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Whole-Liver Based Deep Learning for Preoperatively Predicting Overall Survival in Patients with Hepatocellular Carcinoma

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Abstract. Survival prediction is crucial for treatment decision making in hepatocellular carcinoma (HCC). We aimed to build a fully automated artificial intelligence system (FAIS) that mines whole-liver information to predict overall survival of HCC. We included 215 patients with preoperative contrast-enhance CT imaging and received curative resection from a hospital in China. The cohort was randomly split into developing and testing subcohorts. The FAIS was constructed with convolutional layers and full-connected layers. Cox regression loss was used for training. Models based on clinical and/or tumor-based radiomics features were built for comparison. The FAIS achieved C-indices of 0.81 and 0.72 for the developing and testing sets, outperforming all the other three models. In conclusion, our study suggest that more important information could be mined from whole liver instead of only the tumor. Our whole-liver based FAIS provides a non-invasive and efficient overall survival prediction tool for HCC before the surgery.

Keywords. Hepatocellular carcinoma, hepatectomy, contrast-enhanced computed tomography, deep learning, overall survival

1. Introduction

Liver cancer is a leading fatal malignancy worldwide, and hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 75%~85% of the liver cancer cases [1]. Surgical resection is recommended as the first choice in the treatment of HCC patients with well-preserved liver function. The overall survival of HCC remains low though the survival rate has increased in recent years. It was reported that the 1- and 5-year survival rates were 49% and 20% among Chinese [2]. Identification of patients who are at high risk of poor outcomes in advance of the surgery would enable the clinicians to choose the conservative treatment for them to maximize their benefits.

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Currently, the central role of HCC post-operative prognosis and surgery decision making is occupied by the staging systems, such as the Barcelona Clinic Liver Cancer classification, and the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system [3]. However, these schemes were not developed among the patients receiving the resection surgeries, thus the clinical applicability should be discounted. Artificial intelligence combined with CT (Computed Tomography) imaging has shown to be promising in non-invasively predicting the survival of HCC [3,4].

Previous studies adopted tumor-based methods to analyze the imaging by focusing on extracting features from the tumor area, regardless of the radiomics-based machine learning methods or the deep learning models. However, tumor-based methods rely highly on refined delineation of the tumor boundaries, which was too time-consuming and expensive in practice. Second, these methods were not applicable among patients with poorly defined tumors such as diffuse tumors and portal venous emboli. Finally, the abnormal tissues resulted from diseases like viral hepatitis and liver cirrhosis outside the tumor can also affect the liver function and therefore impact the therapeutic efficacy.

Under the assumption that survival information can be mined from both the regions inside and outside the tumor, we proposed a novel fully automated artificial intelligence system (FAIS) to explore the whole-liver information to predict the overall survival of HCC after resection.

2. Methods

2.1. Study Population

With approval of the ethics committee, we collected patients with histologically diagnosed primary HCC and were treated by curative resection between October 2014 and April 2018 from one hospital in China. Exclusion criteria were unavailable contrast-enhanced CT scans before the surgery, previous history of any anti-tumor treatments such as ablation and transarterial chemoembolization; complicated with other cancers; lost to follow-up. The arterial phase and portal venous phase of the contrast-enhanced CT were extracted for further analysis. We randomly assigned the included patients in a four-to-one ratio into developing and testing subcohorts. The developing subcohort was further randomly split into training and validation subcohorts in a four-to-one ratio for model training and hyper-parameter tuning. Specifically, stratified sampling was applied so that for each subset the event proportion is the same as that in the full dataset.

2.2. Development of the FAIS

The FAIS is composed of two consecutive components: automated liver segmentation and overall survival prediction (Figure 1). Without any human help, the system can accept the original CT images of a patient, automatically processing the images, segmenting the liver mask, and predicting the overall survival based on the liver field.

To achieve the liver mask in an automatic manner, we first applied the nnU-Net model trained for the liver and liver cancer segmentation [5]. Considering the false negatives of nnU-Net, we also used the unet 3+ to segment the liver and the two segmentations were combined [6]. To guarantee the acquisition of the complete liver area, the liver segmentation was further dilated with the connectivity set to 1.

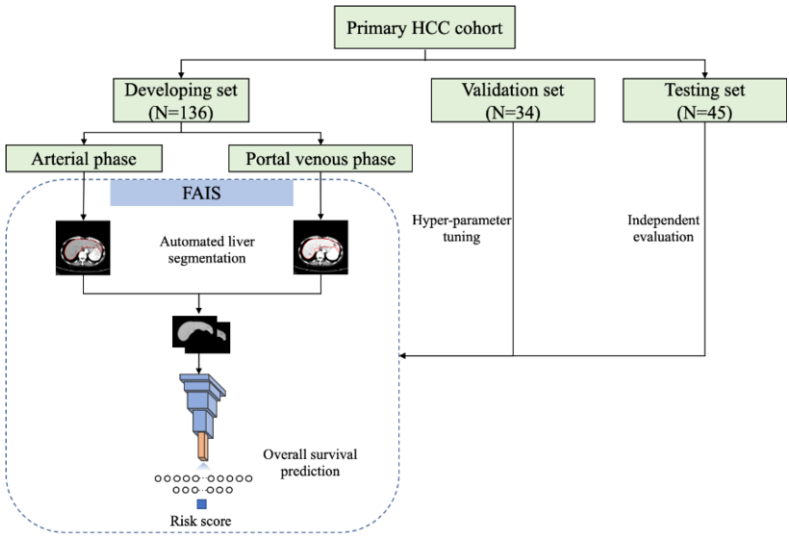

Figure 1. The proposed study design and the FAIS for automatically predicting overall survival in HCC.

We proposed a convolution neural network entitled LiverNet to predict the overall survival of HCC patients after curative resection. LiverNet consists of five residual blocks, where each block is a stack of convolution, batch normalization and activation layer with ReLU. A maxpooling layer was added between each two neighbouring residual blocks. The input and output of each block are combined with element-wise summation. After the last convolutional layer, the feature map is flattened and the output features vector is forwarded to three fully-connected layers with decreasing neurons (i.e. 128, 64, 1). Whole liver regions of the arterial and the portal venous phases were cropped with the corresponding liver masks, registered and then concatenated as a two-channel input to LiverNet. The network output is a 'risk score', representing the logarithm of the ratio of the individual hazard to the baseline hazard. Cox proportional-hazards loss was used for training the survival model.

We compared our LiverNet with three conventional models based on clinical features and/or radiomics features. First, a clinical model was built with gender, maximum diameter of the largest tumor, tumor number, logarithm of alpha-fetoprotein (AFP), albumin-bilirubin (ALBI) grade, and history of liver cirrhosis. As for the radiomics model, a total of 1702 radiomics features, including intensity-based features, shape and size features, texture features and filter-based features, were extracted from the largest tumor region from the two phases of the contrast-enhanced CT. We followed the workflow as our prior studies to perform features reduction, radiomics model training and radiomics+clinical model training [7].

3. Results

3.1. Patient Demographics.

Clinical characteristics of the patients are summarized and the two subcohorts exhibit heterogeneity to some extent (Table 1). Specifically, patients in the developing set have

shorter follow-up time and smaller tumors. Besides, more patients are male and having solitary tumor, ALBI grade 1 and cirrhosis in the developing set.

Table 1. Patient characteristics.

Characteristics	Developing subcohort (n=170)	Testing subcohort (n=45)
Death (n %)	40(23.3%)	11(24.4%)
Follow-up time (months, mean ± SD)	37.1 ± 15.5	40.0 ± 13.9
Male (n %)	141(82.0%)	38(84.4%)
Maximum tumor diameter (centimeter, mean ± SD)	4.3 ± 2.7	4.5 ± 2.6
Solitary tumor (n %)	157(91.3%)	38(86.4%)
Logarithm of AFP (ng/mL, mean ± SD)	4.1 ± 2.9	4.4 ± 3.1
ALBI grade 1 (n %)	155(90.6%)	37(82.2%)
Liver cirrhosis (n %)	131(76.2%)	32(71.1%)

The numbers in parentheses represents percentages. SD: standard deviation. AFP: alpha-fetoprotein. ALBI: albumin-bilirubin.

3.2. Comparison of LiverNet with the Conventional Models.

As shown in Table 2, among the three models our proposed LiverNet had the best performance in predicting the overall survival of HCC, with C-indices of 0.81 and 0.72 for the developing and testing subcohorts, respectively. The model based on radiomics performed worse than LiverNet, with C-indices of 0.74 and 0.68 for the developing and testing subcohorts. The clinical model achieved the worst performance in the testing subcohort with a C-indices of 0.70 and 0.62 for the developin and testing set. Adding the clinical features slightly enhanced the radiomics model, however the performance was not yet better than LiverNet.

Table 2. Prognostic performance measured by C-index of our proposed LiverNet compared with clinical and radiomics model.

Model	Developing subcohort	Testing subcohort
Clinical model	0.70	0.62
Radiomics model	0.74	0.68
Radiomics+Clinical model	0.77	0.69
LiverNet	0.81	0.72

4. Discussion

To our knowledge, this study is the first to propose a whole-liver FAIS for analyzing routine CT imaging and it was demonstrated to be able to non-invasively and preoperatively predict the overall survival of HCC patients better than other models.

In our study, the results showed that the clinical model can predict the overall survival of HCC, suggesting that patient-level liver function level and other characteristics did impact on the survival outcomes. The radiomics model performed better than the clinical model, implicating that tumor-based features are more associated with the survival than the clinical features. The tumor-based imaging features and clinical features might be complementary to each other as the joint model achieved an improved C-index. Our proposed LiverNet was the best model compared to the above three models. The reasons could be that whole-liver region renders much more information than the tumor-only region, such as the status of liver cirrhosis, severity of hepatitis, multiple tumors, and residual healthy liver tissue.

This study has several limitations. First, all the data came from a single hospital. A multi-center study is warranted to validate our findings. Second, integrating other imaging modalities could be helpful to boost the performance.

5. Conclusions

In conclusion, our study suggest that routine contrast-enhanced CT imaging combined with a whole-liver FAIS can non-invasively and preoperatively predict the overall survival of HCC patients. Our results show that whole-liver based information are more essential than the commonly used tumor-based and clinical features for prognostic prediction in resected HCC.

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