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Review Article

Advances in Artificial Intelligence for the Radiological Diagnosis of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths globally. Unlike most other cancers, HCC can be diagnosed solely on imaging for high-risk patients. However, this is frequently complicated by atypical or indeterminate features necessitating biopsy or close follow-up with serial imaging. Artificial intelligence (AI) has the potential to allow for more accurate tumour classification and, thus, avoid unnecessary biopsies. Additionally, earlier diagnosis opens up the potential for curative therapies and improves patient outcomes. A number of artificial intelligence models, including machine learning, convolutional neural networks and radiomics-based models have been tested on ultrasound, CT and MRI images of liver lesions. The following review will outline the most impactful papers in this field.

Key words: Hepatocellular carcinoma, liver neoplasms, artificial intelligence, deep learning, machine learning, radiomics, radiology, computed tomography, magnetic resonance imaging, ultrasound.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world, accounting for approximately 500,000 cases per year (Marrero *et al.*, 2018). It is also the third most common cause of cancer-related deaths globally. Despite recent advances in treatment, the prognosis for unresectable HCC remains poor, mainly due to delays in diagnosis and limited efficacy of current therapies. High risk populations, namely those with cirrhosis, chronic hepatitis B infection or prior HCC, require lifetime surveillance. Artificial intelligence (AI) may help with early radiological diagnosis of HCC and improve survival among these patients (Pellat *et al.*, 2023).

AI is a broad field which encompasses machine learning, radiomics, deep learning and convolutional neural networks (Saba *et al.*, 2019). Machine learning involves algorithms that can learn from data and make predictions without being explicitly programmed to do so. The two most common types of machine learning are supervised and unsupervised learning. In supervised learning the algorithm learns from a database of labeled training data with the goal of being able to correctly label new, unseen data. In unsupervised learning, the algorithm learns patterns and structures from unlabeled data without any specific target output. The goal is to discover relationships or similarities between data.

Deep learning is a subtype of machine learning (Saba *et al.*, 2019). It involves the use of multiple layers of interconnected nodes, or neurons, in an "artificial neural network". The layers of these neural networks are responsible for learning and extracting increasingly complex patterns in the data. The early layers learn simple features, like edges in an image, while the deeper layers learn more complex features, like shapes and textures. This layer-by-layer learning process helps the network extract meaningful information and make accurate predictions or classifications. Convolutional neural networks (CNNs) are a specific type of deep learning where mathematical transformations called filters are applied to images to aid the algorithm in learning features (Yamashita *et al.*, 2018). Unlike other deep learning algorithms, CNNs excel at processing complex visual data, making them perfect for use in radiology.

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Radiomics is yet another application of machine learning. It involves extracting a large number of quantitative features from images of a lesion, such as its size, shape and texture (Kumar *et al.*, 2012). The underlying assumption is that there are detailed textures and patterns in images of lesions that are not perceptible to the human eye. Theoretically, these imperceptible features can provide insight on the phenotype and microscopic structure of a lesion and, therefore, provide important diagnostic and prognostic information. It differs from deep learning in that it involves a separate feature extraction step, whereas a deep learning algorithm will automatically learn features which are "hidden" in the layers of the neural network (Calabrese *et al.*, 2022).

When a liver lesion is detected on surveillance or incidentally, the patient should typically receive a contrast-enhanced CT or MRI of the liver (Pellat *et al.*, 2023). In high-risk patients with characteristic imaging findings of HCC, a diagnosis can be made without the need for a biopsy (Marrero *et al.*, 2018). However, often diagnosis of HCC is not so simple. For high-risk patients with atypical findings, or low-risk patients with any imaging features of HCC, biopsy of the lesion or close follow-up with imaging is indicated. For these patients, AI algorithms may allow for tumour classification with higher confidence and avoid unnecessary biopsies or serial imaging. Additionally, earlier diagnosis opens up the potential for curative therapies and improves patient outcomes (Pellat *et al.*, 2023). This literature review will review recent advances in artificial intelligence models for the radiological diagnosis of HCC. Studies presented in each section will be ordered chronologically.

NON-CONTRAST ULTRASOUND

Current guidelines recommend targeted ultrasound for the surveillance of HCC in high-risk patients (Marrero *et al.*, 2018). However, ultrasound is highly dependent on the skill of the operator, quality of equipment, and other factors such as patient body habitus. The reported sensitivity of ultrasound in detecting HCC ranges from 46 to 63% (Calderaro *et al.*, 2022). Hence, many researchers have directed their attention towards using AI to improve the diagnostic accuracy of ultrasound.

A CNN model published by Schmauch *et al.*, (2019) classified liver lesions as benign or malignant with a mean area under the receiver-operative curve (AUC) of 0.89 in a test set (n=177). This algorithm is yet to be externally validated. Yang *et al.*, (2020) developed a CNN trained using a large ultrasound imaging database from 13 hospitals. The model distinguished between benign and malignant liver lesions with a mean AUC of 0.92 in an external validation cohort (n=328) and showed a similar diagnostic accuracy to 236 radiologists with over 15 years of experience. Ren *et al.*, (2021) developed a machine learning algorithm called a support vector machine (SVM) which could differentiate between high and low histological grade HCC with an AUC of 0.83 in an external validation cohort of 33 patients. Finally, a CNN model developed by Sato *et al.*, (2022) demonstrated an AUC of 0.72 in 108 test patients when discriminating between benign and malignant lesions on ultrasound. After clinical and demographic data were integrated into the model (patient age, sex, AST, ALT, platelet count, and albumin level), AUC increased to 0.99.

CONTRAST-ENHANCED ULTRASOUND

Contrast-enhanced ultrasound (CEUS) can be used to diagnose HCCs when a lesion is found on a non-contrast ultrasound. While CEUS has limited efficacy in some scenarios (e.g. fatty liver or subdiaphragmatic tumours), there are numerous advantages of CEUS including its ability to provide a rapid diagnosis, its convenience, and its cost-effectiveness (Westwood *et al.*, 2013). Furthermore, the diagnostic performance of CEUS for diagnosing HCC is similar to that of contrast-enhanced CT or MRI (Fraquelli *et al.*, 2022). As a result, several studies have investigated the utility of AI models in interpreting CEUS images.

A study by Ta *et al.*, (2018) found a machine learning algorithm had an AUC of 0.88 when classifying 105 focal liver lesions as benign or malignant on CEUS. The algorithm had a similar diagnostic performance to a blinded radiologist with over 20 years of experience. Furthermore, when the algorithm agreed with the radiologist's assessment, the radiologist's accuracy increased from 81% to 90%, and when they disagreed, accuracy increased from 35% to 83%. This demonstrates that AI systems can increase radiologists' reading accuracy by improving confidence when they agree with the algorithm and flagging studies when they disagree. Wang *et al.*, (2021) developed an SVM-based machine learning algorithm to differentiate between high and low histological grade HCC. The model had an AUC of 0.72 in an external validation cohort (n=70), which increased to 0.79 when combined with clinical data such as liver function tests and tumour marker levels. Hu *et al.* (2021) developed a deep learning algorithm for distinguishing between benign and malignant lesions on CEUS. The algorithm demonstrated an AUC of 0.93 in a test set of 211 patients, matching the diagnostic accuracy of 2 consultant radiologists and outperforming 2 radiology residents. When the radiologists received assistance from the deep learning model, their accuracy improved by 5.1-9.9%.

CONTRAST-ENHANCED CT

For high-risk patients with abnormal surveillance results, contrast-enhanced CT or MRI is the preferred modality for further characterisation of the lesion (Marrero *et al.*, 2018). Yasaka *et al.*, (2018) demonstrated that a CNN model was able classify liver lesions as benign or malignant on CT with an AUC of 0.92. This was performed on a test set of 100 patients and was not externally validated. Mokrane *et al.*, (2020) used a radiomics-based machine learning algorithm to classify indeterminate liver lesions as either HCC or non-HCC. They extracted 13,920 imaging features and found that the algorithm reached an AUC of 0.66 in an external validation cohort of 36 patients. A CNN model designed by Zhou *et al.*, (2021) achieved an AUC of 0.92 when classifying liver lesions as benign or malignant in a test set of 154 patients. The model's diagnostic accuracy was superior to a radiologist with 3 years of experience but inferior to a radiologist with 8 years of experience. A different CNN model developed by Cao *et al.*, (2020) classified liver lesions as HCC, liver metastases, benign lesions or hepatic abscesses, and achieved AUCs of 0.92, 0.99, 0.88, and 0.96, respectively (n=107 in a test set). Finally, Mao *et al.*, (2020) developed a radiomics-based machine learning model which was able to differentiate between high and low histological grade HCC with an AUC of 0.67 in a test set (n=60); however, when combined with clinical data, this improved to 0.80.

CONTRAST-ENHANCED MRI

MRI can also be used for the diagnosis of HCC as it has a comparable diagnostic accuracy to contrast-enhanced CT (Roberts *et al.*, 2018). MRI is often done with an extracellular gadolinium-based contrast agent but a hepatobiliary contrast agent such as gadoxetate may also be used. Jansen *et al.*, (2019) developed a machine learning algorithm which achieved an AUC of 0.91 when differentiating between HCC and non-HCC lesions and an AUC of 0.94 when differentiating between benign vs malignant lesions on 95 gadolinium-enhanced MRIs. A CNN model developed by Hamm *et al.*, (2019) reached an AUC of 0.99 when classifying HCC and non-HCC lesions on 60 gadolinium-enhanced MRIs, outperforming 2 consultant radiologists. A radiomics-based machine learning algorithm by Oyama *et al.*, (2019) had an AUC of 0.95 when differentiating HCCs from metastases or hemangiomas in 93 non-contrast MRIs. Zhen *et al.*, (2020) developed a CNN to distinguish between HCC from metastases or other primary malignancies and externally validated it on 201 patients. Without clinical data, the model had an AUC of 0.88, but with clinical data (age, gender, medical history, tumour markers, liver function tests), the AUC was 0.95. The diagnostic accuracy of both models was on par with 3 experienced radiologists. The study also found that the CNN model performed similarly whether or not it received contrast-enhanced images. Therefore, the authors concluded that CNN models have the potential to obviate the need for contrast when investigating liver lesions with MRI.

SEGMENTATION

Segmentation involves isolating the pixels of an image corresponding to a liver lesion from the rest of the image. Accurate segmentation allows for evaluation of tumour burden, aids preoperative planning and enables monitoring of treatment response (Bilic *et al.*, 2023). Additionally, localising the tumour is a prerequisite for treatment options such as percutaneous ablation, surgical resection or radiotherapy. Segmentation is usually carried out manually, however this is time consuming and is susceptible to both inter- and intra-rater variation. Automatic segmentation using AI is emerging as an alternative. In 2017, the Liver Tumour Segmentation Challenge (LiTS) called upon 75 teams to develop liver and tumour segmentation algorithms (Bilic *et al.*, 2023). The best liver segmentation algorithm achieved a Dice score of 0.96 whereas the best tumour segmentation algorithm achieved a Dice score of 0.74. The main challenges limiting tumour segmentation included variations in CT/MRI acquisition parameters, small tumour sizes and poor contrast with background liver parenchyma. Nevertheless, the LiTS challenge prompted significant advances in this field and has set the foundations for future research.

CONCLUSIONS

The findings of this literature review are promising and highlight the exponential increase in research in this area over the past few years. The following conclusions can be drawn from the published data:

1. There is a scarcity of studies that specifically explore the use of AI in HCC diagnosis. However, several AI models have demonstrated excellent accuracy in differentiating between benign and malignant liver lesions (AUC > 90).
2. Generally, CNN algorithms performed better than machine learning or radiomics-based algorithms.
3. Most studies used small sample sizes in their training and validation cohorts which limits their generalizability.

The research outlined in this review will pave the pathway for larger scale validation studies, with the aim of integrating AI into a clinical setting and enhancing patient outcomes.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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