

# A Radiomics Model in Predicting Recurrence Time of Small Hepatocellular Carcinoma After Hepatectomy Base on MR by ANN

Weiwei Wang<sup>1</sup>, Weimin An<sup>1, \*</sup>, Jinghui Dong<sup>1</sup>, Jianzeng Zhang<sup>1</sup>, Peng Li<sup>1</sup>, Zhenjie Wu<sup>2</sup>, Fangfang Shi<sup>1</sup>, Mengmeng Zhang<sup>1</sup>

<sup>1</sup>Radiological Department, The Fifth Medical Center of PLA General Hospital, Beijing, China

<sup>2</sup>China School of Microelectronics, Xidian University, Xi'an, China

## Email address:

2448250186@qq.com (Weimin An)

\*Corresponding author

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**Abstract:** Objective: The recurrence time of small hepatocellular carcinoma (sHCC) after resection are heterogeneous. Prediction the recurrence time of sHCC after resection is propitious to the fine management and individualized treatment of patients with sHCC, especially preoperative noninvasive. Methods: Collected the patients who with SHCC resection, and performed MR before operation one month long, cases with complete follow-up data in the Fifth Medical Center of the Chinese PLA General Hospital during January 2010 to January 2017. Abstract radiographic features of MR LAVA sequence Mask images by pyradiomics and input ANN. Results: A total of 179 cases were enroll into the study, of which 89 were early recurrence ( $\leq 24$  months) cases and 90 were non-early recurrence ( $> 24$  months) cases. Abstract 121 radiographic features of MR LAVA sequence Mask images. Input ANN model into training group (150 cases) and test group (29 cases), the AUC value is 0.64. The correlation factors of AFP and tumor size were 0.03 and 0.06 respectively. Conclusion: the ANN model of Mask features of MR T1 LAVA sequence can be used to predict the recurrence time of sHCC after resection before the operation, to establish the operative strategy and determine the Image examination frequency of postoperative follow-up.

**Keywords:** ANN, MR, eHCC, Recurrence Time

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## 1. Introduction

In present, the incidence of hepatocellular carcinoma (HCC) is the fifth in the world and has been increasing in recent years [1, 2]. It is one of the causes of cancer leading death [3]. More than 500000 new cases were diagnosed every year [4]. The main treatments for HCC include surgical resection (anatomic and non-anatomic resection), liver transplantation, radiofrequency or microwave ablation, interventional therapy, radiotherapy and targeted drug therapy [1]. Among them, surgical resection and liver transplantation are the best choices for early patients with good outcomes, especially for patients with no underlying liver disease or good liver function reserve [3, 5, 6].

The recurrence rate of HCC after hepatectomy is very high, the highest recurrence rate even up to 80%, which is the main factor that affects the survival time of patients after operation [7, 8]. Because of the higher recurrence rate and poorer outcomes after the operation of HCC, it is necessary to select the pre-operative prediction and treatment plan, and it is the premise of the precise treatment. With the clinical application of various individualized therapies, accurate prediction of HCC patients before treatment has become an urgent need.

For the patients suitable for hepatectomy, determining the time of recurrence after resection will be helpful for accurate stratification of patients with HCC. The patients who predicte

as early recurrence preoperative, intraoperative and postoperative adjuvant treatment measures should take in time, and increase the frequency of blood test and imaging examination follow-up, to early detection of recurrent lesions and timely take comprehensive necessary treatment measures to improve the survival time of patients. For patients who predicte as non-early recurrence, lower frequency blood test and imaging examination can be selected, some unnecessary therapeutist interoperative or postoperative can be omitted to reduce the economic and psychological burden of patients, improve the quality of life in addition [9].

There are many potential risk factors for postoperative recurrence of HCC. Although recent studies have shown that tumor size and number, microvascular infiltration and alpha-fetoprotein (AFP) levels are risk factors for postoperative recurrence, the clinical practical preoperative prediction method has not been established [10, 11].

The characteristics of radiomics can reflect the biological characteristics of pathological changes [12], and the accuracy of clinical prediction can be improved by the analysis and prediction of the characteristics of radiomics based on CT. ANN has achieved good results in the diagnosis and prognosis of lung cancer and central nervous system tumors [13, 14]. In this study, the radiomics features of sHCC were extracted, the ANN model was built and trained, the sensitivity and specificity of the model were verified, in order to predict the recurrence time of sHCC after resection.

## 2. Method

### 2.1. Study Population

This study retrospectively collected patients who met the following criteria in the Fifth Medical Center of the General Hospital of the Chinese People's Liberation Army from January 2010 to January 2017. The inclusion criteria were as follows: (1) the diameter of the lesion was below 3cm and the lesion was a single lesion; (2) the patient underwent MRI examination within one month before the operation. (3) the patient did not receive other liver therapy before MRI examination (such as interventional, radiofrequency, radiotherapy, etc.). (4) The follow up data should complete. Exclusion criteria: (1) no hepatectomy was performed after MRI examination; (2) the follow-up time was shorter than 24 months without recurrence; (3) MR images could not be analyzed; and (4) MR images had visual artifacts.

A total of 179 patients who met the selection criteria were included, and the screening process was shown in Figure 1.

151 of 179 patients were male, accounting for 84.36%. The average age of the patients was 52.11 years (28-75 years); The patients were divided into two groups: the group of early recurrence ( $\leq 24$  months) and the group of non-early recurrence ( $>24$  months). Among them, 89 cases (89 / 179) were early recurrence, and 89 cases (89 / 179) were early recurrence. The recurrence time ranged from 1-83 months. Other specific information about the patient is shown in Table 1.

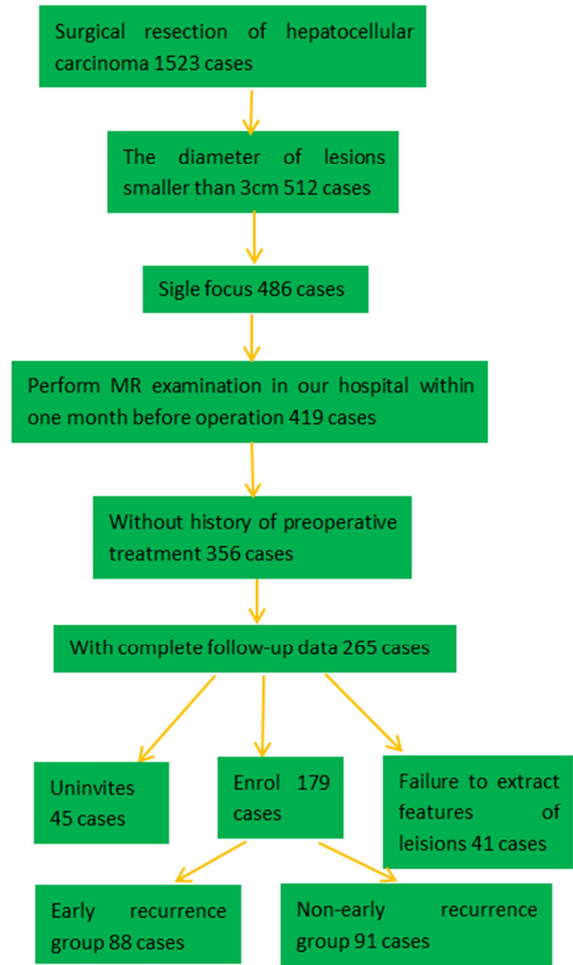


Figure 1. Flowchart of search stratege used according to research requirements.

Table 1. Distribution of basic information about patients in the early recurrence and non-early recurrence of sHCC after hepatectomy.

Variables	Early recurrence (n=88)	Non-early recurrence (n=91)
Age	52.98	51.2
Male gender	75 (85.22%)	75 (82.41%)
Basic illness		
Hepatitis C	2	3
hepatitis B	74	77
Alcoholic liver	1	1
Multiple mixes and others	11	10
AFP value	114.69	198.96
AFP result (positive)	43 (48.86%)	40 (43.95%)
AFP result (negative)	45 (51.14%)	51 (56.05%)
MVI result (positive)	56 (63.63%)	49 (53.84%)

\*When the AFP value is greater then 10, we consider its AFP grade to be positive.

### 2.2. Follow-up

After hepatectomy, the patients were followed up with conventional imaging (CT, MR or interventional) follow-up, the frequency of follow-up was 3 to 6 months. The end point of follow-up was found the recurrence tumor or find no recurrence tumor in more than 24 months. Follow-up time

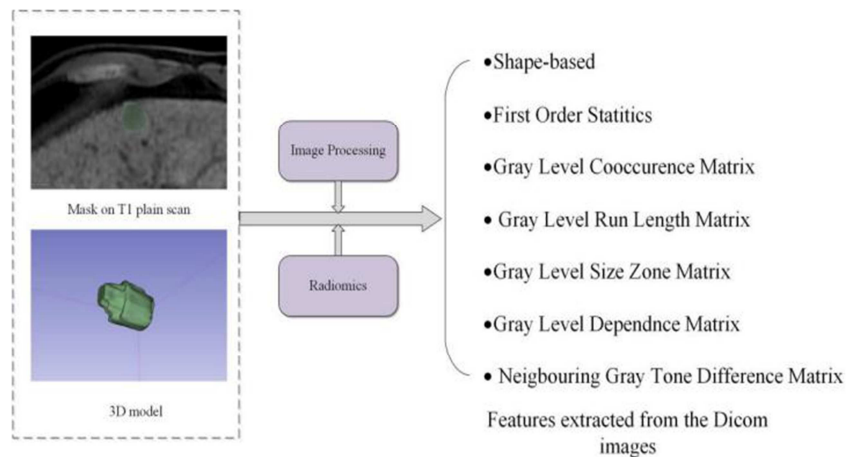
between 1-83 months, average 26.68.

### 2.3. MRI Series

MRI inspection equipment was 1.5T Signa HDx and 3.0 T Signa HDxt MRI scanner of GE Company. The corresponding T1 LAVA Mask parameters of 1.5T and 3.0T were: TR 3~4ms TE1.5~2.0ms, layer thickness 5mm, interlayer spacing -2.50mm; TR 3~4ms TE 1.0~1.5ms, layer thickness 4mm, interlayer spacing 2.0mm.

### 2.4. Feature Extraction

Philippe Lambin put forward the concept of radiology in 2012, which can transform the medical images that delineate the region of interest (ROI) into minable data in a high-throughput manner, which can be used for the diagnosis of diseases. Prognosis and prediction provide valuable information. At present, it has been used in the auxiliary judgment of benign and malignant lung nodules and in the auxiliary interpretation of hepatocellular carcinoma. In this study, the pyradiomics 2.7 version is used to extract the features of MRI images. Pyradiomics is an open source radiology algorithm based on python, which can be used to extract radiology data from medical images. In this paper, pyradiomic is used to extract the 110-dimensional features of the seven classes of First Order Statistics, Shape-based, Gray Level Cooccurrence Matrix, Gray Level Run Length Matrix, Gray Level Size Zone Matrix, Neighbouring Gray Tone Difference Matrix and Gray Level Dependence Matrix on MRI images.



**Figure 2.** Tumor contours were labeled on each patient's T1WI Mask image.

### 2.6. ANN Model

First of all, we choose the neural network as our basis classifier. The ANN is that the robustness of neural network is better so that we can not adjust the parameters for specific data. We construct a three-layer feedforward neural network, which includes an input layer, three hidden layers, and two output neurons. The learning rule used here is the back propagation of the error. The optimization method selects the stochastic gradient descent method which adjusts the internal parameters of the network during the repeated training cycle to reduce the

### 2.5. Feature Analysis

Because the dimension of feature extraction is large, the ANN will run too slowly, and the problem of dimension disaster will occur, which will reduce the accuracy. So we need to preprocess the high dimension feature first. The feature extraction algorithm we use is PCA (Principal Component Analysis). In PCA, the data is mapped from the original feature space to the new low-dimensional feature space. In order to reduce the 110-dimensional original feature data to k dimension, we need to find k new feature vectors to project the original data, so that the projection error (projection distance) is minimized. The smaller the error, the more the data after dimensionality reduction can represent the data before dimensionality reduction. The error is set to 0.01, which indicates that the feature data can retain 99% information after dimensionality reduction. In the implementation of PCA, our team covariance matrix performs singular value decomposition to obtain its eigenvalue matrix. The expression for PCA error is equivalent to the following formula.

$$1 - \frac{\sum_1^k S_i}{\sum_1^m S_i} \leq 0.01$$

Finally, the new feature space with 99% original feature information is 26 dimensional, that is, the linear correlation degree is low, and the 26-dimensional feature of most principal components is retained. The process of screening the entire feature of methods can be referred to Figure 2.

overall error. The training terminates when the sum of square errors is minimal. First, the 26-dimensional feature of PCA reduced dimension is input into the neural network. After 1000 times forward and back propagation of the neural network, the neural network makes a good fit for the training set. In order to achieve better ensemble effect, the number of neurons in each layer of our neural network is different, and the number of neurons in each layer is a random number of 40-100, which can effectively increase the randomness of a single classifier. Each base classifier is biased towards different features. The structure

of the ANN was shown in Figure 3.

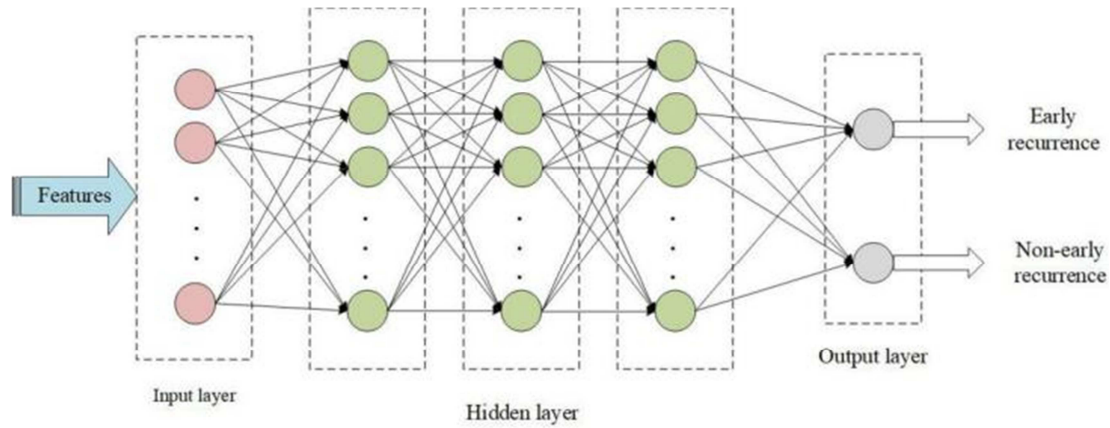


Figure 3. The basic structure of the ANN constructure in this study.

2.7. Integrated Learning

After the individual classifier model is trained, we use the bagging strategy in integrated learning to greatly enhance the generalization ability and accuracy of the model. The so-called integrated learning is to construct and combine multiple learning devices to complete the learning tasks, that is to say, multiple weak learning devices can obtain a strong learning device with a certain combination strategy to achieve the purpose of classification. In this paper, we train 50 independent ANN models as learning devices, vote their outputs and use the majority prediction results as the final prediction results.

3. Results

A total of 179 cases were enroll into the study, of which 89 were early recurrence cases and 90 were non-early recurrence cases. Abstract 121 radiographic features of MR LAVA sequence Mask images. Input ANN model into training group (150 cases) and test group (29 cases), the AUC value is 0.851. The results after bagging (ROC) was shown in Figure 4.

4. Discussion

In this study, we retrospectively analyzed the preoperative MR T1 mask images of patients with sHCC. According to the time of recurrence, they were divided into early recurrence group (recurrence time  $\leq 24$  months) and non-early recurrence group (recurrence time  $> 24$  months). The radiologics features of imaging images were extracted and analyzed. The radiologics features of MR LAVA sequence T1 mask images were correlated with the time of recurrence after resection of sHCC. ANN model was used to predict the recurrence time after resection of sHCC. The AUC value is 0.851. This prediction model can promote the fine management of sHCC, prolong the patients' survival time and tumor-free period, and improve the quality of life.

Recurrence after hepatectomy is a major factor affecting the long-term survival of HCC patients [15]. It is reported in the literature that the radiology features of medical images can reflect the biological characteristics of the lesions and are related to the development and evolution of the lesions [12]. Similarly, our study showed that preoperative MR LAVA sequence T1 mask radiography could predict the recurrence time of sHCC after resection.

Accurate prediction of recurrence time after hepatectomy is very important significance far selecting preoperative, intraoperative and postoperative adjuvant treatment measures and determine the frequency of follow-up after hepatectomy [16-19]. It can avoid unnecessary treatment, imaging examination, and blood examination, reduce the toxic and side-effects of the patients, and can find the early recurrence lesions in time, then take appropriate treatment measures, achieve the goals of prolonging the survival time of the patients.

It is reported that the number of the tumor, tumor size, microvascular invasion, and AFP level are related to the recurrence time of HCC after liver transplantation or surgical resection [20-27]. But no reliable model has been established to predict the personalized risk of liver cancer recurrence time [25].

Several models for predicting recurrence of HCC have been

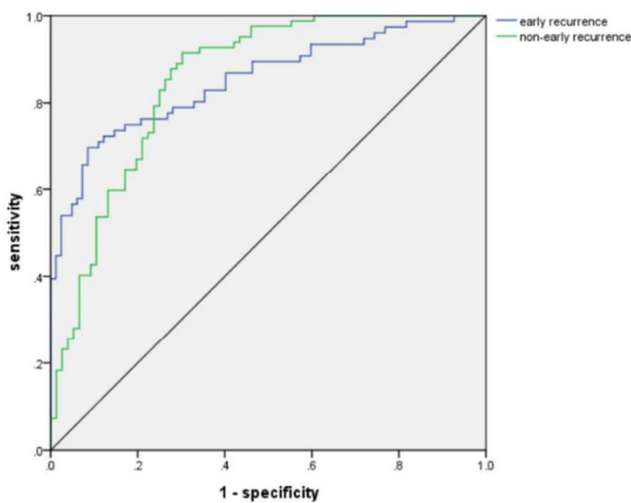


Figure 4. The result of blue is bagging (ROC=0.851).

reported in recent literature. The pathological features of small hepatocellular carcinoma are related to the development of the disease. The prediction model based on TNM, differentiation grade and microvessel invasion<sup>24</sup> can predict the recurrence time after sHCC resection, but this prediction model depends on the postoperative pathological diagnosis. Unable to predict the risk of recurrence before the operation, unable to identify patients who need to take auxiliary measures before and during operation. The pathological results can be obtained by biopsy in addition to operation. However, the biopsy is invasive and limited in materials, which can not show the lesions completely, and some malignancy may lead to the spread of the lesions. In this study the model is a pre-operative prediction that can be used to avoid the above-mentioned defects and to provide pre-operative prediction and a comprehensive preoperative and intraoperative assistance for patients with poor prognosis. A predictive model based on a hepatocyte-specific contrast agent. The liver cell-specific contrast agent can show the function of the liver, the specific contrast agent of the focal hepatocyte is based on the correlation of MVI and medical image feature, so it is indirect prognosis. The model of the current MVI and the recurrence time after the resection of the HCC has not been established, and the prediction model needs to increase the number of patients to take image examination and prolong the scanning time, as to the satisfactory examination effect is more difficult for some patients who can't be tolerated. Our study used historical data, did not increase the examination sequence, did not increase the patient's expense, did not increase the inspection time, did not increase the technician's labor volume. The prediction model based on the results of blood test, including HBV viral load, transaminase and Barcelona grade, can predict the recurrence time of liver cancer by AUC value of 0.645 [19, 27]. The AUC value of this study is 0.57, but imaging can show the spatial information and location relationship of the lesions. The spatiotemporal heterogeneity of tumor has been a key obstacle to the development of accurate medical methods. Image phenotype is the development direction of accurate medicine. It represents the quantification of tumor phenotype by the medical image. Observation of medical images can provide a comprehensive macro picture of tumor phenotype and its environment, which is very suitable for the development of tumor phenotype before and after quantitative therapy. As a noninvasive technique, medical imaging can be performed in low-risk situations, capturing important information for diagnosis, prognosis and prediction purposes [28]. Gene analysis is accurate and reliable. The AUC value of genotyping for predicting postoperative recurrence of HCC is 0.633 [29]. However, gene sequencing calculation is more expensive, compared with our study, this study is simple, easy and low cost. There is no need to collect additional data. At present, MR has been widely used in the screening and follow-up of sHCC. The examination parameters are gradually unified, the image quality is obviously improved, and the success rate of the examination is improved significantly. However, only 20 kinds of image information features are obtained by visual vision. Radiomics can extract more than 136 kinds of image features. The use of radiomics to analyze

medical images can significantly improve the image utilization rate, and make deep learning of image information to obtain a large amount of information. However, the relevance between extracted information and clinical concerns needs to be demonstrated.

Shortcomings and deficiency: 1, our study is a single center retrospective study, selective migration is inevitable; 2, our study sample size is limited, may not fully reflect the characteristics of sHCC radiomics; 3, this study only carried out mainstream ANN algorithm operation, there may be better algorithms to be further verified.

## 5. Conclusion

The radiomics features of T1 Mask images of MR LAVA sequence can be extracted and ANN analysis can be used to predict the recurrence time after resection of sHCC, but the accuracy needs to be further improved.

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