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DIFFERENTIAL DIAGNOSIS OF MALIGNANT HEPATIC TUMORS USING CLINICAL INFORMATION AND MULTI-PHASE CONTRAST-ENHANCED CT

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Abstract

Liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death in the world according to 2020 global cancer statistics [1]. A substantial number of malignant liver tumors are primary tumors, including HCC and ICC [2]. In clinical settings, the metastasis of tumors to the liver is also frequently encountered [3]. The treatment regimen for the different subtypes of hepatic tumors is all distinct [4], and multi-phase CECT has become the primary tool for diagnosis of hepatic tumors before surgery [5]. However, the differential diagnosis of malignant hepatic tumors is challenging, and misdiagnosis prior to surgery can mislead the treatment decision. An automated diagnostic model is desirable to be developed, which can assist doctors in hepatic tumors diagnosis, reduce observer variations and improve diagnostic efficiency. Few preliminary studies utilized deep learning to differentiate hepatic tumors [6,7,8,9], but they lacked detailed classification for malignant hepatic tumors, especially for ICC. Herein, we proposed a novel deep learning model, which was specifically customized for the differential diagnosis of malignant hepatic tumors based on patients' preoperative multi-phase CECT and clinical features. All 723 patients enrolled in our study were pathologically confirmed with one of the following malignant hepatic tumors: HCC, ICC and metastatic liver cancer (Fig. 1A). The training and test sets were split, with 499 and 113 patients from center 1, respectively.

Differentiation between benign and malignant hepatic tumors: a preliminary study

As a preliminary study, we trained the STIC model for benign and malignant hepatic tumors classification on a relatively small dataset, with 152 pathologically confirmed benign hepatic tumors and 159 malignant hepatic tumors (Additional file 2: Table S3). Using five-fold cross-validation, our proposed model achieved the mean accuracy of 93.2% and AUC of 0.987 (Fig. 1C and Additional file 2: Table S4), which demonstrated the ideal classification ability of the STIC model.

Binary classification of primary malignant hepatic tumors

We then trained the STIC model for differentiating two primary malignant hepatic tumors on the training set and achieved the accuracy of 86.2% on the test set. For comparison, we also built two benchmark models, Naïve RGB model and Naïve joint model (Additional file 2: Figure S2), which used channel assignment strategy reported by previous studies [7]. According to ROC analysis, the STIC model achieved better performance than two benchmark models, with AUC of 0.893 .

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Multinomial classification of malignant hepatic tumors and performance of the STIC-assisted diagnosis

We extended the proposed STIC model to classify three types of malignant hepatic tumors and achieved the total accuracy of 72.6% on the test set. The micro-average and macro-average AUC of the STIC model was 0.868 and 0.852 (Fig. 2A). The AUC for diagnosis of HCC, ICC and metastasis was 0.937, 0.727 and 0.878, respectively (Fig. 2B). We further evaluated the performance of doctors' consensus diagnosis and model assisted diagnosis on the test set. The total accuracy of the doctors' consensus was 70.8%, and three STIC-assisted doctors achieved the average accuracy of 79.1%, with an increase of 8.3% than doctors' consensus (Fig. 2C and Additional file 2: Table S7). There were no significant differences in accuracy, sensitivity and specificity for each type of tumors between the STIC model and doctors' consensus diagnosis (Fig. 2C and Additional file 2: Table S8), which showed that our proposed STIC model is comparable with human experts' performance.

Case study of test samples that doctors initially misdiagnosed

We performed the case study of test samples that doctors initially misdiagnosed to illustrate the process of STIC-assisted diagnosis. We list three cases pathologically diagnosed with ICC (Fig. 2D) and three cases pathologically diagnosed with metastasis (Fig. 2E) on the test set as examples. The enhancement pattern of ICC case 1 was typical for ICC samples, but ICC case 2, 3 represented the ICC samples that have atypical radiological features and were easily misdiagnosed clinically. The scores outputted by the STIC model for ICC case 3 effectively assisted doctors to make an accurate diagnosis, which can guide them specifying the surgical protocol. Clinically, it is important but challenging to differ ICC from metastasis. Metastases 1, 2 and 3 were all misdiagnosed as ICC by doctors' consensus. With the assistance of our STIC model, doctors were more likely to diagnose them as metastasis correctly.

Generalization performance of the STIC model on the external test set

On the external test set from center 2, our STIC model achieved an accuracy of 82.9%, the micro-average AUC of 0.944 and the macro-average AUC of 0.931 (Fig. 2F and Additional file 2: Table S10). The accuracy, sensitivity and specificity for each type of malignant tumors have no significant difference on the test set from center 1 and on the external test set from center 2 (Fig. 2G). Using AUC as the evaluation index, our STIC model even achieved significant better performance for HCC and ICC diagnosis on the external test set (Fig. 1G and Additional file 2: Table S10), which may be related to the lower missing rate of clinical data on the external test set (Additional file 2: Table S1). The completeness of preoperative clinical data is expected to further improve the accuracy of our model. The diagnostic performance on the external test set from center 2 verifies the generalization ability of the STIC model. Considering the flexibility of our model's architecture, the prediction of some prognostic indicators such as MVI for hepatic tumors and differentiation of metastases among distinct primary cancers will be incorporated in our future work.

In conclusion, our proposed deep learning model can differentiate HCC, ICC and metastasis through using deep CNN and gated RNN to integrate multimodal input of multi-phase CECT images and clinical

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features, with promising performance comparable with experienced doctors and good generalization ability on different centers. Doctors assisted with our model can improve diagnostic performance, especially for the diagnosis of ICC, showing the great potential of AI assistance system in precise diagnosis and treatment of liver cancer.

Abbreviations

CECT: Contrast-enhanced computed tomography
HCC: Hepatocellular carcinoma
ICC: Intrahepatic cholangiocarcinoma
CNN: Convolutional neural network
RNN: Recurrent neural network
AI: Artificial intelligence
MVI: Microvascular invasion

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