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Review

Radiomics/Radiogenomics in hepatocellular carcinoma: Applications and challenges in interventional management

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ABSTRACT

Hepatocellular carcinoma is one of the leading causes of cancer-related death worldwide. Recently, radiomics and radiogenomics have been introduced as novel dimensions in oncology research. In the current review, we summarize the clinical applications of radiomics and radiogenomics in hepatocellular carcinoma.

1. Introduction

Globally, hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death [1]. China accounts for more than half of all new HCC cases and fatalities worldwide [2]. Surgical and local ablative therapies are considered as radical HCC treatments [3]. However, the postoperative 5-year recurrence rate of hepatitis B virus-related HCC remains as high as 78.7% [4]. HCC is heterogeneous cancer and is difficult to treat. The heterogeneity is mainly caused by the accumulation of genetic changes resulting from aberrant cell proliferation [5]. Therefore, the genomic landscape, such as the PI3K/Akt/mTOR pathway, is linked to chemotherapy [6]. However, this information was acquired through postoperative pathology, which is lagging information. Moreover, preoperative needle biopsy using a single sample cannot provide comprehensive information about malignancy [7]. Therefore, it is essential to identify non-invasive methods to characterize genomic alterations in patients with HCC.

Medical imaging has traditionally been fundamental for diagnosis, staging, clinical decision, and survival monitoring. The imaging finding has been supplemented by quantitative aspects, leading to the development of image biomarker assessment, called radiomics [8]. Radiogenomics is a combination of the above modalities with underlying molecular features at the genomic, transcriptomic, and proteomic levels. This new technology has the potential to identify the biological basis of phenotype imaging [9].

The current review summarizes the clinical applications of radiomics and radiogenomics in HCC. Additionally, the challenges associated with radiomics and radiogenomics in terms of their limited application in the clinic will be focused on, thereby highlighting the role that may influence patient management in interventional treatment (Fig. 1).

2. Evaluation of pathological data

2.1. Evaluation of MVI status

Interventional radiologists face many limitations in the management of patients with HCC; characterizing the status of microvascular invasion (MVI) and genomic alterations is regarded as the first priority.

MVI is an independent factor associated with postoperative recurrence aggressiveness and early recurrence of HCC, defined as the invasion of tumor cells into the vascular endothelial cell space, such as microvessels of the portal vein, hepatic artery, and lymphatic vessels [10]. A recent study showed that recurrent intermediate-stage cases with MVI have more possibility getting survival benefits than patients with negative MVI by applying the combined treatment therapy (sorafenib plus transarterial chemoembolization, TACE) [11]. However, the MVI status mainly detected through immunohistochemical and pathological analyses of postoperative tissue specimens [12]. The inability to identify MVI preoperatively leads to incomplete surgical resection and increases the risk of postoperative recurrence. The effectiveness of treatment was limited. And furthermore the long-term survival time of HCC may be affected. Thus, radiomics may be a supplementary and quantitative tool for precise diagnosis of MVI. Many researchers found that the parameters of radiomics were linked with the MVI status.

Recently, a meta-analysis study involving 22 studies with 4129 patients indicated that radiomics is a non-invasive tool with a good

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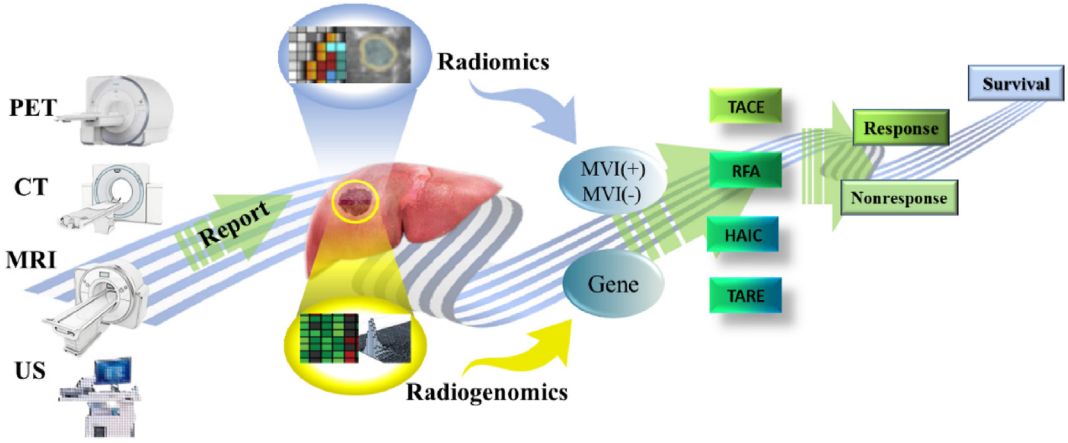

Fig. 1. The current study route of radiomics and radiogenomics.

diagnostic performance for MVI status, with a sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) of 0.84, 0.83, and 0.90, respectively [13]. Nevertheless, small sample size (15/23), univariable selection (11/23), lack of calibration evaluation (12/23), and lack of internal validation cohorts (3/23) were the leakages. Interestingly, no significant difference was found between radiomics models from computed tomography (CT) and magnetic resonance imaging (MRI) ($p = 0.469$). Furthermore, the CT and MRI radiomics models were higher than ultrasound radiomics models ($p < 0.05$) [13].

Majority of investigations paid attention to the inter-tumor radiomics rather than the peritumoral region. The peritumor area contains additional data outside the oncology, but MVI may still occur in the hepatic. The region of interest extracted from peritumor site seldom has been studied. Gao et al. investigated the multi-sequence MRI (T2WI, pre-contrast T1WI, artery phase, portal venous phase, delay phase) across various regions (whole, periphery, whole + periphery, and interface). Those different models were established with four algorithms. The multivariable logistic regression was used to select significant factors from clinical and radiomics parameters. They found a fusion model, T2WI-artery radiomics signature with non-smooth tumor margin was a potential biomarker for the preoperative prediction of MVI [14].

2.2. Correlation between Radiomics/Radiogenomics and HCC gene landscape

In addition to MVI status, the HCC gene landscape represents a clinically significant problem while making pharmacological choices. For example, multitargeted tyrosine kinase inhibitors that target the PI3K/Akt/mTOR pathway are now accessible as first-line medicines and direct sorafenib treatment [15]. Genetic testing is expensive, invasive, and time-consuming, making it unavailable for all patients. Radiogenomics, a fusion of radiomics and genomic tumor data, may play a vital role in providing accurate imaging surrogates [9].

In 2007, Segal et al. first discovered that the HCC gene distribution into modules defined by imaging traits was not random but highly enriched for specific and diverse biological functions and processes [16]. Comparing gene membership in modules versus published Gene Ontology annotations revealed significant overlaps, allowing many fundamental physiologic properties of tumors to be gleaned from CT images. The results demonstrated that 28 features on CT images could accurately predict 78% of the gene expression profiles. Hectors et al. [17] suggested that the expression levels of early HCC markers, such as *BIRC5*, *HSP70*, *LYVE*, and *EZH2*, angiogenesis marker *VEGFA*, and immune checkpoint CD274 significantly correlated with both central tendency and heterogeneity parameters. Thus, they used quantitative MRI to quantify intratumor heterogeneity in HCC lesions and connect MRI parameters with gene expression analysis [17]. Hoshida et al. [18] revealed that radiomic features (10 Haralick texture features and one other quantitative feature) were correlated with the expression levels of 14 genes ($r = -0.61$–0.56, $p < 0.043$). A radiogenomics feature derived from pretreatment Fluorodeoxyglucose-positron emission tomography (FDG-PET) was linked with mTOR pathway genes [19].

2.3. Radiomics/Radiogenomics in clinical decision-making treatment options

Patients with HCC often present with liver dysfunction. Factors affecting mortality rates in patients with HCC include tumor burden and organ failure, such as liver function deterioration [20]. Therefore, toleration should be considered during liver cancer treatment. Hepatectomy is the first choice for the treatment of patients with liver cancer [21]. TACE is minimally invasive; however, residual tumor cells may be present even after treatment. Because of technological development, the scope of application of hepatectomy and TACE continues to expand and overlap [22,23]. Therefore, the optimal treatment should be selected according to the patient's status.

Hepatectomy and liver transplantation are limited in their applicability because of factors such as liver malfunction, illness, or insufficient liver source [24]. Presently, local surgical procedures, such as radiofrequency ablation, microwave ablation, and cryoablation, have widely entered clinical practice [25]. However, they have their limitations regarding clinical applicability when it comes to treatment modality selection, such as physician subjectivity in treatment selection and inadequate treatment validation.

Hence, a new technique to non-invasively and objectively select hepatectomy or local HCC treatment for patients is required to assist in the development of tailored and personalized treatment plans [26]. To address this issue, Fu et al. [27] constructed a model for adjuvant hepatectomy and TACE treatment selection using preoperative CT image data from 520 patients with HCC in five hospitals. The traditional imaging features included tumor location, absence or presence of fusion lesions, shape, tumor capsule, and enhancement type. Patients were weighed to control the difference in baseline data, and the Cox regression model was constructed with progression-free survival (PFS) as the endpoint [27]. The results revealed that the prediction model had good identification and correction ability: the AUC of 3-year PFS in the training set and the test set were 0.80 and 0.75, respectively [27]. They finally constructed a nomogram for the corresponding treatment (hepatectomy or TACE) to be selected according to different scores. Patients were classified according to the score threshold (threshold = −5.00), and when the score was ≤−5.00, hepatectomy showed a longer PFS than TACE (hazard ratio [HR]: 0.52; 95% confidence interval [CI]: 0.29–0.93; $p = 0.026$); therefore, hepatectomy was a better treatment option. No

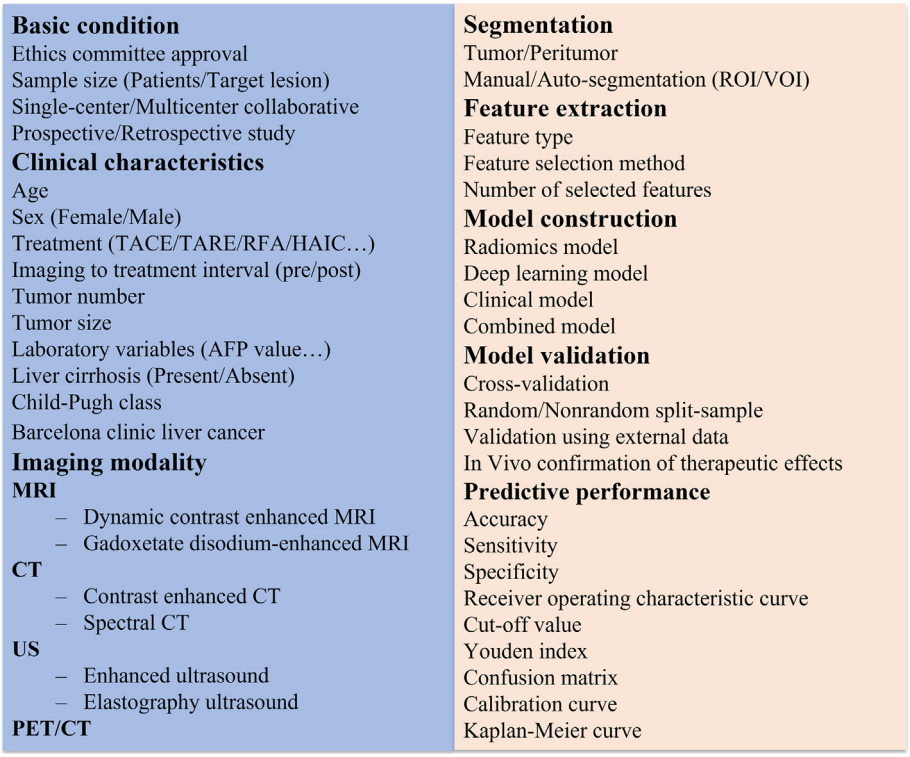

Fig. 2. Commonly used parameters in paper.

statistical difference was found in the PFS for hepatectomy and TACE with a score of >−5.00 (HR: 1.14; 95% CI: 0.69–1.85; $p = 0.614$), but TACE was less invasive [27]. Therefore, it was a better treatment option. Although the curative effect has been confirmed, the use of combination therapy of TACE is controversial [28]. There is uncertainty in the appropriate application and modality of therapy in current clinical practice guidelines. As a result, Allen Mo et al. investigated a retrospective observational study [29]. The patients were diagnosed with stage I-III HCC for decade, treated with TACE, followed by adjuvant radiofrequency ablation (RFA), Stereotactic body radiation therapy (SBRT), or no additional liver-directed modality. The results showed that the machine learning model was able to provide treatment recommendations for HCC who had undergone prior TACE. Additional treatment in line with model recommendations was associated with significant improvement in PFS, suggesting a potential benefit for machine learning-guided medical decision-making. It is the tip of the iceberg. Further prospective studies, such as immune checkpoint inhibitors with TACE, need to investigate more combination therapy.

2.4. Prediction of response

The initial treatment response of TACE and RFA is a predictor of PFS and overall survival [30]. Several investigations [31–35] have performed non-contrast CT, contrast CT, and multi-parameter MRI to construct exact models for predicting the early response to TACE and RFA.

Guo et al. [31] investigated the short-term response for TACE treatment in patients with HCC based on non-contrast CT radiomics and clinical features. They extracted 30 CT radiomic features. The AUCs of the model for TACE response were 0.840 and 0.815 in the training and validation groups. Like this approach, Kim et al. [32] investigated radiomic features on pretreatment CT in patients with HCC undergoing TACE and concluded that treatment outcomes were associated with entropy, skewness, and kurtosis [32]. These features might reflect high tumor heterogeneity and most importantly the presence of intratumoral angiogenesis. Liu et al. [33] reported that the model that combined MRI radiomics with clinical factors displayed better performance with an AUC of 0.813 in the training group and 0.781 in the validation group for predicting the response.

Another key point is the possibility of predicting the response from RFA with pretreatment MRI. Both Alexandra and Nataly et al. [34,35] revealed that radiomic analysis of pretreatment MRI could predict the complete RFA response. However, the relatively small sample size limited the broad clinical translation.

2.5. Application in survival prediction

Following TACE and RFA treatment, predicting the recurrence rate and recurrence-free survival of patients is clinically important to establish follow-up strategies, such as shortened follow-up intervals and prompt medication adjustments [24].

Yuan et al. [36] included 184 patients with HCC to develop the radiomics nomogram that could predict early recurrence after curative ablation. They extracted the radiomic features from the three-phase enhanced CT images. Among all radiomic models, the portal venous phase radiomic model performed best in the validation set, with a C-index of 0.74 (95% CI: 0.63–0.84). The optimal predictive performance was obtained by com bining portal venous phase radiomics with clinicopathological factors. Additionally, the validation set C-index was 0.76 (95% CI: 0.65–0.86), which was significantly improved compared with the clinical model using clinical variables alone (C-index = 0.56; 95% CI: 0.47–0.64). Additionally, Song et al. [37] presented similar results with MRI that the combined model exhibited better performance than the clinical-radiological model alone.

Alexandra et al. assess the Liver Imaging Reporting and Data System and radiomic features in pretreatment MRI for predicting PFS in patients with nodular HCC treated with RFA [38]. There were 65 patients with 85 tumors in this retrospective study. The authors point out that imaging features such as multifocality, continuity of an enhancing capsule appearance, and a higher radiomic signature based on nodular and perinodular radiomic features in HCC were predictors for poorer PFS within the first 2 years. The studies have shown that pretreatment radiomic data of patients with HCC could be used to predict survival and provide help for personalized patient treatments. However, they did not perform an additional assessment of the nearest ablation zone which is

regarded as a known predictor of recurrence.

2.6. Challenges and future perspectives

Radiomics and radiogenomics are rapidly gaining attention in the interventional field. However, these are associated with significant challenges and are now limited to interventional management in the scientific literature. Most research were retrospective and includes a small sample [30–35]; therefore, more prospective and multicenter studies are required to obtain more data in the future. Furthermore, the standardization of parameters extraction remains inadequate (Fig. 2). Moreover, radiomic characteristics include a wide array of parameters. Each study leads to a different model; therefore, it is currently not a clear modeling method to determine such biological aspects. Deep learning and multi-omics are emerging tool in the radiomics and radiogenomics area. Especially, for multi-omics, there is the urged need for multidisciplinary coordination with the oncologists, radiologists, geneticists, statisticians, data analysts, and medical engineers [39].

3. Conclusion

Radiomics and radiogenomics support the decision-making process for HCC intervention; this could be used as a basis to guide personalized care. The aim of this research is to integrate radiomics and radiogenomics with clinical practice; however, this will be a long process.

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Author contributions

Ying-hua Zou, Li Song, Xiao-qiang Tong, Jian Wang, Min Yang contributed to the conception of the study; Shou-jin Cao helped perform the analysis with constructive discussions; and Jia Fu performed data analyses and wrote the manuscript.

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Declaration of competing interest

No conflict of interest

Data available statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

Ethics approval were waived for this study because no patients' data were reported.

Informed consent

Formal patient consent is not required for this study.

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