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Research Article

Contemporary outcomes of metastatic renal cell carcinoma in a single-center real-world cohort

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Abstract

Objective: The objective of this study was to describe contemporary outcomes in a real-world cohort of patients with metastatic renal cell carcinoma managed within an integrated udo-oncology program and to explore prognostic factors associated with survival.

Methods: We conducted a retrospective study using the Uro CCR database. Patients with confirmed MRCC who received first-line systemic therapy between 2016 and 2024 were included. The primary outcome was OS, defined as time from therapy initiation to death.

Results: A total of 146 patients were included: 42 (28.8%) in the favorable group, 64 (43.8%) in the intermediate group, and 40 (27.4%) in the poor group. The median OS for the entire cohort was 54.2 months. In the favorable group, median OS was 70.9 months, with a 6-month survival rate of 100% and a 60-month rate of 62.8%. The intermediate group showed a median OS of 49.1 months, with a 6-month survival rate of 93.5%, declining to 48.9% at 60 months. The poor group had a median OS of 20.4 months, with a 6-month survival rate of 87.0% and 19.1% at 60 months. Multivariate analysis identified an association between cytoreductive nephrectomy (HR: 0.36, p=0.004) and more favorable OS, while poor IMDC prognosis remained associated with worse survival (HR: 2.67, p=0.04).

Conclusion: This study reports favorable contemporary overall and progression-free survival outcomes in patients with metastatic renal cell carcinoma managed with modern therapeutic strategies. The IMDC classification retained clinically meaningful prognostic value for overall survival in this contemporary setting.

Keywords: Renal cell carcinoma; Metastatic; Surgical treatment; Targeted molecular therapies; Oncologic outcome; Immunotherapy.

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Introduction

Renal Cell Carcinoma (RCC) is the most common type of kidney cancer in adults, with approximately 70% of cases classified as clear cell RCC. At diagnosis, around two thirds of patients with RCC have a localized or locally advanced disease, which is best treated by surgical resection. However, one-third of patients are diagnosed with distant metastases, and up to 30% who undergo surgery for a localized disease will experience recurrence [1].

Over recent decades, the management of MRCC has evolved significantly. Initial treatments with cytokine-based therapies have been subsequently replaced by targeted therapies, and combinations of immune checkpoint inhibitors. These advances have led to substantial improvements in survival, with median overall survival improving from one year in the 1990s to over four years in recent clinical trials [2-6].

The International Metastatic RCC Database Consortium (IMDC) risk model is widely adopted as the standard prognostic tool for patients with Metastatic RCC (MRCC). This model categorizes patients into favorable, intermediate, and poor risk groups based on clinical and biological factors, including Karnowski performance status, time from diagnosis to systemic treatment, hemoglobin, neutrophil and platelet counts, and serum calcium levels [7]. The IMDC model has been widely used to stratify patient risk, estimate survival, and guide first-line treatment selection.

While pivotal clinical trials and large international registries have reported outcomes of patients treated with contemporary systemic therapies, less is known about survival achieved in integrated udo-oncology pathways combining systemic therapy, cytoreductive surgery, and metastasis-directed treatments in routine clinical practice. The aim of this study was to describe contemporary oncological outcomes, including Overall Survival (OS) and Progression-Free Survival (PFS), in a real-world cohort of patients with MRCC managed within an integrated udo-oncology program. Secondary objectives were to assess prognostic factors associated with survival outcomes and to explore the performance of the IMDC classification in this contemporary setting.

Materials and methods

Study design and participants: We conducted a single-center retrospective study using data from the prospective national Uro CCR registry. Uro CCR is registered on ClinicalTrials.gov (NCT03293563) and has received the required French regulatory approvals (CNIL authorization Dr2013-206). All patients provided written informed consent for inclusion in the registry. Patients with a confirmed diagnosis of Metastatic Renal Cell Carcinoma (MRCC) who received first-line systemic therapy between 2016 and 2024 were included. Immune checkpoint inhibitors were progressively introduced in our institution from 2016 onward. Treatment strategies, including systemic therapy and the timing of cytoreductive nephrectomy, were determined during multidisciplinary udo-oncology tumor board meetings in accordance with contemporary clinical practice and international guidelines. As this study consisted of a retrospective analysis of prospectively collected registry data without any additional intervention or data collection, no additional institutional ethics committee approval was required under French regulations. No external funding was received for this study.

Covariates: Demographic and clinical variables included: age, sex, histological subtype, tumor stage, ISUP grade, presence of a sarcomatous component, ECOG performance status at the time of metastatic diagnosis, the localization and number of metastases, local treatments for metastases (mastectomy, radiotherapy, and ablative therapies), type of medical treatment, IMDC risk group, best treatment response based on RECIST 1.1 criteria [8].

Follow-up protocol and outcomes: Follow-up included clinical examinations, laboratory assessments, and CT scans every 3 months, following standard recommendations. The primary endpoints were overall survival (OS) and Progression-Free Survival (PFS). OS was defined as the time from the initiation of systemic therapy to death from any cause or censoring at the last follow-up. PFS was defined as the time from the start of systemic therapy to disease progression or therapy discontinuation due to adverse events.

Statistical analysis

Quantitative variables were reported as medians with Interquartile Ranges (IQRs), while qualitative variables were presented as proportions. Kaplan-Meier survival analysis with log-rank tests was used to compare time-to-event outcomes (OS and PFS) between groups. Univariate and multivariate Cox proportional hazards models were used to identify independent prognostic factors for OS and PFS. We performed sensitivity analyses by redefining OS and PFS, starting from the date of metastatic diagnosis instead of the initiation of systemic therapy. Given the retrospective design and limited sample size, multivariable analyses were considered exploratory. To avoid model overfitting, only clinically relevant covariates associated with outcomes in univariate analyses were included in the final multivariable models. Given the number of events, the number of covariates was limited in accordance with the events-per variable principle to limit overfitting. Additionally, we evaluated the predictive value of nephrectomy specifically in patients with synchronous metastatic disease. All statistical analyses were conducted using R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria). Model discrimination was quantified using the Harrell concordance index (C-index). All tests were two-sided, and a p-value of <0.05 was considered statistically significant.

Results

Patients' and tumor characteristics: A total of 146 patients were included in the analysis. The median age was 66 years (IQR: 58-72). Histological subtypes were clear cell RCC in 134 patients (91.8%), papillary carcinoma in 6 patients (4.1%), chromophobe carcinoma in 2 patients (1.4%), and other renal carcinoma subtypes in 4 patients (2.7%).

Patients were classified according to the IMDC classification as follows: 42 (28.8%) in the favorable prognosis group, 64 (43.8%) in the intermediate prognosis group, and 40 (27.4%) in the poor prognosis group. Synchronous metastases were present in 71 patients (48.6%), while 75 patients (51.4%) had metachronous metastases. The most common metastatic site

was the lung, observed in 84 patients (57%).

First-line systemic treatment consisted of IO-IO combinations in 35 patients (24%), IOTKI in 59 patients (40%), and TKI alone in 52 patients (35.6%). 94 patients (64.4%) received IO as first-line treatment, and 52 patients (35.6%) were given IO in subsequent lines of therapy. The distribution of first-line regimens by year of treatment initiation is shown in (Supplementary Figure 1). Among patients with synchronous disease, 24 (64.9%) underwent upfront nephrectomy, while 13 (35.1%) had a deferred nephrectomy. Local treatment of renal metastases was performed in 47 patients (32.2%): 27 patients underwent surgery, 27 had radiotherapy, and 7 received thermal ablation. Baseline characteristics of patients and tumors are summarized in (Table 1).

Oncological outcomes for the complete cohort: The median OS of the entire cohort was 54.2 months (95% CI: 39.8 - not reached). The Kaplan-Meier analysis showed that the 6-month OS probability was 93.6% (95% CI: 89.7% - 97.7%), decreasing to 80.4% (95% CI: 73.9% - 87.5%) at 12 months, and further declining to 47.6% (95% CI: 37.7% - 60.2%) at 60 months (Figure 1a).

In terms of progression-free survival, the median PFS for the cohort was 15.9 months (95% CI: 12.1 - 22.4 months). The 6-month PFS probability was 78.6% (95% CI: 72.0% - 85.7%), dropping to 58.6% (95% CI: 50.7% - 67.7%) at 12 months, and 28.8% (95% CI: 20.5% - 40.4%) at 60 months (Figure 1b).

Survival according to IMDC prognosis group

Overall survival: Kaplan-Meier analysis demonstrated significant differences in Overall Survival (OS) among the IMDC prognostic groups. Patients in the favorable risk group had a median OS of 70.9 months, with survival probabilities of 100% at 6 months, 94.9% at 12 months, and 62.8% at 60 months. In contrast, the poor risk group had a median OS of 20.4 months (95% CI: 11.8 - not reached), with a survival probability of 87.0% at 6 months. Beyond 36 months, survival estimates in the poor group were not reliable due to the low number of patients at risk. The intermediate risk group had a median OS of 49.1 months (95% CI: 27.9 - not reached), with survival probabilities of 93.5% at 6 months and 48.9% at 60 months (Figure 2A).

Progression-free survival: Progression-Free Survival (PFS) also varied significantly across IMDC prognostic groups. The favorable risk group had the longest median PFS at 30.2 months, followed by the intermediate risk group with a median PFS of 15.9 months. Patients in the poor risk group had the shortest median PFS of 9.6 months (95% CI: 6.1 - not reached) (Figure 2B).

Prognostic factors for survival

Overall survival: In univariate analysis, the presence of synchronous metastases (HR: 2.05; 95% CI: 1.20-3.50; p=0.008) and a poor IMDC prognosis (HR: 4.45; 95% CI: 2.10-9.42; p<0.001) were associated with worse OS, whereas nephrectomy was associated with longer survival (HR: 0.25; 95% CI: 0.14-0.44; p<0.001). The number of metastatic sites or histological subtypes were not associated with worse survival.

In multivariate analysis, cytoreductive nephrectomy (HR: 0.36; 95% CI: 0.18-0.72; p=0.004) and a poor IMDC prognosis (HR: 2.67; 95% CI: 1.05-6.79; p=0.04) were independently associated with OS (Table 2). The IMDC classification demonstrated moderate discriminatory ability for overall survival (Harrell C-index 0.67, 95% CI 0.61-0.74).

In an expanded multivariable model additionally adjusted for the number of metastatic sites and first-line treatment type (IO-based vs TKI), the association between cytoreductive nephrectomy and OS remained essentially unchanged (adjusted HR 0.35, 95% CI 0.17–0.71; p=0.004), and neither covariate was independently prognostic (Supplementary Table 1).

Progression-free survival: In univariate analysis, the presence of synchronous metastases (HR: 2.05; 95% CI: 1.31-3.19; p=0.002) and a poor IMDC prognosis (HR: 2.43; 95% CI: 1.34-4.41; p=0.004) were associated with worse PFS, while CN was associated with improved PFS (HR: 0.56; 95% CI: 0.34-0.92; p=0.02). The number of metastatic sites and histological subtypes did not predict PFS.

In multivariate analysis, there was no clear association of any parameter with PFS, although nephrectomy (HR: 0.79; 95% CI: 0.46-1.36; p=0.40) and poor IMDC prognosis (HR: 1.63; 95% CI: 0.81-3.28; p=0.17) approached significance (Table 3).

Sensitivity analysis: First, performing sensitivity analyses by changing the definition of OS and PFS to start from the diagnosis of metastatic disease, rather than from the initiation of systemic therapy, did not alter our results.

Second, we performed a Kaplan-Meier survival analysis to evaluate OS in 71 patients with synchronous metastatic renal cell carcinoma, stratified into three groups based on nephrectomy status: no nephrectomy (n=34), upfront nephrectomy (n=24), and deferred nephrectomy (n=13). Significant differences were observed across the groups. In the group of patients who did not undergo nephrectomy, the survival probability at 6 months was 82.25% (95% CI: 64.68 - 91.61%), declining to 54.11% at 12 months (95% CI: 34.81 - 69.95%) and 31.4% at 36 months (95% CI: 17.4 - 56.8%). In the upfront nephrectomy group, the survival probability was 100% at 6 months, 90.9% at 12 months (95% CI: 79.7 - 100%) and 60.2% at 60 months (95% CI: 40.2 - 90.0%). Patients in the deferred nephrectomy group had a survival probability of 92.31% at 6 months (95% CI: 56.64 - 98.88%), which dropped to 56.64% at 36 months (95% CI: 24.67 - 79.39%).

Discussion

Our study provides a contemporary real-world description of outcomes achieved in patients with MRCC managed within an integrated udo-oncology practice during the transition from TKI-based therapies to immune checkpoint inhibitor combinations. The median overall survival of 54.2 months observed in our cohort compares favorably with historical series and highlights the substantial improvement in outcomes achieved over the last decade. Beyond advances in systemic therapies, these results likely reflect the contribution of multidisciplinary management integrating systemic treatment, cytoreductive surgery, metastasis-directed therapies, and longitudinal follow-up within a specialized referral center.

In comparison, a previous cohort study conducted in the same department between 2004 and 2009, reported poorer outcomes, with a median OS of 36 months and a median PFS of 14 months, despite similar patients' characteristics [9]. Our findings align with recent literature and clinical trials consistently demonstrated improved OS and PFS with immunotherapy-based combinations [3,5,10]. Although similar findings have

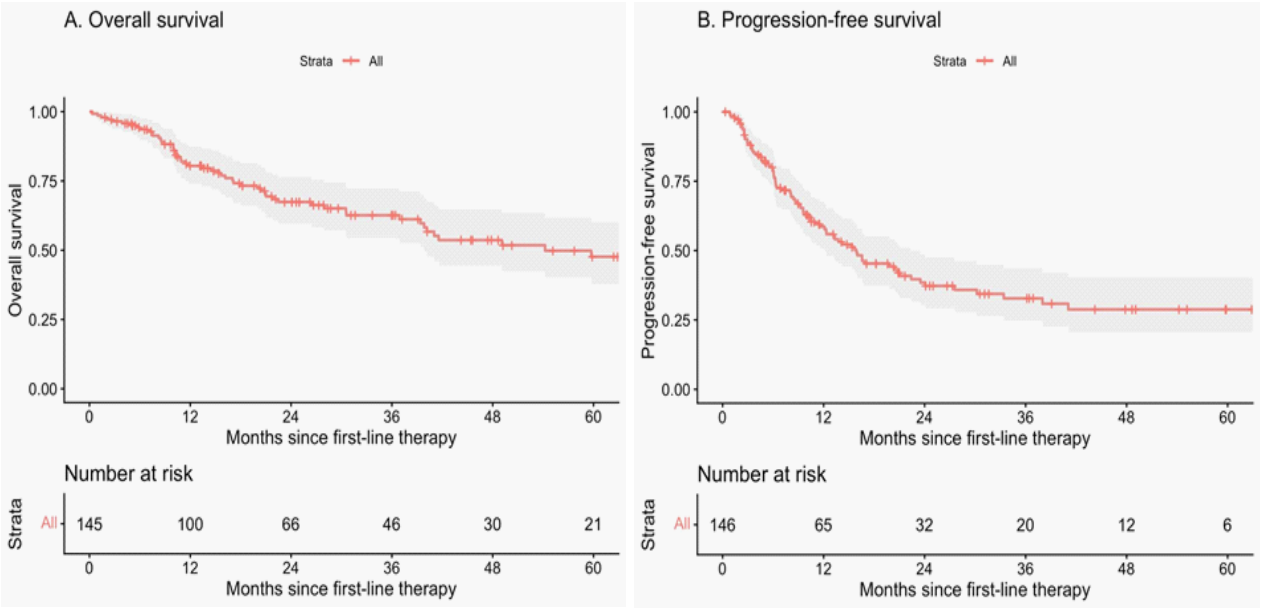

Figure 1: Overall survival (**A**) and Progression Free Survival (**B**) since the instauration of medical therapy for metastatic renal cell carcinoma patients.

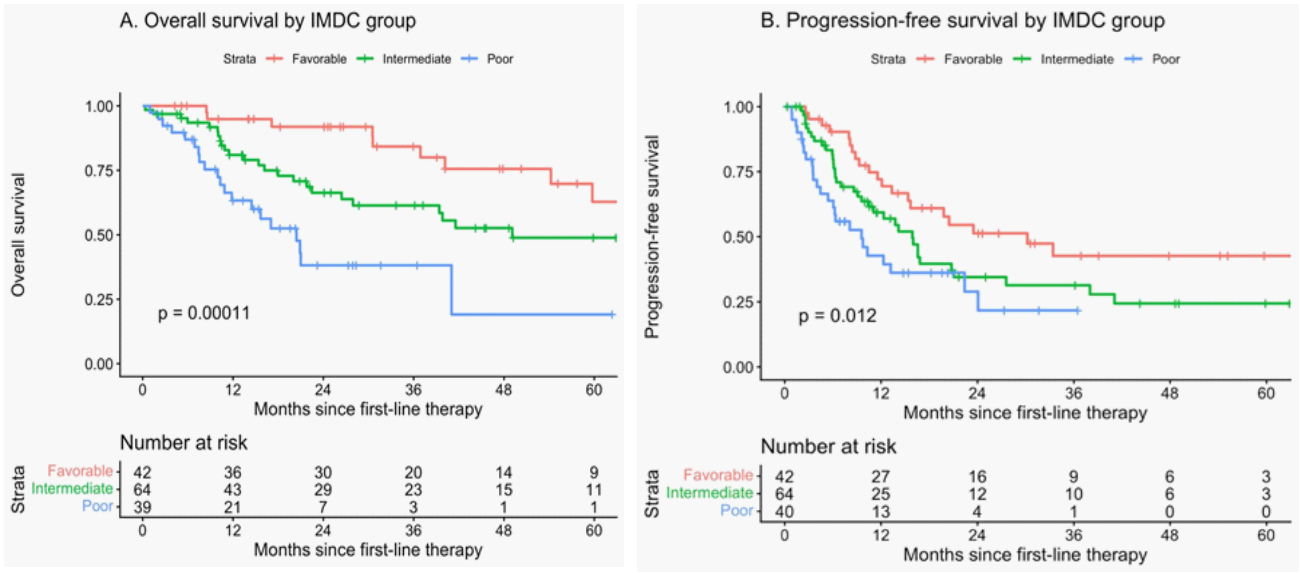

Figure 2: Overall Survival (**A**) and Progression-Free Survival (**B**) by IMDC Classification Since the Initiation of Medical Therapy.

been reported in larger multicenter cohorts, our study provides complementary real-world data from an integrated academic udo-oncology practice combining systemic therapy, surgery, and metastasis-directed approaches.

When stratifying by IMDC risk groups, we observed improvements in OS across all categories. The median OS was 71 months in the favorable-risk group, 49 months for the intermediate-risk group, and 20 months for the poor risk group. This contrasts with Heng and al., who reported median OS of 43, 23, and 8 months in his original publication [11]. In the Heng study, OS was measured from the start of medical therapy to death. To allow for direct comparison, we presented our results similarly. However, assessing OS from metastasis diagnosis revealed significantly longer survival (supplementary data). This distinction reflects the natural history of MRCC, particularly in a cohort where many patients underwent mastectomy or surveillance before initiating treatment.

Our findings suggest that the IMDC classification retains clinically meaningful prognostic discrimination in patients treated during the immunotherapy era, with the most favorable outcomes observed in the favorable-risk group. In our cohort, the distribution of risk groups was more balanced-28.8% favorable, 43.8% intermediate, and 27.4% poor-than in the Heng and al. study [8]. This distribution differed from that reported in the original IMDC cohort and may reflect contemporary referral patterns and patient selection in a tertiary academic center.

Among prognostic factors, poor IMDC risk and cytoreductive nephrectomy emerged as the strongest factors associated with OS. Multivariate analysis demonstrated an association between cytoreductive nephrectomy and improved survival outcomes. However, causal interpretation is limited by the non-randomized design, particularly because patients selected for surgery are generally fitter and may have lower metastatic burden or better response to systemic therapy. This association suggests that selected patients undergoing cytoreductive nephrectomy may experience favorable survival outcomes. However, these findings should be interpreted cautiously given the retrospective design and the substantial risk of selection

Table 1: Baseline characteristics of patients and tumors.

Variable	Patients (n=146)
Median age at metastatic diagnosis (year, IQR)	66.5 (58 – 72)
Gender, n (%)	
Male	99 (67.8)
Female	47 (32.2)
Prognosis Group (IMDC), n (%)	
Favorable	42 (28.8)
Intermediate	64 (43.8)
Poor	40 (27.4)
Synchronous/Metachronous metastatic disease, n (%)	
Metachronous	75 (51.4)
Synchronous	71 (48.6)
Histologist, n (%)	
Clear renal cell carcinoma	134 (91.8)
Papillary carcinoma	6 (4.1)
Chromophobe carcinoma	2 (1.4)
Others renal histologist	4 (2.7)
Sarcomatous component, n (%)	12 (8.2)
ISUP, n (%)	
1	5 (3.4)
2	27 (18.5)
3	54 (37.0)
4	44 (30.1)
Undetermined	16 (11.0)
Metastasis localizations, n (%)	
Lung	84 (57.5)
Liver	32 (21.9)
Bone	22 (15.1)
Brain	7 (4.8)
Adrenal gland	22 (15.1)
First-line medical treatment, n (%)	
TKI alone	52 (35.6)
IO - TKI	59 (40.4)
IO - IO	35 (24.0)
IO treatment, n (%)	
First-line	94 (64.4)
Subsequent line of therapy	52 (35.6)
Cytoreductive nephrectomy (for synchronous disease), n (%)	
Upfront nephrectomy	24 (64.9)
Deferred nephrectomy	13 (35.1)
Local treatment of metastasis, n (%)	47 (32.2)
Surgery	27 (18.5)
Thermal ablation	7 (4.8)
Radiotherapy	27 (18.5)

IO: Immunotherapy; TKI: Tyrosine Kinase Inhibitor; IQR: Interquartile Range. Metastatic Localizations are not Mutually Exclusive (some patients had several sites).

bias, indication bias, and residual confounding. The observed association may also be influenced by immortal time bias, particularly among patients undergoing deferred cytoreductive nephrectomy. In the poor-risk group, 12 patients underwent CN, typically due to tumor-related symptoms or favorable response to first-line therapy. These results align with previous studies, such as Singla and al, which demonstrated improved OS in patients receiving CN plus immunotherapy (median OS not reached at 14 months follow-up) compared to immunotherapy alone (median OS of 11 months) [12]. More recent studies have further explored the role of CN in the immunotherapy combination era. For example, Takemori and al. confirmed CN as an independent favorable prognostic factor (HR 0.45, 95% CI: 0.26-0.78) in patients with metastatic RCC treated with immunotherapy combinations, though selection bias was noted as non-surgical patients were older and less fit [13]. Similarly, Park and al. demonstrated improved OS for patients undergoing systemic therapy followed by CN (HR 0.30, 95% CI: 0.13-0.68) or CN followed by systemic therapy (HR 0.68, 95% CI: 0.47-0.97) compared to systemic therapy alone [14]. More recently, Markakis and al. reported in an individual patient data meta-analysis that cytoreductive nephrectomy was associated with improved overall survival in patients receiving immune checkpoint inhibitor-based therapy. However, the authors also highlighted the persistent risk of selection bias and the need for prospective randomized evidence before definitive conclusions regarding treatment benefit can be drawn [15].

The role of cytoreductive nephrectomy in the immunotherapy era remains an area of active investigation. Ongoing randomized phase III trials, including PROBE and NORDIC-SUN, are currently evaluating the optimal integration of surgery with immune checkpoint inhibitor-based therapies. Therefore, our findings should primarily be considered hypothesis-generating and complementary to prospective evidence. Randomized data from the targeted-therapy era further temper enthusiasm for upfront surgery: the CARMENA trial found sunitinib alone to be non-inferior to nephrectomy followed by sunitinib in intermediate- and poor-risk patients, and the SURTIME trial suggested a possible benefit of a deferred surgical approach [16,17].

Patient selection is critical in determining the role of cytoreductive nephrectomy, as it is typically performed on patients who are fit for surgery, have a lower metastatic burden, or respond well to treatment. CN may also benefit patients with symptomatic relief [18]. We observed an association between CN and more favorable survival but, as in most of the current literature, we have primarily patients with clear cell carcinoma (91.8% of the cohort) and there is a lack of data for metastatic Non-Clear Cell Renal Carcinoma (NCCRCC). Fila and al. did a retrospective study focused on the impact of upfront CN on metastatic NCCRCC outcomes with first-line immune checkpoint Inhibitor (IO) combinations or Tyrosine Kinase Inhibitor (TKI) monotherapy. This suggests that CN may also benefits patients with metastatic NCCRCC, but need to be assessed in larger studies, which is difficult due to the small proportion of metastatic NCCRCC [19].

Unlike some previous studies, we did not find the number or sites of metastases to be significant survival predictors, nor

Table 2: Prognostic factors of overall survival in univariate and multivariate analysis for patients treated for a metastatic renal cell carcinoma between 2016 and 2024.

Variable	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Metastatic disease				
Metachronal	Ref			
Synchrony	2.05 (1.20 - 3.50)	0.008	0.97 (0.48 - 1.96)	0.929
Nephrectomy	0.25 (0.14 - 0.44)	<0.001	0.36 (0.18 - 0.72)	0.004
Prognosis Group (IMDC)				
Favorable	Ref			
Intermediate	1.77 (0.89 - 3.53)	0.104	1.53 (0.73 - 3.22)	0.265
Poor	4.45 (2.10 - 9.42)	<0.001	2.67 (1.05 - 6.79)	0.040
First-line medical treatment				
TKI alone	Ref			
IO-TKI/IO-IO	0.97 (0.55 - 1.71)	0.915	-	-
Number of metastatic sites				
1	Ref			
>1	0.69 (0.41 - 1.17)	0.168	-	-
Age	1.01 (0.98 - 1.04)	0.395	-	-
Histologist				
Other	Ref			
Clear renal cell carcinoma	0.41 (0.18 - 0.90)	0.027	0.65 (0.28 - 1.50)	0.316
Local treatment of metastasis	0.63 (0.35 - 1.12)	0.113	0.88 (0.47 - 1.65)	0.688

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; Ref: Reference Category.
Dashes (–) Indicate Covariates not Retained in The Multivariable Model.

Table 3: Prognostic factors of progression-free survival in univariate and multivariate analysis for patients treated for a metastatic renal cell carcinoma between 2016 and 2024.

Variable	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Metastatic disease				
Metachronal	Ref			
Synchrony	2.05 (1.31 - 3.19)	0.002	1.59 (0.94 - 2.69)	0.081
Age	0.99 (0.97 - 1.01)	0.288	-	-
Nephrectomy	0.56 (0.34 - 0.92)	0.023	0.79 (0.46 - 1.36)	0.399
Number of metastatic sites				
1	Ref			
>1	0.82 (0.53 - 1.28)	0.382	-	-
First-line medical treatment				
TKI alone	Ref			
IO-TKI/IO-IO	1.04 (0.67 - 1.64)	0.851	-	-
Prognosis Group (IMDC)				
Favorable	Ref			
Intermediate	1.62 (0.94 - 2.80)	0.084	1.34 (0.75 - 2.39)	0.322
Poor	2.43 (1.34 - 4.41)	0.004	1.63 (0.81 - 3.28)	0.171
Local treatment of metastasis	1.17 (0.75 - 1.82)	0.500	-	-
Histologist				
Other	Ref			
Clear renal cell carcinoma	0.79 (0.34 - 1.81)	0.571	-	-

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; Ref: Reference Category.
Dashes (–) Indicate Covariates not Retained in The Multivariable Model.

did we observe a surgical benefit for patients treated with immunotherapy combinations over tyrosine kinase inhibitors, likely due to limited statistical power. The OS improvement in MRCC may reflect comprehensive patient management rather than new drug therapies alone.

Our study has several strengths. First, all patients were managed within a single integrated udo-oncology program, limiting variability in treatment strategies and follow-up pathways. Second, the cohort spans a major therapeutic transition from TKI monotherapy to immune checkpoint inhibitor-based combinations and therefore provides a contemporary overview of outcomes achieved in routine practice. Third, the observed median overall survival of 54.2 months illustrates the substantial improvement in prognosis currently achievable in real-world patients with MRCC. Although larger multicenter registries have already established the prognostic value of the IMDC classification and the efficacy of modern systemic therapies, our findings provide complementary data from a tertiary referral center where systemic therapy, cytoreductive nephrectomy, and metastasis-directed treatments are integrated within a single multidisciplinary team.

However, limitations exist. This is a single-center study, which may differ from practices at other institutions. Despite prospective data collection, the retrospective nature of the analysis introduces potential biases. Additionally, the relatively small cohort size limits statistical power, potentially obscuring subtler prognostic effects.

Several additional limitations should be acknowledged. First, treatment heterogeneity across the inclusion period reflects the rapid evolution of first-line MRCC therapies between 2016 and 2024, from TKI monotherapy to IO-based combinations. Second, the relatively limited cohort size restricted the ability to perform robust subgroup analyses according to treatment regimens or metastatic sites. Third, formal discrimination and calibration metrics for IMDC prognostic performance, such as the Harrell C-index, were assessed for discrimination (C-index 0.67 for OS) but formal calibration was not performed. Finally, despite multivariable adjustment, retrospective analyses remain highly susceptible to residual confounding, indication bias, and immortal time bias, particularly regarding deferred cytoreductive nephrectomy.

Conclusion

This study confirms a significant improvement in both overall survival and progression free survival in patients with metastatic renal cell carcinoma treated with contemporary therapeutic strategies. Our findings support the continued prognostic value of the IMDC classification for overall survival in patients treated with contemporary therapeutic strategies. In this retrospective cohort, cytoreductive nephrectomy was associated with favorable survival outcomes in selected patients, although these findings require cautious interpretation due to potential selection bias and residual confounding. Further prospective randomized and multicenter studies are needed to clarify the role of cytoreductive nephrectomy and refine patient selection strategies in the immunotherapy era.

Conflict of interest: PB: Consulting and Investigator for BMS, IPSEN, MSD, PFIZER, EXELIXIS Others have no conflict of interest.

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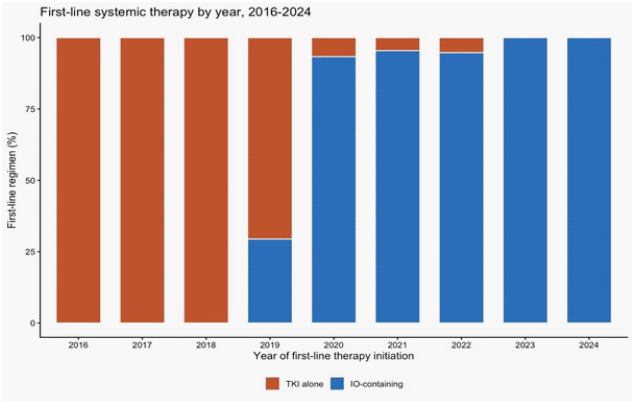

Supplementary Figure 1: Distribution of first-line systemic therapy (IO-based combinations vs TKI monotherapy) by year of treatment initiation.

Supplementary Table 1: Expanded multivariable Cox model for overall survival, additionally adjusted for the number of metastatic sites and first-line treatment type (IO-based vs TKI), in patients treated for metastatic renal cell carcinoma between 2016 and 2024.

Variable	Adjusted HR (95% CI)	P-value
Metastatic disease		
Metachronous	Ref	
Synchronous	1.03 (0.50 - 2.08)	0.945
Cytoreductive nephrectomy (Yes vs No)	0.35 (0.17 - 0.71)	0.004
Prognosis Group (IMDC)		
Favorable	Ref	
Intermediate	1.49 (0.71 - 3.15)	0.295
Poor	2.59 (1.01 - 6.63)	0.048
Histology (Clear cell vs Other)	0.61 (0.26 - 1.43)	0.257
Local treatment of metastasis (Yes vs No)	0.84 (0.45 - 1.57)	0.579
Number of metastatic sites (>1 vs 1)	0.96 (0.55 - 1.65)	0.870
First-line therapy (IO-based vs TKI alone)	0.66 (0.36 – 1.20)	0.176