VHL Gene Mutation Prediction of Clear Cell Renal Cell Carcinoma Based on CT Images

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Abstract

Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cell carcinoma (RCC) with the highest mortality rate among genitourinary cancers. Clinical research has shown that genetic statuses are important risk factors of such disease. Therefore, identification of corresponding gene mutations has huge potential to help determine the precise treatment and predict prognosis. Inspirited by the concept of Radiomics and Radiogenomics, in this dissertation we attempted to develop an accurate prediction model to detect the von Hippel-Lindau tumor suppressor (VHL) gene mutation status, which is the most prevalent one in ccRCC, based on patients' computer tomography (CT) images replacing the traditional intrusive gene sequencing. Three major works have been done to deploy this research: semi-automatic segmentation of kidney tumor in CT images, fully automatic segmentation of kidneys and kidney tumor, and prediction of VHL gene mutation.

Introduction

Clinical experts has found that several visible semantic features on CT images are related to specified gene mutation incidents, such as calcifications, collecting system invasion etc. shown in Figure 1.

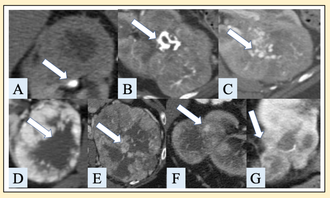
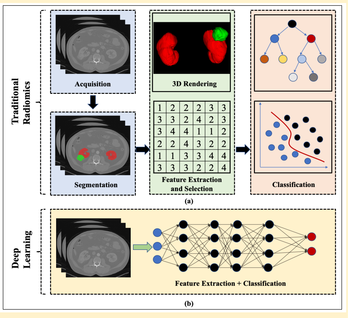


Figure 1. Semantic features related to underlying gene mutation status of ccRCC on CT images. A, Calcification. B, Collecting system invasion. C, Gross appearance. D, Necrosis. E, Nodular enhancement. F, Renal vein invasion. G, Ill-defined margin.

However, it is difficult to design these above specified semantic features manually. In contrast, under the concept of Radiomics, we employ the high-through features to build the prediction model. Two paradigms of radiomics are shown in Figure 2, based on traditional machine learning and deep learning respectively.

Figure 2. Over-simplified representation of Radiomics paradigms.(a) Traditional radiomics comprises image segmentation, feature extraction and selection, and classification. (b) Deep learning method integrates autonomous feature extraction and classification into the network with multi layers.



Therefore, our work follows the paradigm of Radiomics and comprehensively explores segmentation algorithms due to its fundamental position for the following feature extraction.

Semi-automatic Segmentation

Motivation: It is always challenging to segment tiny kidney tumor from a whole CT scan. Thus we first develop a semi-automatic method based on the manually extracted tumor ROI.

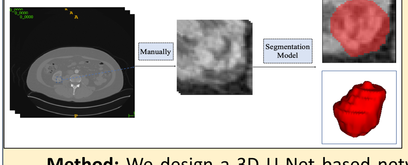
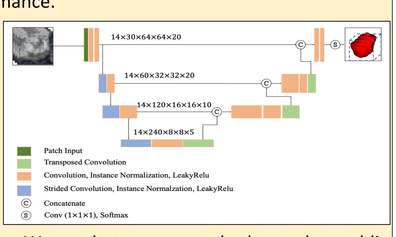


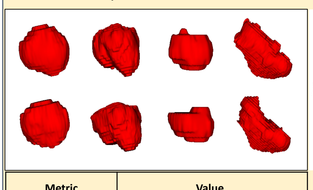
Figure 3. The scheme of semi-automatic segmentation. This model works on the ROI first marked by experts.

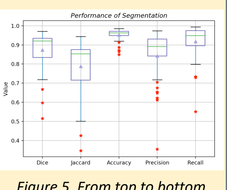
Method: We design a 3D U-Net based network enhanced by our powerful data augmentation techniques both applied during training and testing. This simple architecture is well devised according to the data's properties, hence showing excellent performance.

Figure 4. The architecture of our proposed 3D U-Net, with only 4 layers including the bottleneck.



Experiments: We evaluate our method on the public KiTS19 dataset, which consists of CT volume scans of 210 patients. Result on testing dataset, 42 patients, shows the Dice coefficient up to 0.87.





Metric	Value
Dice	0.8731
Jaccard	0.7878
Accuracy	0.9522
Precision	0.8432
Recall	0.9180

Figure 5. From top to bottom, left to right: (a) visualization of testing samples, (b) the boxplot of all the testing patients, (c) the average values of results.

Fully-automatic segmentation

Motivation: We furthermore attempt to develop a fully-automatic segmentation method, which segments the kidneys and kidney tumor simultaneously from the raw CT volumes. It is obviously more practical and benefits clinics further.

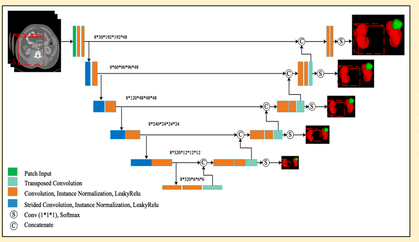
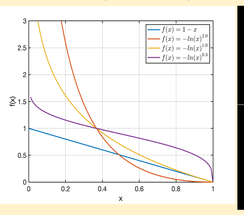
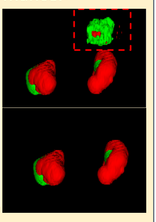


Figure 6. The architecture of our proposed multi-scale supervised 3D U-Net.

Method: We propose a multi-scale supervised 3D U-Net to segment the tiny tumor and kidneys at the same time. Also we employ exponential logarithmic loss and a component-based post-processing method to improve the performance.

Figure 7. Left to right: (a) the exponential logarithmic loss make the loss nonlinear, (b) component-based post processing.





Experiments: Our result on the KiTS19 challenge ranks the 7th place among all the 106 teams, with the Dice of kidney up to 0.974 and tumor to 0.818.

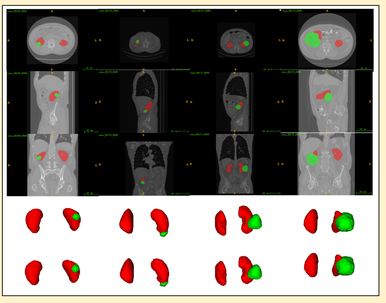


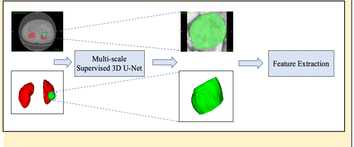
Figure 8. Results on the KiTS19 dataset, where each column denotes one patient, and from top to down they are images in transverse plane, sagittal plane, coronal plane, 3D view of inferences and the ground truth.

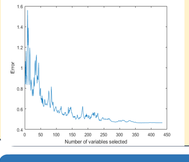
Prediction of VHL Gene Mutation

Abstract: We first segment the tumor using the pre-trained multi-scale supervised 3D U-Net, and then extract 460 dimensions features from the tumor area. A sparse representation based algorithm, as Equation (1), is employed to select features. Finally, we use ensemble subspace KNN as classifier and aggregate the slices results by voting. Experiment on TCGA-KIRC dataset shows the accuracy as 0.8.

Extracted Features:

- Intensity: 16
- Shape: 15
- Texture: 73
- Wavelet: 356





$$\hat{\alpha} = \arg\min_{\alpha} \|\boldsymbol{l} - \boldsymbol{F}\alpha\|_2^2 + \lambda \|\alpha\|_0 \quad (1)$$

Figure 9. From top to bottom, left to right: (a) features we extract from the tumor area on each slice, (b) scheme of the prediction, (c)the process of performing sparse representation.

Summary

These works are conducted aiming to develop a CT images based prediction model of underlying gene mutation status. The main contribution of this thesis is three fold.

First, as a compromise, we propose a semi-automatic segmentation method to segment the tumor area from ROIs. Second, we further propose an end-to-end fully-automatic method and achieve satisfying performance. At last, based on the pre-trained segmentation model, we employ the classic Radiomics methods to build a prediction model. The result on public dataset indicates that our method is meaningful and practical.