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Prognostication of Hepatocellular Carcinoma Using Artificial Intelligence

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Hepatocellular carcinoma (HCC) is a biologically heterogeneous tumor characterized by varying degrees of aggressiveness. The current treatment strategy for HCC is predominantly determined by the overall tumor burden, and does not address the diverse prognoses of patients with HCC owing to its heterogeneity. Therefore, the prognostication of HCC using imaging data is crucial for optimizing patient management. Although some radiologic features have been demonstrated to be indicative of the biologic behavior of HCC, traditional radiologic methods for HCC prognostication are based on visually-assessed prognostic findings, and are limited by subjectivity and inter-observer variability. Consequently, artificial intelligence has emerged as a promising method for image-based prognostication of HCC. Unlike traditional radiologic image analysis, artificial intelligence based on radiomics or deep learning utilizes numerous image-derived quantitative features, potentially offering an objective, detailed, and comprehensive analysis of the tumor phenotypes. Artificial intelligence, particularly radiomics has displayed potential in a variety of applications, including the prediction of microvascular invasion, recurrence risk after locoregional treatment, and response to systemic therapy. This review highlights the potential value of artificial intelligence in the prognostication of HCC as well as its limitations and future prospects.

Keywords: Radiomics; Deep learning; Artificial intelligence; Machine learning; Hepatocellular carcinoma; Hepatoma; Liver; Cancer; Malignancy; Neoplasm

Image-Based HCC Prognostication: Traditional Approaches

The current treatment strategy for hepatocellular carcinoma (HCC) is primarily based on the overall tumor burden and liver function [1]. However, HCC is a biologically heterogeneous tumor with varying degrees of aggressiveness and risk of recurrence/metastasis. Consequently, patients with HCC with the same stage, even those with early or very early-stage HCC, can experience diverse prognoses. Several histopathologic, molecular, and genetic features of HCC have been identified as prognostic markers. These include microvascular invasion (MVI), stemness features (i.e., cytokeratin 19 positivity), vessels encapsulating tumor clusters, and scirrhous and macro-trabecular massive subtypes [2,3]. Furthermore, gene expression profiling has revealed two distinct HCC subclasses: the proliferative class, characterized by chromosomal instability, aggressive histologic phenotype, and poor prognosis; and the non-proliferative class, with chromosomal stability and favorable prognosis [4]. However, these molecular and histologic prognostic markers are only accessible when tumor tissue is obtained via biopsy or surgery. Given the current strategy of non-invasive, image-based diagnosis of HCC, these histopathologic prognostic markers are not available in many patients with HCC, which underscores the clinical significance of image-based prognostication in the management of HCC. Furthermore, owing to the increased understanding of biologic heterogeneity of HCC and availability of new therapeutic options, prognostic imaging is being increasingly recognized as a clinically relevant approach for implementing personalized medicine.

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Increasing evidence suggests that the radiologic characteristics of HCC reflect its histologic and molecular features, and thus the biological behavior of the tumor. For example, radiologic features, such as non-smooth tumor margin, arterial phase peritumoral enhancement, and hepatobiliary phase peritumoral hypointensity, are suggestive of the presence of MVI [5]. Rim arterial phase hyperenhancement is also associated with aggressive histopathologic features of HCC, including stemness features, scirrhous and macro-trabecular-massive subtypes, and proliferative class [6,7]. Accordingly, HCC classified as LR-M according to the Liver Imaging Reporting and Data System (LI-RADS) is associated with a worse prognosis compared to that classified as LR-4 or LR-5 [8].

However, the interpretation of radiologic prognostic findings can be subjective, leading to inter-reader variability [9]. Most radiologic prognostic findings rely on a binary decision regarding whether the findings are present or absent. Therefore, determining the presence of a prognostic finding can be challenging, particularly in cases with intermediate findings. Additionally, integrating multiple prognostic findings can be complex, particularly for conflicting findings. In light of these challenges and the unmet needs in traditional radiologic approaches, artificial intelligence (AI), particularly radiomics, has emerged as a promising alternative to image-based prognostication of HCC (Fig. 1). In this review, we have used the term 'AI' in its broadest original sense, not limiting its definition to deep learning alone.

Potential of AI

Unlike classic radiologic analysis, which relies on qualitative visual image interpretation, AI-based image analysis involves extraction of high-dimensional features from images and mining these features to make diagnostic, classification, or prognostic decisions. Radiomics and deep learning, the main AI-based approaches for radiologic image interpretation, comprise different technical processes [10,11]. Radiomic analysis involves a series of procedures, including image preprocessing, tumor segmentation, extraction and selection of radiomics features, and construction of a prediction model using the selected features. The radiomics features encompass multiple

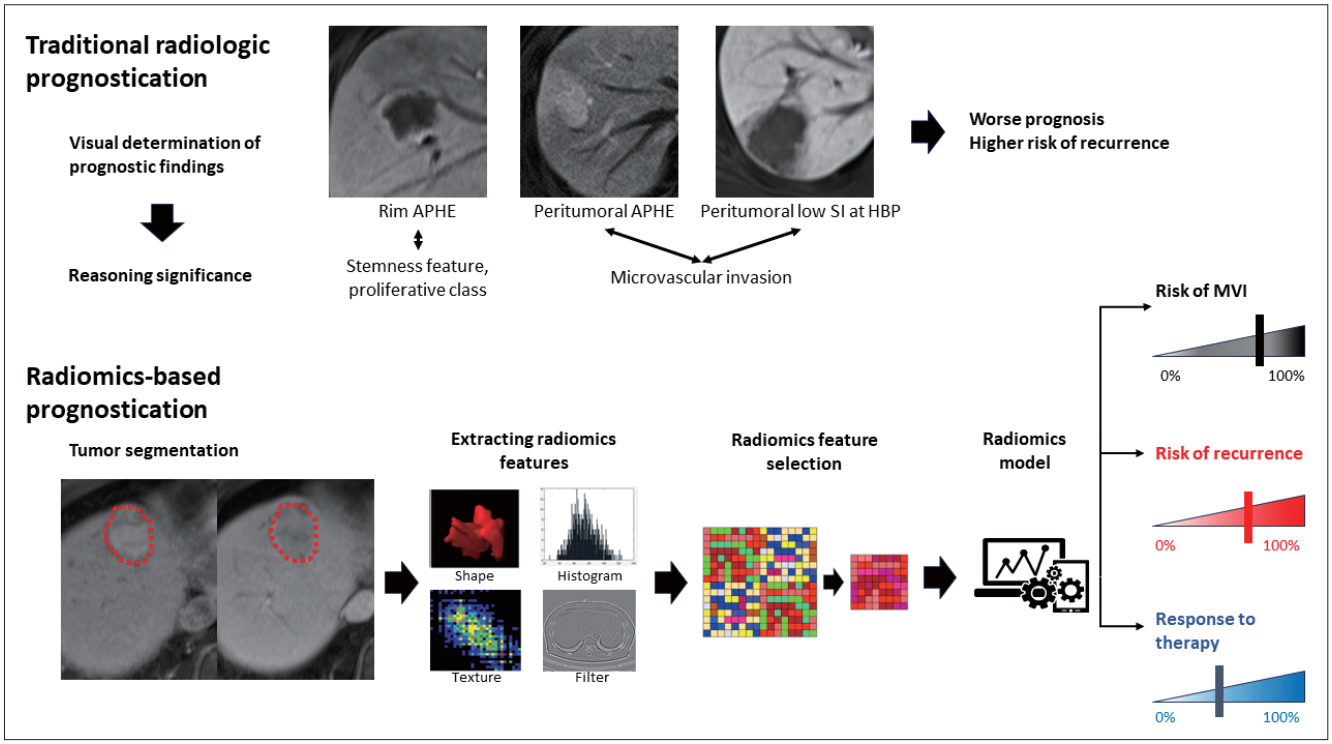

Fig. 1. Comparative schematic descriptions of traditional radiologic versus radiomic approaches in the prognostication of hepatocellular carcinoma. The traditional radiologic method relies on the visual identification of prognostic imaging findings and interpretation of their clinical significance. In contrast, the radiomics approach entails tumor segmentation in images, followed by the extraction of numerous quantitative features, selection of relevant features, and development of a radiomics model for the specific prognostic task. APHE = arterial phase hyperenhancement, SI = signal intensity, HBP = hepatobiliary phase, MVI = microvascular invasion

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categories, including shape, histogram, texture, and higher-order features which refer to texture features extracted after applying image filters. Radiomic analysis is based on classic machine learning, wherein a human expert predefines the key factors in the entire process. In contrast, deep learning algorithms are based on representation learning, in which no predefined feature engineering is implemented and instead, the algorithm learns the best way to solve the problem on its own by using training datasets. Regarding the assessment of HCC, radiomics and deep learning have the potential to offer an objective and comprehensive analysis of tumor phenotypes, which could overcome the limitations of conventional image analysis methods. However, AI comes with its own limitations, which will be discussed later in this review.

AI for HCC Prognostication

Most AI applications for HCC prognostication are based on the radiomics approach. Multiple studies have demonstrated the feasibility and potential of radiomics in the prognostication of HCC, of which the key studies are summarized in Table 1 [12-24]. Several studies have also explored the feasibility of deep learning in the prognostication of HCC (Table 2) [25-30]. Notably, some researchers have combined deep learning and radiomic approaches, known as deep learning radiomics. In this approach, a convolutional neural network is used to extract deep learning radiomic features, and subsequent feature selection and modeling are conducted using the typical radiomic approach.

Prediction of HCC Recurrence Following Ablation, Resection, and Transplantation

Radiomics has been utilized to predict the recurrence risk of HCC following potentially curative treatments, such as radiofrequency ablation therapy [24,25], resection [16,17,25,31,32], and liver transplantation [15]. Most of these studies focused on patients with early or very early-stage HCC. Ji et al. [16] developed preoperative and postoperative nomograms incorporating CT-based radiomic models to predict recurrence after surgical resection of HCC. They demonstrated that the integration of radiomic signatures improved nomogram performance, resulting in high predictive performances of preoperative and postoperative nomograms with C-indices of 0.78 and 0.82, respectively. Liu et al. [25] developed deep learning algorithms based on contrast-enhanced ultrasound (US), and then created two different nomograms by incorporating these algorithms and clinical variables to predict recurrence following either radiofrequency ablation or surgical resection in patients with a single HCC lesion measuring 3 cm or smaller. Both nomograms were found to have good prediction performance with C-indices of 0.73 and 0.74 in the internal validation cohort. These nomograms may be valuable for selecting the appropriate treatment for patients with HCC who are eligible for both radiofrequency ablation and surgical resection, provided that the nomograms are further validated to confirm their generalizability.

Prediction of Therapeutic Response in Intermediate to Advanced HCC

Several studies have previously explored the potential value of radiomics in predicting the response to palliative treatments such as trans-arterial chemoembolization [18,33], immune checkpoint inhibitors (ICIs) [13,19,34], and multi-kinase targeted therapy [12] in patients with intermediate to advanced stage HCC. It was demonstrated that radiomics enables the identification of HCCs with high immune cell infiltration [35] and those expressing the programmed cell death-ligand 1 or 2 [19,34], which may correlate with the response to ICI therapy. However, no study has investigated whether radiomic models can predict the response to ICI treatment, indicating a need for further research in this area. A recent study by Bo et al. [12] explored the feasibility of a radiomic model in predicting the response to lenvatinib monotherapy in patients with unresectable HCC. In this study, unsupervised clustering analysis revealed the presence of two distinct subtypes of HCC based on radiomic features, which demonstrated markedly different response rates to lenvatinib monotherapy [12]. This finding suggests that tumor phenotype assessment based on radiomics may play a crucial role in personalizing treatment strategies for HCC, although further research is required to validate these findings. Zhang et al. [28] developed a deep learning radiomics model for predicting survival of patients with HCC after trans-arterial chemoembolization plus sorafenib treatment using contrast-enhanced CT images. Notably, in this study, a convolutional neural network was used to extract the deep learning radiomic features, and subsequent modeling was performed using penalized regression. The final nomogram integrating the deep learning radiomic signature and clinical data demonstrated good discrimination performance with a C-index of 0.739.

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Table 1. Representative studies on radiomics for prognostication of hepatocellular carcinoma

Reference	Task and imaging	Patient number	Study setting and validation method*	Main findings†
Xu et al., 2019 [22]	MVI, CT	Training: 350 Test: 145	Single center, internal validation	Performance of clinicoradiologic radiomics nomogram: AUC of 0.889, sensitivity of 0.89, and specificity of 0.79
Xia et al., 2023 [21]	MVI, CT	Training: 334 Test: 142 (internal) and 121 (external)	Multicenter, internal, and external validation	Performance of clinicoradiologic radiomics model: AUC of 0.86 (internal) and 0.84 (external)
Kim et al., 2019 [17]	Recurrence after resection, MRI	Training: 128 Test: 39	Single center, internal validation	Performance of clinicopathologic radiomics model: AUCs of 0.72
Ji et al., 2020 [16]	Recurrence after resection, CT	Training: 177 Test: 118	Multicenter, external validation	Model performance: C-indices of 0.78 for the preoperative radiomics-clinical model and 0.82 for the postoperative radiomics-clinical-pathologic model
Guo et al., 2019 [15]	Recurrence after LT, CT	Training: 93 Test: 40	Single center, internal validation	Performance of clinical and radiomics model: C-index of 0.785
Yuan et al., 2019 [24]	Recurrence after RFA, CT	Training: 129 Test: 55	Single center, internal validation	Performance of clinical and radiomics model: C-index of 0.755
Peng et al., 2022 [18]	TACE response, CT	Training: 141 Test: 121 and 51	Multicenter, external validation	Performance of radiomics model: AUC of 0.9 and 0.91
Chen et al., 2019 [13]	Immune score, MRI	Training: 150 Test: 57	Single center, internal validation	Performance of radiomics clinical model: AUC of 0.934
Tao et al., 2023 [19]	PD-L2 expression, MRI	Training and test: 108	Single center, internal validation	Performance of radiomics model: AUC, 0.87
Bo et al., 2023 [12]	Lenvatinib response, CT	Training: 74 Test: 35	Multicenter, external validation	Two subgroups identified by clustering analysis showed different response rates and survival
Wang et al., 2020 [20]	CK-19 status, CT	Training: 159 Test: 68	Single center, internal validation	Performance of clinicoradiologic radiomics model: AUC of 0.85
Yu et al., 2022 [23]	VECT status, MRI	Training: 128 Test: 54	Single center, internal validation	Performance of radiomics model: AUC of 0.92 Predicted VECT was associated with early recurrence
Feng et al., 2023 [14]	MTM subtype, CT	Training: 169 Test: 88 (internal) and 108 (external)	Multicenter, external validation	Performance of radiomics model: AUC of 0.80 (internal test) and 0.74 (external test)

*Validation methods were classified as internal (i.e., cross-validation, bootstrapping, split-sample, and temporal validation) or external (geographic validation), †Model performance reported was test performance.
MVI = microvascular invasion, AUC = area under the curve, LT = liver transplantation, C-index = concordance index, RFA = radiofrequency ablation, TACE = trans-arterial chemoembolization, PD-L2 = programmed cell death ligand 2, CK = cytokeratin, VECT = vessels encapsulating tumor cluster, MTM = macro-trabecular massive

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Table 2. Representative studies on deep learning or deep learning radiomics for prognostication of hepatocellular carcinoma

Reference	Task and imaging	Patient number	Study setting and validation method*	Main findings†
Zhang et al., 2022 [30]	MVI, CEUS	Training: 301 Validation: 102 Test: 33	Single center, internal validation	Deep learning algorithm based on manually segmented CEUS video and clinical variables Performance: AUC of 0.865, sensitivity of 83.3%, and specificity of 81.0%
Zhang et al., 2021 [29]	MVI, MRI	Training: 158 Test: 79	Single center, internal validation	Fusion model combining three deep learning algorithms based on manually segmented T2 and portal venous phase T1 images Performance: AUC of 0.72, sensitivity of 55%, specificity of 81%
Song et al., 2021 [26]	MVI, MRI	Training: 461 Test: 140	Single center, internal validation	Deep learning algorithm and radiomics model developed based on manual tumor segmentation on MR images Deep learning model outperformed radiomics model (AUC of 0.915 vs. 0.731)
Liu et al., 2020 [25]	Recurrence after RFA or resection, CEUS	Training: 149 (RFA) and 144 (resection) Test: 65 (RFA) and 61 (resection)	Single center, internal validation	Deep learning algorithm based on manually segmented CEUS video Nomograms incorporating deep learning score and clinical variables Performance of RFA nomogram: C-index of 0.73 Performance of resection nomogram: C-index 0.72
Zhang et al., 2020 [28]	Survival after TACE plus sorafenib, CT	Training: 120 Test: 81	Multicenter, external validation	Deep learning radiomics model employing manual tumor segmentation, feature extraction using dense net, and modeling using elastic net Performance: C-index of 0.714
Xu et al., 2023 [27]	Objective response after TAIC, CT	Training: 310 Test: 77 (internal), 71 (external)	Multicenter, external validation	Separate deep learning and radiomics models developed using deep learning based automated tumor segmentation and manual correction on CT images. Combined nomogram developed by incorporating deep learning and radiomics models and clinical variables Performance: AUC of 0.896

*Validation methods were classified as internal (i.e., cross-validation, bootstrapping, split-sample, and temporal validation) or external (geographic validation), †Model performance reported was test performance.
MVI = microvascular invasion, CEUS = contrast-enhanced ultrasound, AUC = area under the curve, RFA = radiofrequency ablation, C-index = concordance index, TACE = trans-arterial chemoembolization, TAIC = trans-arterial infusion chemotherapy

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Prediction of MVI

MVI is a critical prognostic factor linked to early recurrence of HCC following surgery and local ablation therapy [36,37]. Several studies have explored the use of radiomics [21,22,38-40] and deep learning [26,29,30] for predicting MVI in HCC, most of which developed prediction models by integrating AI algorithms as well as clinical, laboratory, and radiologic data. Among these studies, a recent multi-institutional study conducted by Xia et al. [21] reported high performance of the radiomic and hybrid models, with areas under the curve (AUCs) of 0.72 and 0.84, respectively. Furthermore, the models' prediction of MVI presence was found to be associated with poor overall and recurrence-free survival. Additionally, gene expression analysis conducted in this study revealed that MVI-associated differentially expressed genes were commonly involved in glucose metabolism [21]. Song et al. [26] developed both deep learning and radiomic models using MRI, and showed that the performance of the deep learning algorithm was superior to that of the radiomics model (AUC of 0.915 vs. 0.731) in predicting MVI. However, the performance of the models was evaluated only through internal validation, thus leaving the generalizability of the models unproven.

Prediction of Other Prognostic Pathologic Features

Radiomics has been applied for the prediction of the prognostic histopathologic characteristics of HCC, such as cytokeratin-19 expression [20], vessels encapsulating tumor clusters [23], and macro-trabecular massive subtype [14]. Previous studies have demonstrated that the predictions of the radiomic models can help in the accurate identification of specific histopathologic characteristics and prognostic stratification of patients [14,20,23]. These findings support the hypothesis that radiologic tumor phenotypes reflect the histopathologic and molecular features and, thereby, the biologic behavior of tumors. However, considering that the biologic behavior of HCC is influenced by a variety of factors, the practical clinical relevance of these radiomic models that focus on a single histopathologic factor remains uncertain.

Limitations and Future Directions

The radiomics approach has certain limitations, which have hindered its application in daily clinical practice. Radiomic analysis involves time-consuming and labor-intensive processes such as segmentation and feature extraction. Recent advancements in deep learning for automated segmentation of CT or MRI images could facilitate the segmentation process. However, while algorithms for organ segmentation have displayed high performance [41,42], liver tumor segmentation using deep learning remains challenging and has failed to demonstrate satisfactory performance [10,43]. Another major concern is the reliability of radiomic features. Radiomic features are highly susceptible to variations stemming from differences in scanners, imaging techniques, image reconstruction algorithms, segmentation results, and methods for computing these features, all of which can impact the reproducibility of radiomic features and models [10,11,44]. To mitigate this problem, the image biomarker standardization initiative published consensus guidelines to standardize the definitions of radiomic features and reporting methods [45]. Furthermore, algorithms to minimize variations in radiomic features across different imaging protocols have also been proposed [46,47]. Nonetheless, ensuring harmonization and reproducibility in radiomics remains a formidable challenge [10,11]. Moreover, replicating a radiomics model from a research paper is extremely difficult, demanding identical training imaging data, segmentation, and computational methods as the original model. This highlights the need for transparent and standardized reporting of methodology and results in radiomics research. In order to assess the quality of the radiomics studies, a radiomics quality score has been proposed [48]. The radiomics quality score encompasses key components of radiomics research that should be clearly reported, including image protocol, methods for segmentation, feature extraction, feature selection, performance assessment, and public data sharing.

Existing research on radiomics for HCC prognostication has predominantly focused on the outcomes following a single treatment method, without comparing it to alternative therapeutic options. A more practical approach is required, which can assist in selecting the most suitable treatment from various available therapeutic options. In addition, the actual clinical impact of radiomics, for example, the survival benefit obtained by radiomic-assisted treatment selection needs to be addressed in future research.

Deep learning for HCC prognostication is considered to be in an even earlier stage of development than radiomics. All studies on deep learning for HCC prognosis preliminarily focus on technical feasibility. The reported algorithms require manual tumor segmentation and are not sufficiently validated for clinical use. Significant progress is required

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for the integration of deep learning algorithms into clinical practice for HCC prognostication. Given the current CT and MRI examination protocols used for the assessment of HCC, a practically applicable algorithm would require multiple complicated functions, including automated liver and tumor segmentation, co-registration of multiphasic or multi-sequence images, and prognostic assessment. Despite the limitations of deep learning algorithms as a standalone method for HCC prognostication, they may be used to facilitate radiomic analysis. This may involve the use of convolutional neural networks for feature extraction and/or selection, application of deep learning-based organ or tumor segmentation to radiomic analysis, and deep learning-based image conversion to improve the reproducibility of radiomic features. This aspect of deep learning needs to be further investigated.

Both radiomic models and deep learning algorithms utilize various image-derived features and are susceptible to the problem of overfitting. Therefore, rigorous clinical validation, preferably through external validation and multi-center data, is mandatory to prove their generalizability in real-world clinical practice. Despite its potential, AI for HCC prognostication is not yet applicable to daily clinical practice due to certain limitations and insufficient validation. The development of well-validated AI algorithms that are suitable for daily clinical workflow and proof of their actual clinical benefit are prerequisites for the clinical adoption of AI for the management of patients with HCC.

CONCLUSION

AI, particularly radiomics, has emerged as a promising tool for the image-based prognostication of HCC. Radiomics has demonstrated strong potential in diverse applications, including predicting MVI, assessing outcomes after locoregional and systemic treatment, and identifying unfavorable prognostic pathologic subtypes of HCC. However, radiomics has not yet been adopted in clinical practice due to some ongoing challenges, including its time-consuming nature and issues with reproducibility. Future studies should aim to streamline and standardize the radiomics process, thus reducing the hurdles for clinical integration. Most studies investigating deep learning for HCC prognosis are considered preliminary, with a focus on technical feasibility. For radiomics and deep learning to be applied in clinical practice, they must be incorporated seamlessly into the daily workflow. The development of well-constructed, accessible, and efficient AI algorithms, validated through rigorous clinical trials, will be pivotal for achieving this goal in the future.

Conflicts of Interest

Seung Soo Lee, who hold respective positions on the Editorial Board Member of the *Korean Journal of Radiology*, were not involved in the editorial evaluation or decision to publish this article. The remaining author has declared no conflicts of interest.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Funding acquisition: Seung Soo Lee. Investigation: all authors. Methodology: all authors. Project administration: Seung Soo Lee. Resources: all authors. Software: all authors. Supervision: Seung Soo Lee. Validation: all authors. Visualization: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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