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Radiomics to predict immunotherapy efficacy in advanced renal cell carcinoma: A retrospective study

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ABSTRACT

Immunotherapy has become a cornerstone for the treatment of renal cell carcinoma. Nevertheless, some patients are resistant to immune checkpoint inhibitors. The possibility to identify patients who cannot benefit from immunotherapy is a relevant clinical challenge. We analyzed the association between several radiomics features and response to immunotherapy in 53 patients treated with checkpoint inhibitors for advanced renal cell carcinoma. We found that the following features are associated with progression of disease as best tumor response: F_stat.range ($p < .0004$), F_stat.max ($p < .0007$), F_stat.var ($p < .0016$), F_stat.uniformity ($p < .0020$), F_stat.90thpercentile ($p < .0050$). Gross tumor volumes characterized by high values of F_stat.var and F_stat.max (greater than 60,000 and greater than 300, respectively) are most likely related to a high risk of progression. Further analyses are warranted to confirm these results. Radiomics, together with other potential predictive factors, such as gut microbiota, genetic features or circulating immune molecules, could allow a personalized treatment for patients with advanced renal cell carcinoma.

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Introduction

Treatment options for metastatic renal cell carcinoma (RCC) are increased during the last years, allowing a relevant survival advantage.[1] After a long time characterized by tyrosine kinase inhibitors (TKIs) only, the treatment algorithm has been dramatically changed from the introduction of immune checkpoint inhibitors (ICIs).[2,3] More recently, combinations of TKIs and ICIs have been demonstrated to improve the clinical outcome.[4–6] The benefit of ICIs has also been shown in adjuvant setting.[7] Therefore, immunotherapy has gained a fundamental role in the treatment of RCC, in different stages of disease and in various clinical settings. Indeed, an ICI can be employed as adjuvant therapy, in first-line metastatic disease associated with TKI or in subsequent lines of metastatic RCC. Furthermore, the combination of anti-PD-1 and anti-CTLA-4 can be considered for intermediate-poor risk patients with advanced disease.[3]

Although the robust data supporting ICIs, no predictive factor is available to select patients who can benefit more from immunotherapy.[8] In addition, selected patients with favorable prognosis according to the International metastatic RCC database consortium (IMDC) could benefit from TKI.[9] Therefore, the possibility to choose the best therapeutic option for every patient has relevant clinical value.

In the recent years, many advances have occurred in the field of omics sciences, investigating several aspects of cell biology, growth pathways and treatment efficacy.[10] Among omics sciences, radiomics represents a measure of quantitative parameters extracted from medical images.[11] These features can be useful to define the tumor heterogeneity.[12–14] Emerging data highlight the role of radiomics in predicting the efficacy of immunotherapy in different tumors.[15–18]

In this study, we evaluated the texture parameters of CT scans in patients affected by metastatic renal cell carcinoma treated with ICIs in order to explore the correlation between the radiomics features and the response to immunotherapy.

Patients and methods

Medical records of all patients with advanced renal cell carcinoma who underwent immunotherapy at Fondazione Policlinico Universitario Agostino Gemelli IRCCS were reviewed. Patients were considered if they met the following criteria: age ≥ 18 y, prevalent clear cell component, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, performance status (Eastern Cooperative Oncology Group) 0–2, no central nervous system metastases.

Staging Computed Tomography (CT) examinations were performed using a multi-detector CT (MDCT) scanner with 64 rows (Light Speed VCT XT, GE Healthcare Medical Systems, USA). The same acquisition protocol was used for all the CT series according to our institutional practice. Gross tumor

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volumes (GTVs) were manually contoured on portal phase of the baseline CT images using a dedicated software (Eclipse, Varian Medical Systems, USA). Response was evaluated on the images according to RECIST version 1.1.

Progression-free survival (PFS) was calculated from the first day of immunotherapy administration to progression or death for any cause. Survival was calculated from the first day of immunotherapy to death for any cause. PFS and overall survival (OS) were evaluated with the Kaplan–Meier method. The differences between patients' subgroups were analyzed with the Log-rank test.

The radiomics analysis was performed with Moddicom, an R library compliant with the Image Biomarker Standardization Initiative.[19,20] From all the contoured GTVs, 231 radiomics features were extracted, belonging to three main families: morphological (related to the shape of the region of interest – ROI – e.g.: volume, surface vs volume ratio, etc.), histogram-based (related to the distribution of the gray-level histogram, e.g.: mean, skewness, kurtosis, etc.) and textural (related to the visible texture of the tumor, e.g.: large zone high gray level emphasis, gray level non-uniformity, etc.).

Considering the limited sample size, in order to provide a more robust statistical test, a univariate non-parametric analysis (Mann–Whitney test) and a cross-correlation measure based on the Pearson correlation coefficient were preferred over the fitting of a parametric model (such as a proportional hazard model). Finally, the two most significant and not cross-correlated features were used to build a space to plot the distribution of the cases. All the shown p.values are the raw p.values (uncorrected) to provide transparent results. In the univariate analysis, we explored the entire set of the covariates instead of limiting the investigation on a restricted set of selected features.

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the subjects involved in the study.

Results

Fifty-three patients who started immunotherapy from September 2017 to September 2020 were considered, 32 males and 21 females. Median age was 66.8 y (range 36–87). Twenty patients received the combination nivolumab + ipilimumab in first-line setting, and 33 patients were treated with nivolumab after 1 or 2 previous systemic treatments. Patients' characteristic are reported in Table 1.

PFS of patients treated with ICIs in first-line setting was 9.5 months (Figure 1a) and in second/third-line setting was 7.0 months (Figure 1b).

Considering the whole population, 18 patients (34%) achieved an objective response (complete response and partial response) to checkpoint inhibitors, 17 (32) a disease stabilization, while 18 patients (34%) had progression as best response. In first-line setting, response rate was 50% (10 out of 20 patients) and disease control (complete response, partial response and stable disease) was 80%. In second/third line, response rate was 24.2% (8 out of 33 patients) and disease control 57.6%. Responses are described in Table 2. Survival of patients with disease control was 32.4 months, while survival of patients with progression was 11.7 months ($p = .008$, HR 0.41, 95% CI 0.18–0.92 – Figure 2). Considering the population receiving ICIs as first-line treatment, median survival was not reached for patients with disease control and 7.2 months for patients reporting a progression as best response ($p = .06$, HR 0.28, 95% CI 0.07–1.16 – Figure 3a). Among the patients treated with ICIs in second-third line, the subjects obtaining a disease control had a median survival of 32.4

Table 1. Patients' characteristics.

	N. (%)
M/F	32/21
Median age (range)	66.8 y (36–87)
1st line	
Intermediate/poor prognosis	20 (100)
2nd–3rd line	
Good prognosis	12 (36.4)
Intermediate/poor prognosis	21 (63.6)
Metastatic sites	
lung	53 (100)
liver	15 (28.3)
lymph-nodes	28 (52.8)
bone	25 (47.2)
other (thyroid, parotid, soft tissue)	9 (17)

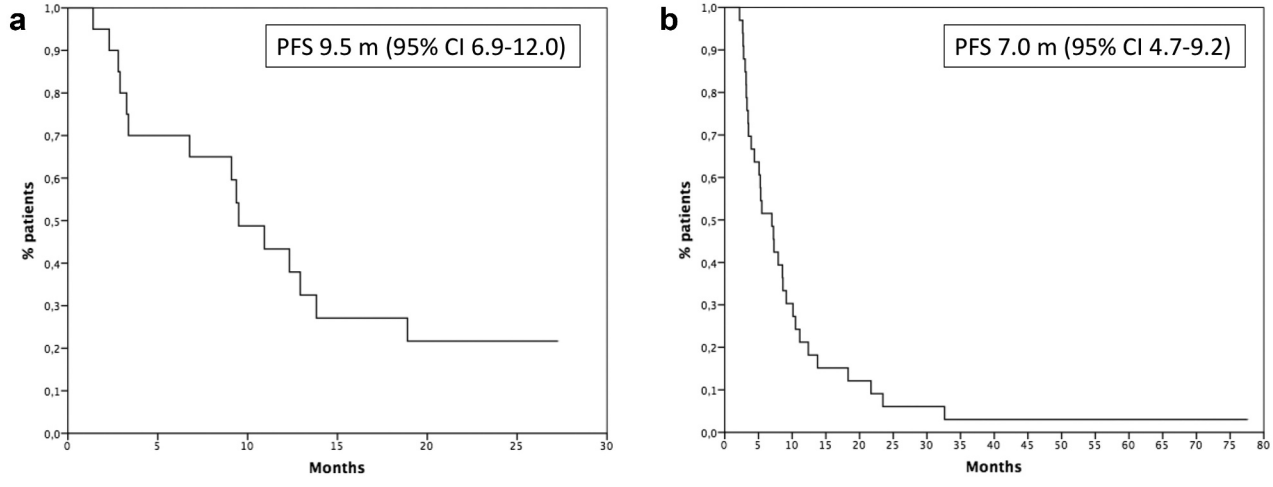

Figure 1. Progression free survival of patients in first (a) and second/third line setting (b).

Table 2. Response rate.

	N. of patients	RR (%)	CB (%)
First line			
Complete response	2	}50	}80
Partial response	8		
Stable disease	6		
Progression	4		
Second/third line			
Complete response	0	}24.2	}57.6
Partial response	8		
Stable disease	11		
Progression	14		

RR: response rate (complete response + partial response).
CB: clinical benefit (complete response + partial response + stable disease).

months, while the patients with disease progression had a survival of 11.7 months ($p = .04$, HR 0.44, 95% CI 0.19–1.00 – Figure 3b).

Several radiomics features were associated with the progression of disease as best response: F_stat.range ($p < .0004$), F_stat.max ($p < .0007$), F_stat.var ($p < .0016$), F_stat.uniformity ($p < .0020$), F_stat.90thpercentile ($p < .0050$). In particular, F_stat.var and F_stat.max are poorly correlated with each other and are eligible for further qualitative bivariate investigations. The spatial distribution of the GTV in the bivariate space is shown in Figure 4. F_stat.max and F_stat.var represent the highest value and the variance, respectively, in the distribution of intensity of the voxels within the ROI. Regarding F_stat_range and F_stat.uniformity, the former is the difference between the maximum and the minimum voxel value and the latter is a measure of the uniformity of the gray-level histogram. F_stat.90thpercentile indicates the 90th percentile of the gray intensity value.[20]

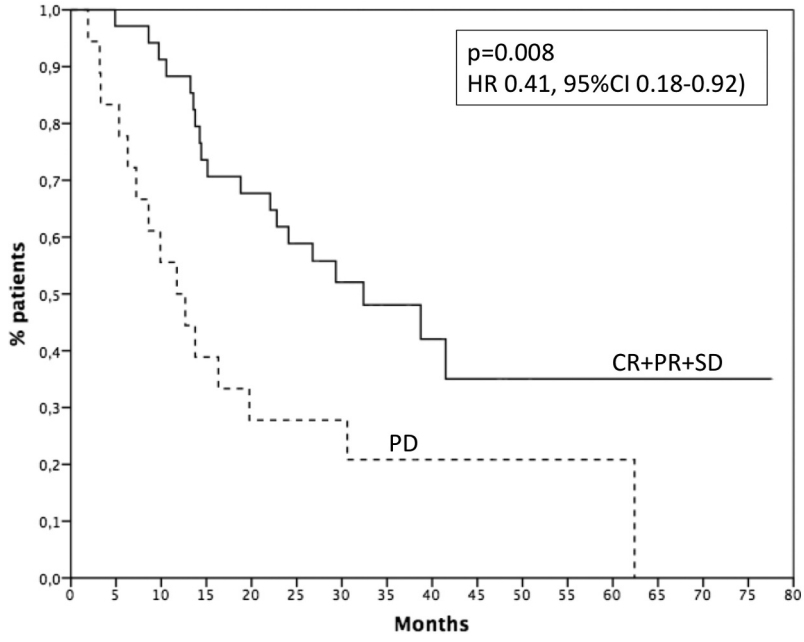

Figure 2. Survival of patients with clinical benefit (solid line) or progression (dashed line). CR: complete response, PR: partial response; SD: stable disease; PD: progression of disease.

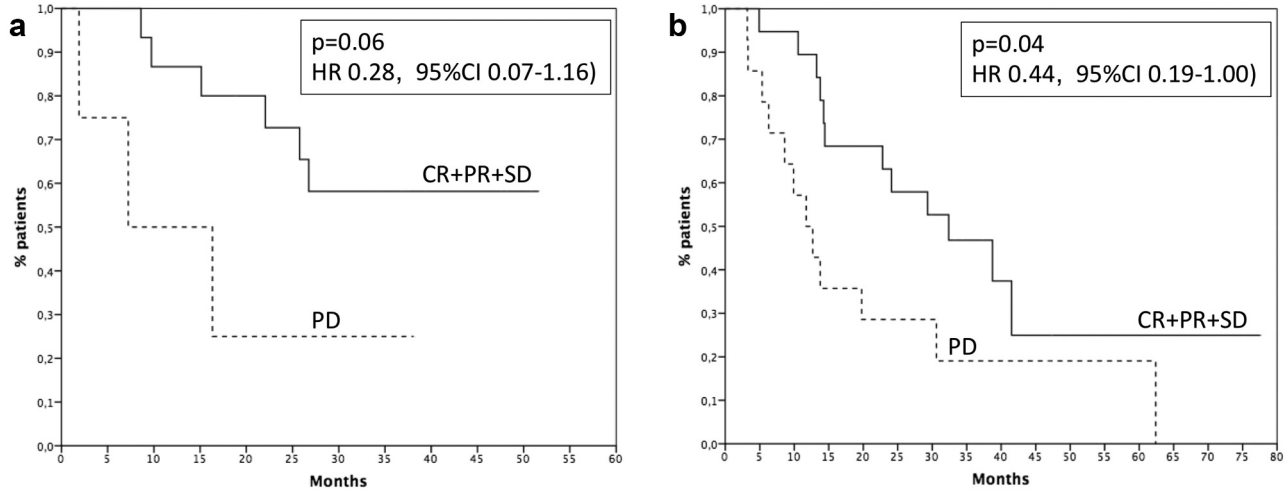

Figure 3. Survival of patients with clinical benefit (solid line) or progression (dashed line) in first (A) and second/third line setting (B). CR: complete response, PR: partial response; SD: stable disease; PD: progression of disease.

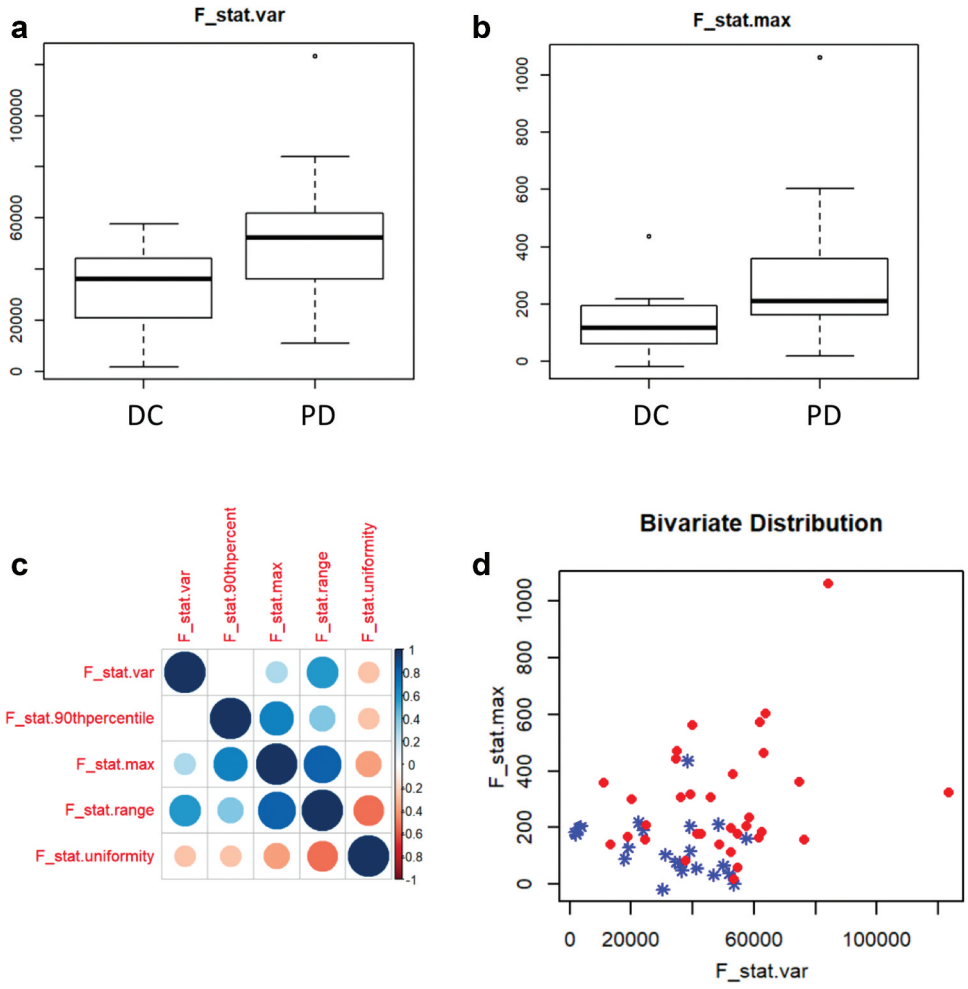

Figure 4. a–b: the boxplots represent the distribution of F_stat_var and F_stat.Max between the two cohorts (DC: patients with disease control; PD: patients with progression of disease). c: Pearson correlation coefficients between the most significant features. d: the distribution of the cases (patients with disease control in blue, patients with progression of disease in red) in a space built with F_stat.Var on the x-axis and F_stat.Max on the y-axis.

Discussion

Immune checkpoint inhibitors have become a milestone for the treatment of RCC. These agents demonstrated an improved clinical outcome in several studies. The anti-PD-1 nivolumab allowed a longer overall survival compared to everolimus in previously treated advanced RCC patients with fewer grade 3–4 adverse events.[2] The association of nivolumab and ipilimumab as first metastatic systemic therapy showed a longer OS and a higher response rate than sunitinib in intermediate-poor risk patients.[3] Of note, nivolumab + ipilimumab demonstrated a remarkable response rate and a survival advantage in patients with sarcomatoid histology.[21] Furthermore, the addition of anti-PD-1 to a TKI showed a benefit compared to sunitinib. The combination of pembrolizumab and axitinib allowed a 47% of reduction in death risk and 31% in disease progression compared to TKI alone.[4] In the CLEAR study, an improved PFS in favor of pembrolizumab-lenvatinib instead of sunitinib has been reported.[5] The CheckMate 9ER trial investigated the combination of nivolumab and cabozantinib versus sunitinib. It has been observed a superiority of the combination arm in terms of both OS and PFS.[6] ICIs can change the natural course of RCC also in adjuvant setting. Indeed, pembrolizumab showed the ability to decrease the risk of recurrence after nephrectomy.[7] Several further clinical trials have been conducted or are ongoing to test ICIs in combinations or as single agents in various settings of RCC. Therefore, it is probable that ICIs will increasingly become part of the treatment options for RCC.

Although more therapeutic alternatives are available, we cannot select patients who can benefit more from immunotherapy. Therefore, no predictive factor can be considered to establish if intermediate-poor patients should be candidate to anti-PD-1 plus TKI or anti-PD-1 plus anti-CTLA-4 combination. Similarly, we cannot identify patients resistant to immunotherapy, for whom other treatment options should be preferred. This is also the case of radically resected RCC patients. In this setting, it is crucial to employ an active treatment, avoiding adverse events of ineffective therapies.

Many studies have been conducted with the aim to identify predictive factors for immunotherapy efficacy.[22] None of them have been validated for routine use.

Our study aimed to investigate correlations between CT-based radiomics features and immunotherapy efficacy in RCC. An interesting association between some CT scan features and progression of disease in RCC patients treated with ICIs has

been found. In particular, F_stat.var and F_stat.max are poorly correlated with each other and are used to build a space where the GTV associated to the different outcomes can be plotted. As shown in Figure 4, the GTVs with a value of F_stat.var lower than 60,000 and F_stat.max lower than 300 are commonly associated with the absence of progression of disease, while the GTVs associated to this outcome are less clustered. According to this geometrical distribution, GTVs with high values of F_stat.var and F_stat.max (greater than 60,000 the former or greater than 300 the latter) are more probably associated to a high risk of progression of disease. Remarkably, we observed that some of the most human interpretable features correlate with the clinical outcome: F_stat.max, F_stat.var, F_stat_range, F_stat.uniformity and F_stat.90thpercentile. These radiomics features could be potentially useful for the interpretation of response to immunotherapy by trained radiologists. Despite the limitation of the sample size, we could also hypothesize that the features which are associated with disease progression during immunotherapy could be related to neoplastic tissues with low inflammatory infiltrate.[23–25] This aspect could justify the poor response to immunotherapy. The biological interpretation of the radiomics features is the focus of the current research.[26]

Our results need to be confirmed with further investigations, due to the limited number of cases and the retrospective nature of the study. However, the possibility of extending these findings in clinical practice could allow to avoid ICIs in refractory patients, for whom other treatment options, such as TKIs, can lead to a longer OS. Indeed, in our study, patients resistant to ICIs reported shorter survival than patients with clinical benefit.

Basing on the above observations, it is reasonable to hypothesize that radiomics can help patients' selection. Prospective clinical trials are needed to validate the role of the features which have been identified in our study. Taking together factors such as radiomics, circulating immune molecules,[27,28] gut microbiota or molecular characteristics,[29,30] a personalized treatment in RCC could be achieved.

Disclosure statement

The authors declare that they have no competing interest. ER had a role as consultant for MSD, Novartis, Pierre Fabre, Immunocore and Pfizer. GT had a role as consultant for BMS, MSD, Astra Zeneca, Servier, Merck Serono and Dompé. GS had a role as consultant for BMS.

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