Non-Invasive Fuhrman Grading of Clear Cell Renal Cell Carcinoma Using Computed Tomography Radiomics Features and Machine Learning

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Abstract

Purpose: To identify optimal classification methods for computed tomography (CT) radiomics-based preoperative prediction of clear cells renal cell carcinoma (ccRCC) grade.

Methods and material: Seventy-one ccRCC patients (31 low-grade and 40 high-grade) were included in the study. All tumors were segmented manually on CT images, and three image preprocessing techniques (Laplacian of Gaussian, wavelet filter, and discretization of the intensity values) were applied on tumor volumes. In total, 2530 radiomics features (tumor shape and size, intensity statistics, and texture) were extracted from each segmented tumor volume. Univariate analysis was performed to assess the association of each feature with the histological condition. In the case of multivariate analysis, the following was implemented: three feature selection including the least absolute shrinkage and selection operator (LASSO), student’s t-test and minimum Redundancy Maximum Relevance (mRMR) algorithms. These selected features were then used to construct three classification models (SVM, random forest, and logistic regression) to discriminate the high from low-grade ccRCC at nephrectomy. Lastly, multivariate model performance was evaluated on the bootstrapped validation cohort using the area under receiver operating characteristic curve (AUC).

Results: Univariate analysis demonstrated that among different image sets, 128 bin discretized images have statistically significant different (q-value < 0.05) texture parameters with a mean of AUC 0.74±3 (q-value < 0.05). The three ML-based classifier shows proficient discrimination of the high from low-grade ccRCC. The AUC was 0.78 in logistic regression, 0.62 in random forest, and 0.83 in SVM model, respectively.

Conclusion: Radiomics features can be a useful and promising non-invasive method for preoperative evaluation of ccRCC Fuhrman grades.

Key words: RCC, Radiomics, Machine Learning,Computed Tomography
Introduction

Renal cell carcinoma (RCC) is the seventh most common cancer in the world, with a mortality rate of 140,000 per year (1). The most common types of renal cancer cells consists of clear cells RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC) (2, 3). Approximately 70% of kidney cancers are made up of ccRCC, pRCC accounts for 10-15% of kidney cancers, and chRCC is the least common type with only 5% of kidney cancer cases (4). A ccRCC diagnosis has a survival rate of less than 5-years and a higher risk of metastasis compared to pRCC and chRCC (5).

The most important step for a physician during cancer diagnosis and treatment is tumor staging and grading. Tumor grading is a description of the differentiation of tumor tissue cells relative to normal tissue cells. It is an indicator of how quickly a tumor is expected to grow and spread. The Fuhrman grading system is widely accepted (6) and is based on the assessment of the following cell nucleus characteristics: nuclear size, nuclear shape, and nucleolar prominence. Based on these assessments, the tumor will be classified into one of four different grades (I-IV). Grades I and II are considered as low-grade tumors with a favorable prognosis, while grades III and IV accounted for high-grade tumors and have an unfavorable prognosis (7).

Currently, fine needle aspiration (FNA) and imaging-guided biopsies are the gold standard methods for preoperative kidney tumor grading. However, these techniques have some drawbacks including infection, bleeding, tumor cells spreading, and provide limited information regarding the whole tumor. For example, a pathologist may diagnose a ductal carcinoma in situ (DCIS) as a non-invasive breast cancer based on the FNA breast sample obtained, when in fact, the patient has infiltrating ductal carcinoma (IDC) in a nearby area (8, 9).
In the recent years, several new non-invasive therapeutic methods for RCC have been developed, including radiofrequency ablation, cryoablation, and active surveillance (10). However, there lacks proper criterion for patient management with these non-invasive/minimally invasive treatment methods, and are often treated surgically post-diagnosis (11, 12). Therefore, it is desirable to produce individualized treatment strategies, where radical approaches (e.g. surgery) are taken for aggressive or high-grade tumors (III, IV) ccRCC, and conservative management (e.g. active surveillance) is provided for low-grade (I, II) lesions (13). To guide this decision, a non-invasive and accurate method for Fuhrman grading of renal cell carcinoma tumors preoperatively is desirable. For this purpose, two approaches are attractive for researchers at present. One is the Apparent diffusion coefficient (ADC) value in MRI imaging (14), and the other is CT-based semi-quantitative and quantitative techniques (15, 16).

Radiomics refers to the comprehensive quantification of tumor phenotypes in order to uncover disease characteristics that fail to be explained by the naked eye (17-20). In fact, it can be said that radiomics serves as the bridge between medical imaging and personalized medicine (21). Radiomics is a new era of science which faces many challenges, including image acquisition (22), reconstruction (23, 24), processing (25), and model development (26, 27) to provide robust and reproducible models. Previous studies have shown that the radiomics signature is valuable for differentiating high/low grade ccRCC tumors (28, 29). This study aims to construct a radiomics feature–based machine learning model to predict the Fuhrman Grade of ccRCC patients preoperatively.
Methods and Materials

Flow chart of the current study is illustrated in Figure 1

**Figure 1.** Illustrates the process flow followed in the paper.
Data was collected from cancer image archive databases from 1980 to 2016 (30). (Table 1)

Table 1. Clinical characteristics of Clear Cell Renal Cell Carcinoma

| Characteristic            | Patient (N=71) |
|---------------------------|----------------|
| Gender                    |                |
| Male                      | 51 (71%)       |
| Female                    | 20 (29%)       |
| Age, Y                    | 60.3 ± 11.7    |
| Grade                     |                |
| Low Grade (I,II)          | 31             |
| High Grade (III,IV)       | 40             |

Image acquisition technique

All patients had undergone a three phasic CT scan, including 1) a routine unenhanced CT scan, 2) a corticomedullary phase (CMP) contrast enhanced scan starting 40 seconds after the contrast material injection, and 3) a nephrographic phase (NP) contrast-enhanced scan performed 70–90 seconds after intravenous injection of iodinated contrast material. The iodine content (300 mg/mL) was infused at an infusion rate of 3 mL/s at an infusion dose of 80–100 mL. All subjects were scanned using a GE and Siemens CT machine with a tube voltage of 120 kV and a tube current of 150–300 mA with daily clinical reconstruction parameters.

Tumor Segmentation

In this study manual volume of interest (VOI) segmentation was performed and verified by a radiologist with 3D slicers.

Image pre-processing
Prior to feature extraction, the voxel size resampling method was applied on the images to create an isotropic dataset. This allowed comparisons between image data from different samples and scanners (31). Laplacian of Gaussian (LOG), wavelet decomposition (WAV), and discretization into 32, 64, and 128 bins preprocessing was performed to generate different set of features. For the LOG filter, different sigma values were used to extract fine, medium, and coarse features. Wavelet filtering yields 8 decompositions per level: all possible combinations of applying either a High or a Low pass filter in each of the three dimensions including HHH, HHL, HLH, HLL, LHH, LHL, LLH, and LLL. Preprocessing steps (including discretization, LOG, and wavelet) were also performed on all intensity, histogram, and textural features.

- **Feature extraction**

Radiomics features were extracted through the PyRadiomics open source python library. Extracted features were then categorized into the following subgroups. Firstly, shape features depict the shape of the tumor volume (VOI) and geometric properties such as volume, maximum surface, tumor compactness, and sphericity. Furthermore, first-order statistics features describe the distribution of voxel intensities within tumor volumes. This includes mean, median, maximum, and minimum values of the voxel intensities on the image. Second-order statistics features (known as textural features) are used as a method to measure inter-relationships between voxel distributions in tumor volumes. This is reflective of changes in image space gray levels. These feature groups include: gray-level co-occurrence matrix (GLCM), gray-level run-length matrix (GLRLM), gray-level size-zone matrix (GLSZM), and gray-level dependence matrix (GLDM) features (see Table 2).
### Table 2: Radiomics Features

| First Order Statistics (FOS) | Gray Level Co-occurrence Matrix (GLCM) | Gray Level Run Length Matrix (GLRLM) |
|-----------------------------|----------------------------------------|-------------------------------------|
| Energy                      | Autocorrelation                        | Short Run Emphasis (SRE)            |
| Total Energy                | Joint Average                          | Long Run Emphasis (LRE)             |
| Entropy                     | Cluster Prominence                     | Gray Level Non-Uniformity (GLN)     |
| Minimum                     | Cluster Shade                          | Gray Level Non-Uniformity Normalized (GLNN) |
| 10th percentile             | Cluster Tendency                       | Run Length Non-Uniformity (RLN)     |
| 90th percentile             | Correlation                            | Run Length Non-Uniformity Normalized (RLNN) |
| Maximum                     | Difference Average                     | Run Percentage (RP)                 |
| Mean                        | Difference Entropy                     | Gray Level Variance (GLV)           |
| Median                      | Difference Variance                    | Run Variance (RV)                   |
| Interquartile Range         | Range                                  | Run Entropy (RE)                    |
| Range                       | Joint Energy                           | Low Gray Level Run Emphasis (LGLRE) |
| Mean Absolute Deviation (MAD)| Joint Entropy                          | High Gray Level Run Emphasis (HGLRE) |
| Root Mean Squared (RMS)     | Inverse Difference Moment (IDM)        | Short Run Low Gray Level Emphasis (SRLGLE) |
| Standard Deviation          | Inverse Difference Moment Normalized (IDMN) | Short Run High Gray Level Emphasis (SRHGLE) |
| Skewness                    | Inverse Difference (ID)                | Long Run Low Gray Level Emphasis (LRLE) |
| Kurtosis                    | Inverse Difference Normalized (IDN)    | 16. Long Run High Gray Level Emphasis (LRHGLE) |
| Variance                    | Inverse Variance                       | **Gray Level Dependence Matrix (GLDM)** |
| Uniformity                  | Maximum Probability                    | Small Dependence Emphasis (SDE)     |
| 19. Uniformity              | Sum Average                            | Large Dependence Emphasis (LDE)     |
|                               | Sum Entropy                            | Gray Level Non-Uniformity (GLN)     |
|                               | 23. Sum of Squares                     | Dependence Non-Uniformity (DN)      |
|                               |                                       | Dependence Non-Uniformity Normalized (DNN) |
|                               |                                       | Gray Level Variance (GLV)           |
|                               |                                       | Dependence Variance (DV)            |
|                               |                                       | Dependence Entropy (DE)             |
|                               |                                       | Low Gray Level Emphasis (LGE)       |
|                               |                                       | High Gray Level Emphasis (HGE)      |
|                               |                                       | Small Dependence Low Gray Level Emphasis (SDLGLE) |
|                               |                                       | Small Dependence High Gray Level Emphasis (SDHGLE) |
|                               |                                       | Large Dependence Low Gray Level Emphasis (DLGLE) |
|                               |                                       | 14. Large Dependence High Gray Level Emphasis (DLHGLE) |
|                               |                                       | **Neighboring Gray Tone Difference Matrix (NGTDM)** |
|                               |                                       | 1. Coarseness                       |
|                               |                                       | 2. Contrast                         |
|                               |                                       | 3. Busyness                         |
|                               |                                       | 4. Complexity                       |
|                               |                                       | 5. Strength                         |

**Shape Features**

| Volume                      | Small Area Emphasis (SAE)              |
| Surface Area                | Large Area Emphasis (LAE)              |
| Surface Area to Volume ratio| Gray Level Non-Uniformity (GLN)        |
| Sphericity                  | Gray Level Non-Uniformity Normalized (GLNN) |
| Spherical Disproportion     | Size-Zone Non-Uniformity (SZN)         |
| Maximum 3D diameter         | Zone Percentage (ZP)                   |
| Maximum 2D diameter (Slice) | Gray Level Variance (GLV)              |
| Maximum 2D diameter (Column)| Zone Variance (ZV)                     |
| Maximum 2D diameter (Row)   | Zone Entropy (ZE)                      |
| Major Axis                  | Low Gray Level Zone Emphasis (LGZLZE)  |
| Minor Axis                  | High Gray Level Zone Emphasis (HGLZLZE) |
| Least Axis                  | Small Area Low Gray Level Emphasis (SALGLE) |
| Elongation                  | Small Area High Gray Level Emphasis (SAHGLE) |
| Flatness                    | Large Area Low Gray Level Emphasis (LALGLE) |
|                            | 16. Large Area High Gray Level Emphasis (LALHGLE) |
• **Univariate analysis**

For univariate analysis, early Pearson correlation tests between features were used to eliminate highly correlated features. Student’s t-tests were then used for comparisons between two groups. To control for the False Discovery Rate (FDR) in multiple hypothesis testing, the Benjamini-Hochberg (FDR) correction method was applied on p-values, and the ultimately reported q-value (32).

• **Feature Set preprocessing**

Due to the different ranges of radiomics features, without feature normalization, some features might appear as a larger weight, while others might appear as a lower weight. This depends on the distribution of feature values. To eradicate this, z-score normalization was applied to the feature values (33).

• **Feature Selection**

Three different feature selections methods (Table 3) were implemented in this framework: enhanced variable selection algorithms based on the least absolute shrinkage and selection operator methods (34), student's t-test (26, 27), and MRMR (Minimum Redundancy Maximum Relevance) algorithm.

• **Multivariate Machine Learning Classifier**

The following three classifiers (Table 3) were implemented and compared: logistic regression, random forest, and support vector machines (SVM).

• **Model evaluation**

The cross validation (CV) technique was applied in order to tune the model parameters. Furthermore, bootstrapped datasets were used for model evaluations. The predictive power of all
models was investigated using the area under the receiver operator characteristic (ROC) curve (AUC). All analysis and evaluation were performed by using the programming software R (version 3.5.2).

Table 3. Feature selection and Classification methods

| Feature Selection Methods | Abbreviation | Classification Methods | Abbreviation |
|---------------------------|--------------|------------------------|--------------|
| T student test            |              | Logistic Regression    | LR           |
| Minimum Redundancy Maximum Relevance | MRMR          | Random Forest          | RF           |
| least absolute shrinkage and selection operator | LASSO         | Support Vector Machine | SVM          |

Results

After applying inclusion/exclusion criteria, 71 (31 low-grade and 40 high-grade) patients were selected. The mean ages of the low- and high-grade groups were 60.05 and 60.08 years old, respectively. In total, there are 51 male and 20 female participants.

Univariate analysis demonstrated that among filtered and non-filtered images only the 128 bin discretized images have a statistically significant difference (q-value < 0.05) in texture parameters with a mean AUC of 0.74±3 (q-value < 0.05). These features include Long Run High Gray Level Emphasis from GLRLM (AUC: 77, q-value: 0.0002), Cluster Tendency from GLCM (AUC: 72, q-value: 0.001), Contrast from NGTDM (AUC: 74, q-value: 0.03), and Dependence Non-Uniformity from GLDM (AUC: 72, q-value: 0.04) (Figure 2).

Table 4 shows the AUC (95% CI) of three different ML-based classifiers. As shown in the table, there is a wide performance range from 0.5 to 0.86. Three different feature selection methods were applied prior to the implementation of each ML-based classifier to determine which is the
best for that model. The results demonstrated that the lasso method performs the best for logistic regression. Furthermore, the student’s t-test proved to be the best for random forest and SVM classifier models. Results for logistic regression suggested that 128 bin discretized images and fine LoG features have the highest performance with a mean of AUC 0.75. According to the results, the predictive performance of the random forest model has a range of 0.48 to 0.67. Among these, wavelet filtered images showed lowest performance and 128 bin discretized images showed highest performance. Among the three classifiers, SVM with a student's t-test feature selection presented the best predictive performance. SVM with Coarse LoG features demonstrated a mean AUC 0.83 (Figure 2).
Figure 2. AUC for discrimination of the high from low grade ccRCC. a. Univariate analysis of best predictor, b. LR model with 128 bin discretizing, c. SVM model with Coarse LoG filter, d. RF model with Wavelet filter. AUC: Area under receiver operating characteristic curve, LR: logistic regression, SVM: Support Vector Machine, RF: Random Forest.
|                  | AUC (95% CI) |      |      |
|------------------|-------------|------|------|
|                  | LR          | RF   | SVM  |
| Original image   | 0.68 ±0.08  | 0.62 ±0.07 | 0.76 ±0.07 |
| 32_bin           | 0.73 ±0.09  | 0.56 ±0.06 | 0.70 ±0.08 |
| 64_bin           | 0.70 ±0.07  | 0.55 ±0.06 | 0.65 ±0.07 |
| 128_bin          | 0.75 ±0.08  | 0.60 ±0.08 | 0.77 ±0.08 |
| LoG              |             |      |      |
| LoG_sigma.0.5    | 0.69 ±0.08  | 0.53 ±0.06 | 0.62 ±0.06 |
| LoG_sigma.1.0    | 0.74 ±0.11  | 0.53 ±0.02 | 0.64 ±0.04 |
| LoG_sigma.1.5    | 0.65 ±0.09  | 0.56 ±0.02 | 0.72 ±0.07 |
| LoG_sigma.2.0    | 0.68 ±0.09  | 0.55 ±0.06 | 0.74 ±0.08 |
| LoG_sigma.2.5    | 0.73 ±0.11  | 0.54 ±0.05 | 0.76 ±0.07 |
| LoG_sigma.3.0    | 0.74 ±0.10  | 0.55 ±0.09 | 0.77 ±0.06 |
| LoG_sigma.3.5    | 0.62 ±0.06  | 0.57 ±0.04 | 0.79 ±0.08 |
| LoG_sigma.4.0    | 0.65 ±0.09  | 0.60 ±0.12 | 0.81 ±0.06 |
| LoG_sigma.4.5    | 0.62 ±0.06  | 0.62 ±0.06 | 0.83 ±0.08 |
| LoG_sigma.5.0    | 0.70 ±0.08  | 0.56 ±0.05 | 0.78 ±0.06 |
| WAVELET          |             |      |      |
| Wav_HHL          | 0.62 ±0.05  | 0.58 ±0.04 | 0.71 ±0.07 |
| Wav_HLH          | 0.65 ±0.06  | 0.55 ±0.08 | 0.62 ±0.06 |
| Wav_LHH          | 0.67 ±0.08  | 0.53 ±0.03 | 0.65 ±0.07 |
| Wav_HLL          | 0.62 ±0.06  | 0.57 ±0.05 | 0.76 ±0.08 |
| Wav_LLH          | 0.68 ±0.07  | 0.56 ±0.06 | 0.59 ±0.08 |
| Wav_LLL          | 0.62 ±0.06  | 0.53 ±0.05 | 0.65 ±0.08 |
| Wav_LHL          | 0.62 ±0.06  | 0.55 ±0.08 | 0.75 ±0.10 |
Discussion

There is an important association between the Fuhrman grade and patient’s prognosis. There are several non-invasive methods proposed to predict the ccRCC Fuhrman grade preoperatively. In MR imaging, the apparent diffusion coefficient (ADC) value is known to be an indicator of tumor activity. Several studies have assessed the utility of the apparent diffusion coefficient (ADC) in distinguishing low- and high-grade clear cell RCC (14, 35). These studies showed that magnetic resonance imaging (MRI) has an acceptable predictive accuracy in the preoperative detection of the high grade RCC (AUC was 0.80) (36). However, MRI is a costly process and a wide range of ADC values for ccRCC have been reported in the literature (37, 38). Therefore, their repeatability needs to be validated further. Furthermore, a large number of CT-based semi-quantitative and quantitative studies have attempted to classify low- and high-grade ccRCC (15, 16). These studies showed that CT is a promising method for this work.

Radiomics approach convert medical images into quantitative, high-dimensional, and mineable features to predict tumor status. However, the abundance of predictive modeling techniques means that it is important to choose the correct one for predicting tumor status. As some previous radiomics studies (16, 28), for Fuhrman grade prediction did not include shape features in their analyses, this study combined shape features and texture features to differentiate low- and high-grades of ccRCC. It was observed that shape features cannot be ignored from multivariate machine learning models.

Univariate analysis of extracted radiomics features demonstrated that among filtered and non-filtered images only the 128 bin discretized images showed statistically significant texture parameters. In a similar univariate analysis, Zhan Feng et al (29) analyzed CT texture parameters and found effective quantitative parameters to evaluate the heterogeneity of ccRCC. After applying
the LoG filter, they reported that only entropy has a statistically significant difference after FDR corrections in all image phases. In this study four features showed statistically significant differences between two groups. These features include: Long Run High Gray Level Emphasis from GLRLM, Cluster Tendency from GLCM Contrast from NGTDM, and Dependence Non-Uniformity from GLDM matrix. Among these features, the Long Run High Gray Level Emphasis demonstrated the highest AUC (AUC: 77, q-value: 0.0002).

The first machine learning model applied in this study was logistic regression. It is a machine learning classification algorithm used to predict the class probability of a categorical dependent variable. It was observed that among three different features selection methods, the best results for the Logistic Regression model was obtained when using the lasso algorithm. These results suggest that the AUC logistic regression model is approximately similar to results obtained in previous studies. Juice Dinga et al (16) used a texture-score based logistic regression model on a training cohort and the AUC was 0.878. When predictive models were applied on the validation cohort, good results were still obtained (AUC > 0.670). Jun Shu et al (39) extracted radiomics features from the corticomedullary (CMP) and nephrographic phases (NP) of CT images of all patients. They constructed logistic regression classification models to discriminate high and low grades ccRCC. Application of the model on CMP and NP showed an AUC of 0.766 (95% CI:0.709-0.816) and 0.818 (95% CI:0.765-0.838), respectively. Another machine learning model applied was random forest, which is an ensemble learning method that consists of a collection of decision trees. It uses a weighted average of those trees for the final decision (40). It works correctly for a large range of data, but is susceptible to overfitting. In this study, applying the random forest model on the dataset yielded unsatisfactory results (table 1). The SVM was the best-performing classifier in this study. SVM creates a decision boundary between two classes that
enables the prediction of labels from one or more feature vectors. After applying the SVM model on filtered and unfiltered images, the best classification result was obtained when coarse LoG features were used with a mean AUC of 0.81. LoG filtering is an advanced image-filtering method that combines Laplacian filtering and Gaussian filtering. In a similar single-center retrospective study (28), the performance of quantitative CT texture analysis combined with different ML based classifier methods is evaluated for discriminating low and high grade ccRCC. Despite differences in procedure, they also determined that highest predictive performance is achieved by an SVM classifier. In summary, both of these studies support each other with a similar conclusion that CT texture analysis is a useful and promising non-invasive method to predict the Fuhrman grades of ccRCCs preoperatively.

The limitations of this study were as follows. (1) This study was a retrospective study with no external data validation, (2) the sample size was relatively small, (3) since the tumor boundary is manually drawn, the interference of the volume effect cannot be completely avoided.

**Conclusion**

The results of this study show that CT based SVM classifier with t-test features selection can be a useful and promising non-invasive method for the prediction of low and high Fuhrman nuclear grade ccRCCs. Additionally, the results demonstrated that 128 bin discretized pre-processing is an effective method under these conditions. Large, multicenter and externally prospective studies are needed for further validation of CT base machine learning models.
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