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Clinical-radiomic model in advanced kidney cancer predicts response to tyrosine kinase inhibitors

ADRIÁN A. NEGREROS-OSUNA[1], DIEGO A. RAMÍREZ-MENDOZA[1], CLAUDIO CASAS-MURILLO[1], ABRAHAM GUERRA-CEPEDA[2], DAVID HERNÁNDEZ-BARAJAS[2] and GUILLERMO ELIZONDO-RIOJAS[1]

Departments of [1]Radiology and [2]Oncology, School of Medicine and University Hospital 'Dr. José Eleuterio González', Autonomous University of Nuevo Leon, Monterrey, NL 64460, México

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Abstract. Renal cancer has a global incidence and mortality of 2.2 and 1.8%, respectively. Up to 30% of these patients are intrinsically resistant to tyrosine kinase inhibitors (TKI). The National Comprehensive Cancer Network guidelines do not include any predictive factors regarding response to systemic therapy with TKI in recurrent and advanced diseases. The present study aimed to explore whether a model based on radiomics could predict treatment response in patients with advanced kidney cancer treated with TKIs. The current study included 62 patients with advanced kidney cancer (stages 3 and 4) that underwent a CT scan in the arterial phase from March 2016 to November 2020. Texture analysis was run on the largest cross-sectional area of the primary tumor from each CT scan. A total of three different models were built from radiomics features and clinical data to analyze them by logistic regression and determine whether they correlated with the response to TKI. A receiver operating characteristic curve analysis was performed in each model to calculate the area under the curve (AUC) and the 95% confidence interval (CI). Significant radiomics features and clinical variables were identified and then a clinical model was created (AUC=0.90; sensitivity 75%; specificity 82.35%; CI 95%, 0.78-1.00), a radiomic model (AUC=0.66; sensitivity 16.67%; specificity 89.47%, CI 95%, 0.45-0.87) and a combined model (AUC=0.94; sensitivity 83.33%; specificity 94.12%; CI 95%, 0.84-1.00). Overall, models based on clinical data and radiomics could anticipate response to systemic therapy with TKI in patients with advanced kidney cancer.

Correspondence to: Dr Guillermo Elizondo-Riojas, Department of Radiology, School of Medicine and University Hospital 'Dr. José Eleuterio González', Autonomous University of Nuevo Leon, Avenida Francisco I. Madero S/N, Monterrey, NL 64460, México
E-mail: elizondoguillermo@hotmail.com

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Introduction

Renal cancer has a global incidence and mortality rate of 2.2 and 1.8%, respectively (1), ranking the eighth cause of cancer in America. Approximately 16% are metastatic at the time of diagnosis (2).

At present, immunotherapy is the first-line treatment for renal cell cancer. However, its high cost makes it difficult to obtain in some regions (3). Therefore, in this subgroup of patients with advanced disease, therapy with Tyrosine Kinase Inhibitors (TKI) drugs such as Sunitinib and Pazopanib has become the standard of treatment in patients with favorable risk and some with intermediate and poor risk since 2005 (4-6). Nevertheless, up to 30% of these patients are intrinsically resistant to this type of therapy (7). High stages are associated with a five-year survival of 12% (8). Although TKI increases this rate, median overall survival remains around 8 and 11 months (9-11).

Currently, the National Comprehensive Cancer Network (NCCN) guidelines do not include any predictive factors regarding response to systemic therapy with TKI in recurrent and advanced disease, but rather stratify patients into risk groups according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) scale (5). Therefore, exploring potential biomarkers that identify patients with a high probability of failure to systemic therapy with TKI is crucial to avoid spending valuable time and resources.

Radiomics, including Tomographic Texture Analysis (TTA), are not new imaging techniques (12). Recent advances in computational processing and the availability of technology have facilitated its application in imaging studies. Radiomics extract large amounts of quantifiable features from the images that are impossible to see for the human reader and reflect the underlying biological components in terms of texture and shape. Radiomic analysis is a tool that can be used as a biomarker for tumor characterization, to assess response to treatment, and as a prognostic factor. This imaging tool predicted the development of metastatic disease (13) and five-year survival in patients with colorectal cancer (14,15) and served as a prognostic factor in esophageal cancer (16). Furthermore, its association with tumor glucose metabolism and stage has been demonstrated in non-small cell lung cancer (17).

In terms of prediction, Smith *et al* found a correlation with the survival of patients with melanoma treated with

anti-angiogenic drugs (18). Regarding kidney tumors, the Radiomic texture analysis showed an area under the curve (AUC) of 0.80 to discriminate between renal cell carcinoma and papillary carcinoma (19). In a recent study, radiomic texture analysis parameters Entropy (ENT) and standard deviation (SD) showed a correlation with overall survival in clear cell carcinoma treated with Sunitinib (20).

This study aimed to determine whether Radiomic parameters can predict response to systemic therapy with TKI in advanced stage renal cancer.

Materials and methods

Design. We carried out a retrospective study approved by our IRB under the number RA20-00007, requiring no informed consent. We obtained the patient information from the medical record system at the Oncology Department from March 2016 to November 2020. Inclusion criteria were the following: adults older than 18 years old, diagnosis of renal-cell cancer in stages 3 or 4 by imaging and confirmed by histopathology, available images of contrast-enhanced abdominal CT in the arterial phase before treatment in our system, treated with TKI (i.e., sunitinib and pazopanib). Exclusion criteria were the presence of synchronous tumors, baseline CT abdomen performed after one month of treatment, clinical stages 1 and 2, incomplete or unavailable clinical and imaging records, and treatment with radiochemotherapy.

Other variables obtained from the medical record were sex, age, IMDC risk, the Eastern Cooperative Oncology Group (ECOG) score, smoking status, and comorbidities (i.e., diabetes, hypertension, and heart disease).

Imaging protocol. All the baseline CT scans were performed on a General Electric CT99 Light Speed scanner at the Radiology Department. CT scans parameters were as follows: tube voltage 120 kVp, a slice thickness 2.5 mm and increment of 1.5 mm. A weight- based dose was used to determine the amount of intravenous contrast media administered of either Optiray® 300 mg/ml (Guebert, Villepinte, France) or Ultravist® 375 mg/ml (Bayer, Whippany, USA). This was followed by a 20-30 ml saline chaser at 3 ml/sec.

Radiomics. Texture analysis was performed using the texture protocol of LifeX software version 6.0 (https://lifexsoft.org/) (21). A single operator drew one region of interest (ROI) on the largest cross-sectional area of the primary tumor from each CT scan in the arterial phase (Fig. 1). We set the software to obtain features in the following categories: texture features (Grey Level Co-occurrence Matrix, GLCM; Neighborhood Grey-Level Difference Matrix, NGLDM; Grey-Level Run Length Matrix, GLRLM; Grey-Level Zone Length Matrix, GLZLM), shape indices (sphericity, compacity, volume), first-order features from the histogram (entropy, entropy_log2, energy), conventional indices (quartiles, min, mean, max, peak, skewness, kurtosis), and discretized indices (quartiles, min, mean, max, peak, skewness, kurtosis). We obtained a total of 58 radiomic parameters.

Statistical analysis. We applied a backward stepwise selection process to obtain the variables for building the logistic regression models (22). We began with a model composed of all the variables. Then we tested the elimination of each variable to choose the ones that best fit the model to the desired criterion (in this case, response to treatment). The goal is to reduce the predictor variables to those necessary and contribute most of the variance in the model. The process is done automatically by the software. After this step, we ran a logistic regression analysis of the variables in three models to explore a possible correlation with the systemic therapy response.

We performed a Receiver Operating Characteristic (ROC) curve analysis to calculate the AUC and the 95% confidence interval (CI) in each model. We performed all statistical analysis in Stata/IC 16.1 (https://www.stata.com/).

Results

Of 348 patients initially considered, we excluded those with incomplete or unavailable clinical and imaging records (n=144), other treatments (n=132), clinical stage 1 and 2 (n=8), non-renal synchronous tumors (n=2), and baseline CT performed after one month of treatment (Fig. 2). The final cohort comprised 62 patients (mean age 57.5, +/- 12.2, 18 women and 44 men) (Table I).

Most common sites of metastases were the following: lymph nodes 44/62 (71%), lung 42/62 (68%), adrenal glands 20/62 (32%), brain 18/62 (29%), liver 14/62 (23%), soft tissue 14/62 (23%), and bone 10/62 (16%). The primary tumor was in the right kidney in 36/62 (58%) and in the left kidney 26/62 (42%) (Table II).

After the stepwise selection, we selected the following variables to be part of the radiomic features to build the logistic regression model. We divided the variables into clinical (sex, age, tumor size, lymph nodes, risk, ECOG scale, therapy) and radiomic features (glcm_entropy_log2, conventional_HUmean, and glcm_dissimilarity).

Three different models were tested to predict response to systemic therapy, i.e., the clinical model (clinical data alone), the radiomic model (radiomic features alone), and a combined model (clinical data plus radiomic features). After performing the ROC curve analysis, the clinical model showed an AUC of 0.90 with a sensitivity and specificity of 75 and 82.35% respectively (standard error of 0.06, 95% CI 0.78-1.00), the radiomic model an AUC of 0.66 with a sensitivity and specificity 16.67 and 89.47% respectively (standard error of 0.11, 95% CI 0.45-0.87), and the combined model an AUC of 0.94 with a sensitivity and specificity 83.33 and 94.12% respectively (standard error of 0.04, 95% CI 0.84-1.00) (Fig. 3).

Discussion

Although novel therapies exist, up to 30% of patients present intrinsic resistance and early treatment failure, this is a complex problem for which we do not have a prediction method (23,24). Furthermore, an early progression is related to lower overall survival and is costlier than a late one (25).

In this study, we have tested three models to predict the response to treatment to TKI in advanced renal cancer, finding that the radiomic information can improve the efficacy of the algorithm to predict response shifting from an AUC of 0.90 in the clinical model alone to 0.94 when combining with radiomic features.

The concept of applying radiomics to predict response is not new (26-29). Zhi Ji *et al* predicted response to immunotherapy

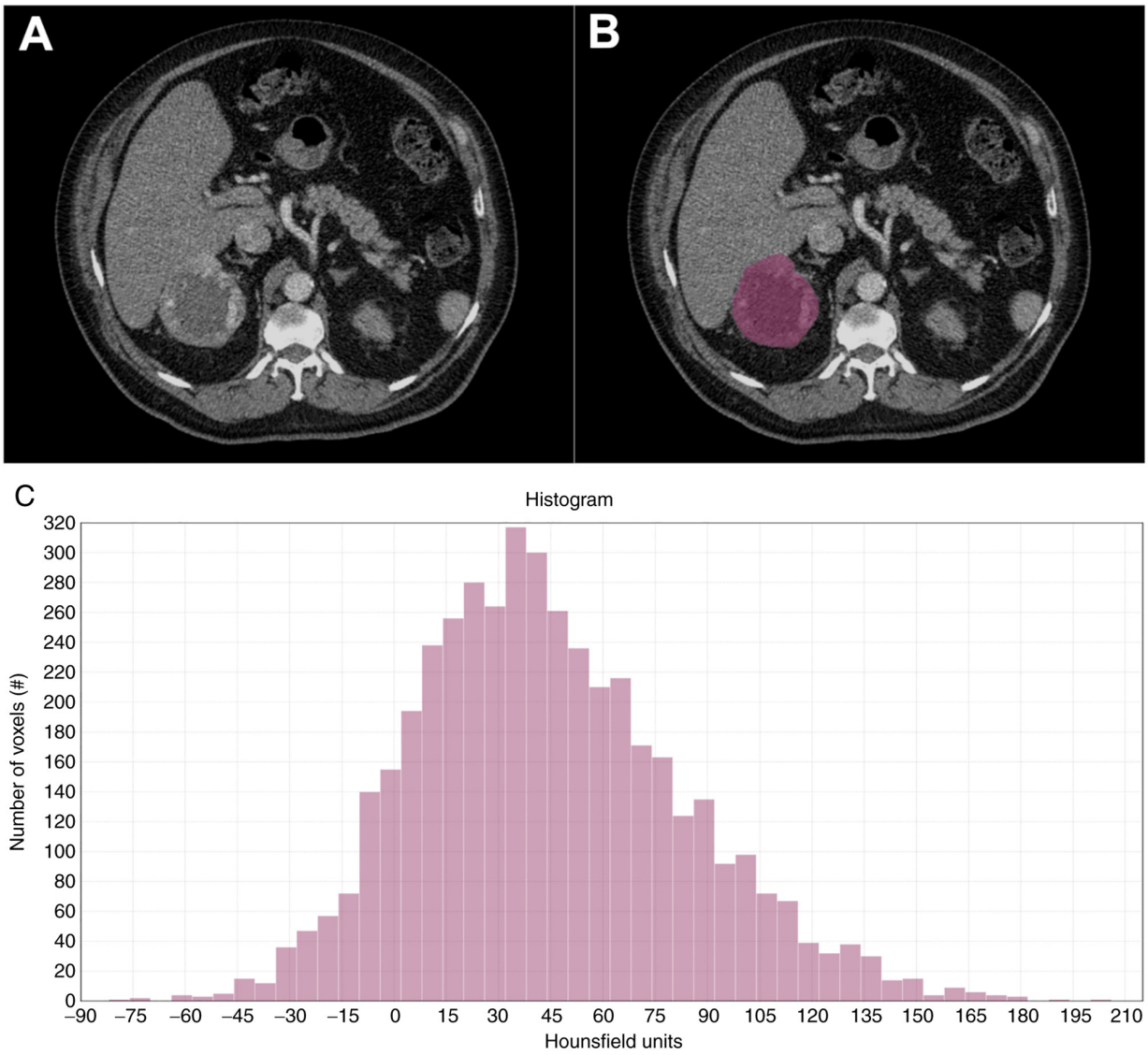

Figure 1. Texture analysis process. (A) Computed tomography abdomen with contrast in arterial phase and (B) region of interest selection. (C) Histogram showing the distribution of Hounsfield Units.

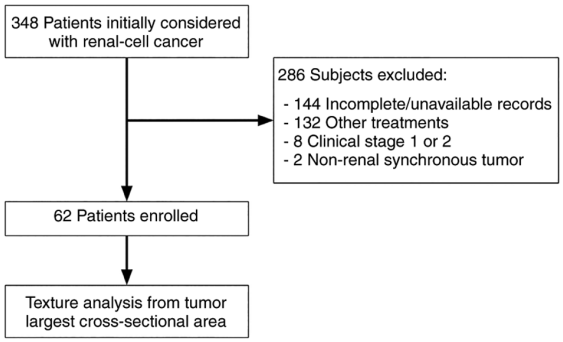

Figure 2. Patient selection process.

utilizing radiomics in 87 patients with gastrointestinal malignant tumors obtaining a model with an AUC of 0.80 with a sensitivity and specificity of 83.3 and 88.9% respectively. In this model, they did not combine clinical data (26). Yang B *et al* predicted response to immunotherapy in 92 patients with lung cancer. The model combined 15 radiomic features and clinicopathologic data obtaining an AUC of 0.90, a sensitivity of 85.7%, and a specificity of 88.4% (27). We strongly believe that adding clinical data to the model is paramount to obtaining a robust model. Park K *et al* built a Radiomics-based model to predict response to anti-PD-1/PD-L1 in 62 patients with metastatic urothelial carcinoma. The AUC of this model was 0.87 (95% CI, 0.65-0.97) and 0.88 (95%CI, 0.67-0.98) for predicting objective response and disease control, respectively (28). Radiomics has shown a promising performance regarding renal cell cancer. In respect of RCC subtypes, Zhang *et al* built a radiomic model from different CT phases (non-contrast, corticomedullary, nephrographic, and excretory phases). With this, they obtained an accuracy of 0.80 and an AUC of 0.89 for distinguishing clear cell RCC from non-clear cell RCC. The sensitivity and specificity for clear cell RCC were 0.85 and 0.83; for papillary RCC 0.60 and 0.91; and for chromophobe RCC 0.66 and 0.91, respectively (29).

Regarding overall survival, Nazari *et al* created a combined model (radiomic features and patient stage and grade) to

Table I. Demographic characteristics of the study population.

Variables	Patients (n=62)
Age, mean (SD)	57.5 (12.2)
Sex, n (%)	
Male	44 (71%)
Female	18 (29%)
Risk, n (%)	
Favorable	7 (11%)
Intermediate	35 (56%)
Poor	20 (32%)
ECOG scale, n (%)	
0	22 (35%)
1	24 (39%)
2	9 (15%)
3	7 (11%)
Treatment, n (%)	
Pazopanib	36 (58%)
Sunitinib	26 (42%)
Treatment response, n (%)	
No	38 (61%)
Yes	24 (39%)

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table II. Characteristics of the kidney tumors.

Variables	Patients (n=62)
Size in mm, mean (SD)	101.0 (32.2)
Histological type, n (%)	
Renal-cell cancer	62 (100%)
Location, n (%)	
Right kidney	36 (58%)
Left kidney	26 (42%)
Site of metastasis, n (%)	
Lymph nodes	44 (71%)
Lung	42 (68%)
Adrenal glands	20 (32%)
Brain	18 (29%)
Liver	14 (23%)
Soft tissue	14 (23%)
Bone	10 (16%)

SD, standard deviation.

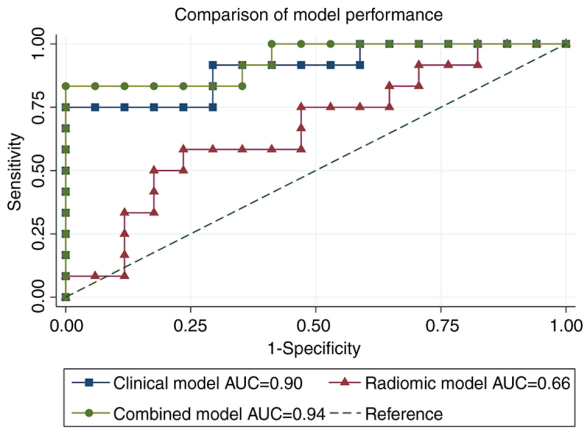

Figure 3. Comparison of model performance. Receiver Operating Characteristic curves of the three different models for treatment prediction. AUC, area under the curve.

predict the risk of death in 5 years in patients with clear cell RCC. This model had an AUC of 0.95-0.98, an accuracy of 0.97-0.98, sensitivity of 0.93-0.98, and specificity of 0.93-0.96 with a 95% confidence interval (~1)' (30).

Some limitations in our study are that we included a small number of participants since only a few patients in our clinic have access to the treatment with TKI, which also affected the number of features utilized in the model to avoid overfitting. A critical step for internal and external validation of our models is to test them with different datasets. Unfortunately, lack of recruitment and limited access to external databases hampers this process.

One strength in the study is that this is the first study aiming to predict response to TKI in advanced Kidney cancer. To find this type of predictor is paramount to avoid the expenditure of valuable time and monetary resources on unsuccessful therapies. Although we found a promising model to predict response combining radiomic features and clinical information, the mentioned limitations prevent us from making solid conclusions. Collaborative efforts should be made between specialties to build robust models that integrate essential clinical, genetic, and radiological information. Moreover, the institutions should guarantee the quality and reproducibility of data to shape accurate databases.

In summary, models combining clinical data and radiomics could anticipate response to systemic therapy with TKI in patients with advanced kidney cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GE and AAN contributed to the conception and design of the study. AAN, DAR, GE, CC, AG, and DH collected the data. CC performed the imaging analysis. AAN and DAR performed the statistical analysis. All authors contributed to the discussion of the results, manuscript writing and review.

AAN and AG confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the University Hospital 'Dr. José Eleuterio González' (Monterrey, México) under approval number RA20-00007, which required no informed consent from the patients.

Patient consent for publication

Not applicable.

Authors' information

ORCID: Dr Adrián A. Negreros-Osuna, 0000-0002-9800-0169; Dr Diego A. Ramírez-Mendoza, 0000-0002-5067-8317; Dr Claudio Casas-Murillo, 0000-0002-4353-6919; Dr Abraham Guerra-Cepeda, 0000-0002-6408-1116; Dr David Hernández-Barajas, 0000-0001-8899-000X; Dr Guillermo Elizondo-Riojas, 0000-0002-9555-430X.

Competing interests

The authors declare that they have no competing interests.

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