Prognostic factors in patients receiving third-line targeted therapy for metastatic renal cell carcinoma.

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ABSTRACT

Purpose: Several prognostic models have been proposed for metastatic renal cell carcinoma (mRCC) but none has been validated in patients receiving third-line targeted agents. We aim to evaluate the prognostic factors in patients affected by mRCC who received a third-line of targeted agent.

Materials and Methods: Data about 2,065 patients affected by clear cell mRCC and treated with targeted therapies in 23 centres in Italy were retrospectively reviewed. A total of 281 patients treated with three targeted agents were included in the final analysis. Overall survival (OS) was the main outcome. Cox proportional hazards regression, followed by bootstrap validation, was used to identify independent prognostic factors.

Results: Three clinical characteristics (ECOG-PS >1, presence of metastases at diagnosis, and presence of liver metastases) and two biochemical factors (hemoglobin < LLN and neutrophils > ULN) were found to be prognostic. Patients were classified in three categories of risk based on the presence of zero or one risk factors (low-risk), two risk factors (intermediate-risk) and >2 risk factors (high-risk). The median OS was 19.7, 10.1, and 5.5 months, while the 1-year OS was 71%; 43%, and 15%, respectively. Major limit is the retrospective nature of this study and the absence of external validation.

Conclusions: This nomogram included both clinical and biochemical prognostic factors and it may be useful for selection of patients in clinical trials and for the defining prognosis in clinical practice.

Key Words: mRCC; prognosis; third-line; targeted therapy; overall survival.

Running Head: 3rd line & prognosis in mRCC patients

Introduction

Treatment of metastatic renal cell carcinoma (mRCC) has dramatically changed since targeted agents have been introduced in the clinical armamentarium. Despite the low curative rate, the median overall survival has increased over the years: from 10 months in the era of cytokines to about 30 months in the era of targeted therapies[1-3].

The increased survival and the growing number of available targeted agents have resulted in a greater number of patients treated with two or more lines of therapy. Considering this wealth of new agents, identification of prognostic factors remains a cornerstone for clinical management of advanced disease. Prognostic factors allow stratification of patients based on cancer-related risk of death, and give important information about disease evolution. Moreover, this allow homogeneous stratification of patients for clinical trials in the attempt to avoid bias related to selection and consequently, identify the group in which a target agent has the greatest activity.

Until now, the most-frequently used prognostic criteria were those elaborated by Motzer in patients treated with interferon immunotherapy and chemotherapy at Memorial Sloan-Kettering Cancer Centre (MSKCC)[4], and subsequently validated in a retrospective analysis on 353 patients treated at the Cleveland Clinic[5].

Subsequently, Heng et al. reported a large analysis performed on patients treated with tyrosine kinase inhibitors (TKIs) as up-front or second-line therapy and included in the International mRCC Database Consortium (IMDC)[6]. The role of low hemoglobin and high serum corrected calcium values, such as Karnofsky PS and the time from diagnosis to initiation of therapy were confirmed as independent predictors of short survival. Furthermore, the value of neutrophils and platelet count greater than the upper limit of normal (ULN) were also found to be prognostic[6]. Similar to previous analysis, there were no prognostic differences if patients received targeted agents as first-line or after cytokines; moreover the role of histology was not investigated[7].

Despite their validation in therapy naïve patients, the MSKCC model has also been used in patients enrolled in second-line trials and, more recently, the IMDC model has confirmed its discriminatory capacity also in this setting[8].

This study sought to evaluate prognostic factors in patients with mRCC who receive a third-line of targeted agent and to compare these factors with current nomograms.

Patients and Methods

Patients

Data of 2,065 patients with mRCC and treated with targeted therapies in 23 centres in Italy were retrospectively reviewed. Only patients receiving three lines of targeted agents were included in the final analysis. Patient inclusion criteria were: diagnosis of metastatic clear cell RCC and treatment with three targeted therapies, while patients treated with a combination of therapies **or previous cytokines** were excluded.

Baseline demographic, clinical and laboratory data and characteristics previously found to have prognostic value were collected retrospectively by using uniform database templates to ensure consistent data collection. Outcome data on overall survival (OS) were collected from patient files and by telephone contact. The study received Internal review board approval.

Statistical Analyses

The primary outcome was OS, defined as the time from initiation of third line therapy to death as a result of any cause or was censored at the date of last follow-up. The median OS with 95% CIs was estimated by using the Kaplan-Meier method. Associations between OS and potential prognostic factors were assessed by using the log-rank test in univariable analysis. P-values at univariable analysis were adjusted for multiplicity using the Bonferroni correction. The Cox proportional hazards model was then fitted in multivariate analyses. Model selection was performed using a

forward step-wise procedure. The proportionality of hazards assumption was assessed graphically by using plots of log (log[survival]) versus log of survival time.

Once the prognostic factors were identified and the final model was fit, a risk-group variable was created by counting the number of unfavourable features for each patient.

The predictive performance of the newly constructed score(s) was assessed by means of the C-index, which corresponds to the area under the ROC curve and represents the ability of a score to correctly predict events. A concordance index of 1 represents perfect ability to distinguish patients; an index > 0.5 implies good prediction ability, while index of 0.5 implies no predictive ability.

We also assessed the predictive performance of the final model by internal validation by using two-step bootstrap resampling procedures. In the first step, 1000 bootstrap samples were generated randomly with replacement from the original study population. The stepwise Cox regression procedure was employed to each sample with the same selection criteria as the original modeling, described earlier in this methods section. We then calculated the frequency of inclusion of each variable in the resulting models within the 1000 bootstrap samples. Risk factors that were present in more than 50% of the models were considered significant. In the second validation step, we validated parameter estimates of the final model. One thousand bootstrap samples were generated randomly from the original study population for the final model. For each of the samples, we refit the Cox regression model by using the variables selected in the final model, and we calculated the regression parameters and hazard ratios. The means, standard deviations, and CIs were computed from the 1000 samples and were compared to the model by using the original study population.

Improvement in comparison to other scores was assessed by means of continuous Net Reclassification Index (NRI) and median improvement in risk scores (MIRS), which were computed as described by Pencina *et al.*[9] The NRI gives roughly the proportion of misclassified cases that are classified correctly with the new information, a NRI of 1 indicates perfect ability to correctly reclassify patients, and a negative NRI indicates that the score is worse than its competitor.

The NRI was evaluated at 1 year, and a sensitivity analysis comparing with 6 and 18 months revealed no dependence on the cut-off chosen. The MIRS gives the median increase in score for the cases, a large positive MIRS indicates that the predicted risk for patients with events is increased on average, while a large negative MIRS indicates that the predicted risk is decreased.

All statistical analyses were undertaken by using R, and $P < .05$ (two sided) was considered statistically significant.

Results

Patients

After the screening, 281 patients treated from August 2006 to June 2011were included in the final analysis. The baseline patient characteristics are reported in **Table 1.** At the cut-off time, 73.7% of patients had progression on targeted therapy and 26.3% had ongoing third line treatment. A total of 46.6% of patients are dead at the time of the analysis, the median follow-up is 8 months and the maximum 42 months. The median overall survival for the entire cohort was 13.8 months (95%CI, 11.2 – 18.3) and the 1-year overall survival was 54% (95%CI, 47.6% – 61.6%) (**Figure 1**).

Univariable Analysis

All baseline characteristics were tested for predictive value at univariable analysis as reported in **Table 2**. The predictive variables associated with poor overall survival were ECOG PS, metastatic disease at diagnosis, hemoglobin lower than the LLN, value of ULN of neutrophils, LDH greater than the ULN, two or more sites of metastases and the presence of hepatic or bone metastases.

Multivariable Analysis

The predictive variables associated with poor overall survival at multivariable analysis were ECOG PS, the presence of metastases at diagnosis, age greater than 60 years, hemoglobin lower the LLN,

ULN of neutrophils and the presence of liver metastases. Some of these factors have been validated in other classifications such as the MSKCC, the IMDC and the French models.

We employed five of these prognostic factors to classify patients into three categories and in the Italian RCC Third-Line (IRTL) prognostic score, while age greater than 60 years was excluded due to the mild effect on prognosis (e.g. reduction of 2% of the risk of death) (**Table 3**). Patients with zero or one risk factor were classified as low-risk; patients with two risk factors were classified as intermediate-risk and patients with more than two risk factors were classified as high-risk; sixteen patients were not classified. The 153 patients with low-risk had a median OS of 19.7 months (95%CI, 17.4 – 28.9) and a 1-year OS of 71%; 67 patients with intermediate-risk had a median OS of 10.1 months (95%CI, 8.0 – 16.8) and a 1-year OS of 43%, and the 45 patients with high-risk had a median OS of 5.5 months (95%CI, 4.1 – 9.4), and a 1-year OS of 15% (**Figure 2**). The overall HR comparing high vs. intermediate risk was 2.20 (95%CI, 1.37 – 3.53; p=0.0011); while intermediate vs. low risk had an HR of 2.47 (95% CI, 1.64-3.71, p<0.0001).

Bootstrap Validation

The stepwise Cox regression procedure was employed with each of the 1,000 random bootstrap samples with the same selection criteria as the original modeling.

The regression parameters and hazard ratios produced from the 1,000 bootstrap samples were similar to the original model, which suggests excellent internal validation (**Supplementary Table 1**). The bootstrap biased-corrected C-index of this model was 0.723 (95% CI, 0.653 – 0.789).

Validation of previous prognostic nomograms

We performed a sensitivity analysis to identify the prognostic role of nomograms validated in patients with mRCC treated with first-line therapy. The distribution of patients and the median overall survivals based on prognostic group for each nomogram was reported in **Table 4**.

In the MSKCC model the HR between the good and intermediate group was 2.41 ($p<0.001$) and between the intermediate and poor group was 2.66 ($p<0.001$). In the CCF model the HR between the good and intermediate group was 3.21 ($p<0.001$) and between the intermediate and poor group was 1.51 ($p<0.001$). In the French model the HR between the good and intermediate group was 2.44 ($p=0.080$) and between the intermediate and poor group was 2.25 ($p=0.002$). In the IMDC model the HR between the good and intermediate group was 1.54 ($p=0.004$) and between the intermediate and poor group was 3.19 ($p<0.001$). C-indexes between IRTL prognostic score and other prognostic classifications are reported in **Supplementary Table 2.**

The data reported in previous models may be equally effective to predict prognosis for third line therapy. Therefore, we decided to compare our model with the previous ones both comparing the prognostic factors and the prognostic categories using the net-reclassification-index (NRI) and the Median Improvement in Risk Score (MIRS). Both analyses suggest that the IRTL prognostic score may be useful compared to MSKCC, CCF, French and IMDC prognostic models in defining the prognosis of these patients both in terms of prognostic factors and prognostic categories (**Supplementary Table 3**).

Discussion

In this article, we assess clinical factors associated with prognosis in mRCC treated with two previous lines of targeted agents and eligible for a third one. Prognostic factors have been widely investigated in treatment naïve mRCC patients and used to select patients for clinical trials.

The first model analyzing 670 patients enrolled in clinical trials with immunotherapy and chemotherapy at MSKCC, found that hemoglobin, lactate dehydrogenase, corrected calcium, nephrectomy, and Karnofsky PS were independent risk factors for survival[4]. Ten years later, Heng *et al.* confirmed the prognostic role of low hemoglobin, high serum corrected calcium, low Karnofsky PS and time from diagnosis to therapy less than 1 year and added the absolute value of neutrophils and platelets counts greater than ULN[6]. The study reported a median OS of 43.2 months

in the favorable risk group, 22.5 months in the intermediate risk, and 7.8 months in the poor risk group. This model was also externally validated on more than 840 patients; it was found as IMDC has a good concordance index (c-index: 0.66) and is able in reclassifying patients more correctly than the majority of other models[10].

Our model, similarly to others, was able to confirm the prognostic role for some clinical and biochemical factors previously identified by Motzer and Heng also in the third-line setting and added the presence of liver metastases. Our analysis confirms that different prognostic groups of patients may be found before first-line as well as before third-line where the median life-expectancy is generally shorter.

About further lines, the literature reports that 50% of patients receive two lines of therapy and about 15% will receive three lines[11, 12]. It has been recently shown that patients who are able to receive several lines of therapy survive longer. Yet, there are no predictive tools to select who will be eligible for further lines[13]. The final OS reported by the population included in this analysis (i.e. 13 months), is comparable with results of a prospective phase III trial comparing dovitinib to sorafenib in the third-line setting[14]. This long survival may suggest that prediction of prognosis still remains an important factor because low-risk patients have a median OS increased by three times as compared to high-risk patients.

Our analysis also reports the clinical characteristics of patients who received third-line therapy: as for naïve patients, major site of metastases were lung, followed by lymph-nodes, bones and liver[15]. Despite the high number of baseline clinical characteristics investigated, the most important prognostic factors were comparable to previous classifications such as PS, platelet count and neutrophils count.

Differently from the MSKCC and IMDC models, the present analysis reports the independent prognostic role of liver metastases and includes this factor in the final model, similar to the French model[16]. This factor was also investigated in patients included in the IMDC model revealing that 19% of patients had liver metastases at the beginning of first-line therapy, confirming its negative

prognostic role also when compared to other prognostic factors[17]. This data suggest that the presence of liver metastases is an independent prognostic factor in patients treated with targeted agents over different lines of therapy and probably, it worsened prognosis in subsequent lines. When the IRTL model was compared to other nomograms using the NRI and MIRS tests, these suggest a better performance, especially when the comparison was based on prognostic factors more than when based on prognostic categories.

Our study has some limitations: first and foremost is its retrospective nature that did not ensure a complete data collection for all patients. Moreover, we included only patients with clear cell histology and no data are available on papillary or chromophobe renal tumors. The use of other prognostic score not designed and not yet validated in patients treated with two previous lines of therapy may affect the comparison with a score specifically designed for this population. On the other hand, previous prognostic model have been evaluated and validated on larger patient populations compared to those reported in this study. Nevertheless, considering the low number of patients receiving three lines of therapy this nomogram may be considered a useful tool to study this population.

Conclusions

The IRTL prognostic score included three clinical prognostic factors such as the ECOG PS, the presence of metastases at diagnosis, the presence of liver metastases and two biochemical ones; such as hemoglobin below the LLN and the neutrophils count above the ULN. The discriminatory power among prognostic groups indicates that this model may be useful for selection of patients for clinical trials and for the definition of prognosis in clinical practice even if an external validation is recommended.

Author Disclosures

Authors have not conflict of interest related to this work

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Legend of the Figures:

Figure 1: Final overall survival.

Figure 2: Overall survival by IRTL prognostic group.

Table 1: Baseline characteristics of the patients.

Variable	Patients (%)
Median age, years (IQR)	62.6 (15.1)
Male sex	74.7
Nephrectomy	77.2
Metastatic at diagnosis	37.7
Interval < 1 year	50.2
First line targeted agents	
Sunitinib	62.5
Sorafenib	22.9
Bevacizumab+ IFN	9.6
Temsirolimus	2.5
Other	2.5
Second line targeted agents	
Sunitinib	28.1
Sorafenib	33.1
Everolimus	27.8
Temsirolimus	10.0
Other	1.0
Third line targeted agents	
Sunitinib	7.5
Sorafenib	32.5
Everolimus	51.1
Temsirolimus	5.0
Other	3.5
ECOG Performance Status	
0	27.3
1	55.3
2	17.3
Previous RT	34.4
Sites of metastases ≥ 2	84.3
Sites of metastases	
Lung	77.3
Bone	32.1
Liver	28.6
Adrenal	21.7
Brain	12.3
Pancreatic	9.4
Lower lymphnode	24.3
Upper lymphnode	34.8
Soft tissue	14.9
Hb < LLN	46.3
LDH > 1.5 ULN	20.1
Neu > ULN	10.8
PLT > ULN	7.5
Corrected Ca^{2+} > ULN	3.6

Table 2: Univariate analysis based on patient characteristics before the third-line of therapy. The p-values at univariablee analysis are Bonferroni adjusted for multiplicity.

Variable	*Univariate Analysis*			*Bootstrap validation*
	HR	**95% CIs**	***p-value***	***% times selected***
Nephrectomy (Y/N)	0.58	0.23 – 1.41	0.226	20.9
Metastatic at diagnosis (Y/N)	1.66	1.17 – 2.37	0.005	81.9
Sex (M/F)	1.11	0.74 – 1.67	0.621	26.8
Age > 60 years	0.98	0.96 – 0.99	0.003	97.1
ECOG Performance Status (*0/1 vs. 2)*	1.91	1.47 – 2.49	<0.001	93.4
Interval < 1 year (Y/N)	1.36	0.97 – 1.93	0.078	36.1
Previous RT (Y/N)	1.58	0.97 – 2.31	0.221	59.1
Hb < LLN (Y/N)	2.07	1.46 – 2.94	<0.001	93.3
LHD > 1.5 ULN (Y/N)	1.85	1.25 – 2.74	0.029	33.3
Neu > ULN (Y/N)	2.35	1.45 – 3.80	<0.001	78.5
PLT > ULN (Y/N)	1.72	0.96 – 3.08	0.884	42.1
Corrected Ca^{2+} > ULN (Y/N)	2.71	0.88 – 6.21	0.247	23.0
Sites of metastases ≥ 2 (Y/N)	1.43	1.01 – 2.02	0.044	43.4
Lung metastases (Y/N)	1.40	0.89 – 2.21	0.142	63.6
Bone metastases (Y/N)	1.96	1.38 – 2.80	<0.001	93.2
Liver metastases (Y/N)	1.88	1.29 – 2.74	0.013	93.1
Adrenal metastases (Y/N)	1.10	0.66 – 1.25	0.555	35.3
Brain metastases (Y/N)	1.45	0.87 – 2.43	0.153	88.3
Pancreatic metastases (Y/N)	0.55	0.28 – 1.09	0.085	35.3
Lower lymphnode metastases (Y/N)	1.12	0.76 – 1.66	0.559	61.8
Upper lymphnode metastases (Y/N)	0.99	0.69 – 1.41	0.941	63.5
Soft tissues metastases (Y/N)	1.57	0.98 – 2.51	0.063	95.1

HR= hazard ratio; CIs= confidence intervals; Y= tes; N= non; M= male ; F= female ; Hb= hemoglobin ; Neu= neutrophils ; LLN= low limit of normal ; ULN= upper limit of normal; PLT= platelets; LDH= lactate dehydrogenase.

Table 3: Results of Multivariate Analysis.

Variable	Multivariate analysis		*p-value*
	HR	**95% CIs**	
Metastatic at diagnosis (Y/N)	2.25	1.54 – 3.28	< 0.001
ECOG Performance Status			
0/1 vs. 2	1.91	1.44 – 2.53	<0.001
Hb < LLN (Y/N)	1.68	1.16 – 2.43	0.006
Neu > ULN (Y/N)	1.99	1.21 – 3.27	0.006
Liver metastases (Y/N)	1.83	1.24 – 2.70	0.002

HR= hazard ratio; CIs= confidence intervals; SD= standard deviation; Y= yes; N= non; Hb= hemoglobin; Neu=neutrophils; ECOG= Eastern Cooperative Oncology Group.

Table 4: Distribution of patients based on prognostic nomogram.

Prognostic Group	Prognostic Nomograms:							
	MSKCC		French		CCF		IMDC	
	(%)	Median OS (95%CIs)	(%)	Median OS (95%CIs)	(%)	Median OS (95%CIs)	(%)	Median OS (95%CIs)
Good	20.6	NR (20.3 – NA)	5.3	NR (11.1 – NA)	20.3	NR (NR – NR)	31.0	17.5 (13.2 – NR)
Intermediate	66.2	15.2 (11.7 – 18.4)	80.8	14.3 (11.5 – 18.5)	34.5	15.3 (10.2 – 23.4)	61.9	13.8 (10.1 – 19.4)
Poor	13.2	6.3 (5.2 – 9.4)	13.9	6.1 (4.7 – NR)	45.2	10.2 (8.6 – 13.8)	7.1	5.2 (3.0 – NR)

MSKCC= Memorial Sloan Kettering Cancer centre; CCF= Cleveland Clinic Foundation; IMDC= International mRCC Database Consortium; OS= overall survival; CIs= Confidence Intervals; NR= not reached.

Supplementary table 1: Results of bootstrap validation of the multivariate model.

Variable	Bootstrap means		SD of HR
	HR	95% CIs	
Metastatic at diagnosis (Y/N)	2.15	1.46 – 3.15	1.22
ECOG Performance Status			
0/1 vs. 2	2.30	1.49 – 3.57	1.23
Hb < LLN (Y/N)	1.77	1.22 – 2.59	1.23
Neu > ULN (Y/N)	2.25	1.34 – 3.77	1.30
Liver metastases (Y/N)	1.78	1.20 – 2.66	1.22

HR= hazard ratio; CIs= confidence intervals; SD= standard deviation; Y= yes; N= non; Hb= hemoglobin;Neu=neutrophils; ECOG= Eastern Cooperative Oncology Group.

Supplementary table 2: C-indexes based on comparison of the Italian RCC Third Line (IRTL) prognostic model and other prognostic nomograms.

Prognostic Nomogram	C-index	95% CIs	p-value
MSKCC	0.64	0.58 – 0.71	0.017
CCF	0.62	0.54 – 0.69	0.010
French	0.57	0.51 – 0.63	<0.001
IMDC	0.61	0.55 – 0.67	<0.001

MSKCC=memorial Sloan Kettering cancer centre; CCF=Cleveland clinic Foundation; IMDC=International mRCC Database Consortium.

Supplementary Table 3: Comparison between Italian RCC Third Line (IRTL) prognostic model and other prognostic models in mRCC. Comparison was based on numbers of prognostic factors (prognostic factors) or based on categories of risk found in each model (prognostic score).

Prognostic models		IRTL prognostic model			
		Prognostic factors		Prognostic categories	
		Median (95%CIs)	*p-value*	Median (95%CIs)	*p-value*
MSKCC	NRI	0.29 (0.01 – 0.45)	0.040	0.25 (-0.06 – 0.41)	0.120
	MIRS	0.05 (0.00 – 0.14)	0.020	0.233 (0.09 – 0.31)	0.159
CCF	NRI	0.25 (0.04 – 0.41)	0.007	0.17 (0.00 – 0.32)	0.053
	MIRS	0.10 (0.00 – 0.20)	0.007	0.12 (0.00 – 0.24)	0.020
French	NRI	0.27 (0.06 – 0.41)	0.007	0.26 (0.06 – 0.40)	0.013
	MIRS	0.16 (0.00 – 0.26)	<0.001	0.26 (0.00 – 0.32)	<0.001
IMDC	NRI	0.25 (0.05 – 0.41)	0.013	0.25 (0.02 – 0.38)	0.020
	MIRS	0.02 (0.00 – 0.12)	0.007	0.25 (0.00 – 0.31)	0.007

MSKCC= Memorial Sloan Kettering Cancer centre; CCF= Cleveland Clinic Foundation; IMDC= International mRCC Database Consortium; NRI= net reclassification index; MIRS= Median Improvement in Risk Score; CIs= Confidence Intervals.