overall, similar diagnostic performance was observed regardless of the etiology of the chronic liver disease. However, it should be noted that most current radiomics studies have evaluated patients with chronic viral hepatitis B or C. Nonalcoholic fatty liver disease, which is becoming the major cause of chronic liver disease and cirrhosis in Western countries, was investigated by only a minority of studies [15, 16, 18].

In the initial experience of Lubner et al. [18] quantitative texture analysis was performed on contrast-enhanced CT images from 289 patients with different etiologies of chronic liver disease, with a fair-to-good performance in discriminating between different stages of fibrosis. In a subsequent study, Lubner et al. [19] enrolled a cohort of 556 patients that included both healthy subjects and patients with hepatitis C and various degrees of hepatic fibrosis. Texture features were extracted by drawing an ROI that covered the entire liver. A good diagnostic performance was achieved for detecting significant and advanced fibrosis of models incorporating multiple features. A multiparametric approach that combines radiomics features and other CT-based methods for staging hepatic fibrosis has demonstrated excellent results in the stratification of fibrosis degree, improving the performance of individual parameters [21]. A recent study of MRI [15] investigated the performance of texture analysis in NAFLD patients, reporting a fair accuracy of entropy and standard deviation for the diagnosis of significant and advanced fibrosis, based on pre-contrast sequences.

Compared to other noninvasive imaging-based methods for assessment of hepatic fibrosis, the major advantage of radiomics and texture analysis is that they can also be applied retrospectively to extract additional data from images that have already been acquired, and can potentially be performed with any type of imaging study. However, a lack of standardization, variability in radiomics features and available software, and vulnerability to image acquisition parameters still pose significant challenges for applying radiomics in routine clinical practice. Further studies should focus on validation in multicenter cohorts, and on comparison with other non-invasive techniques for fibrosis evaluation.

Radiomics in focal liver lesions

Focal liver lesions include a wide spectrum of benign and malignant lesions that can occur in both normal liver and in cirrhosis. The differential diagnosis of focal liver lesions should consider the background liver parenchyma, presence of risk factors, clinical parameters, and imaging appearance on multiphasic contrast-enhanced studies. Although some lesions may demonstrate typical enhancement patterns on CT or MR images, the differential diagnosis in clinical practice remains challenging, and a histopathological confirmation is often required to reach the final diagnosis.

In patients without history of chronic liver disease or extrahepatic malignancies, focal liver lesions are most commonly benign, and the differential diagnosis includes hemangioma, focal nodular hyperplasia (FNH), and hepatocellular adenoma (HCA). Differentiating between FNH and HCA is challenging due to the overlap in the imaging appearance and the presence of multiple subtypes of HCA [24]. While FNHs are indolent lesions, HCAs carry a risk of complications such as hemorrhage and malignant transformation. Lesion biopsy is therefore often required to reach the definitive diagnosis [24]. Recent studies have demonstrated that the application of radiomics could help

increase the diagnostic performance for the differential diagnosis between FNH and HCA, with significant improvements compared to conventional qualitative evaluations [25, 26]. In particular, a retrospective study [26] reported that texture-based parameters obtained from gadoxetate disodium-enhanced MRI on T2-weighted and hepatobiliary phase imaging can distinguish FNH from HCA in up to 96% of cases.

In patients with underlying cirrhosis or chronic liver disease, hepatocellular carcinoma (HCC) represents the most common primary malignancy, accounting for up to 90% of all liver cancers [27, 28]. Several studies have adopted a radiomics approach to quantify lesion heterogeneity in HCC. In particular, recent studies have explored the potential of radiomics for preoperative assessments of HCC with prediction of recurrence-free survival and overall survival after curative resection, recurrence following liver transplantation, correlation with histopathological markers of HCC aggressiveness (i.e., microvascular invasion), and evaluation of treatment response in patients undergoing locoregional therapies or systemic therapies in cases with advanced tumors [29–40]. Anh et al. [31] found that imaging findings and texture-based features on preoperative gadoxetate disodium-enhanced MRI were helpful for predicting early recurrence after curative resections in patients with single HCC. Feng et al. [35] developed a preoperative radiomics model for prediction of microvascular invasion based on gadoxetate disodium-enhanced MRI. Park et al. [38] investigated the role of CT-based texture analysis in the prediction of therapeutic response in HCC after transcatheter arterial chemoembolization.

Conclusions

Radiomics is emerging as a promising tool with large potential for the assessment of chronic liver disease and focal liver lesions, providing excellent diagnostic performance for multiple applications in research studies. Future implementation of radiomics models should focus on addressing current limitations that pose challenges for its application in everyday clinical practice.

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