Histopathological prognostic factors and survival in metastatic renal cell carcinoma: a retrospective analysis of 95 cases at Hassan II University Hospital of Fez

Background:
Metastatic renal cell carcinoma (mRCC) has undergone major therapeutic advances with the introduction of tyrosine kinase inhibitors (TKIs) and, more recently, immune checkpoint inhibitor-based combinations. However, real-world data from North Africa remain limited.
Objective:
To describe the epidemiological, clinicopathological, and therapeutic characteristics of patients with mRCC and to identify prognostic factors associated with survival.
Methods:
We conducted a retrospective, single-center study including consecutive patients diagnosed with histologically confirmed mRCC between January 2016 and June 2023. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method. Prognostic factors were explored using univariate and multivariate analyses with a Cox proportional hazards model.
Results:
A total of 95 patients were included (median age: 62 years; 64.2% male). Clear cell carcinoma was the predominant histological subtype (84.2%). According to the IMDC classification, 36.8% of patients were classified as high-risk. First-line treatment consisted of pembrolizumab plus axitinib (40.0%), TKIs alone (27.4%), bevacizumab-based therapy (16.8%), or watchful waiting (15.8%).
Median OS was 18.0 months (95% CI: 15.0–21.0), and median PFS was 10.0 months (95% CI: 7.0–13.0). In univariate analysis, factors significantly associated with poorer OS included WHO performance status ≥3, high-risk IMDC score, vascular invasion, non-clear cell histology, and partial nephrectomy. In multivariate analysis, WHO performance status ≥3, high-risk IMDC score, and vascular invasion remained independently associated with poorer overall survival.
Conclusion:
Our findings confirm the prognostic relevance of established clinical and pathological factors in mRCC. Survival outcomes in our cohort remain intermediate compared with clinical trials, likely reflecting limited access to immunotherapy combinations. Expanding access to modern treatments and promoting earlier diagnosis are key priorities in resource-limited settings.
Keywords: metastatic renal cell carcinoma, prognostic factors, survival, bevacizumab, pembrolizumab, axitinib, Morocco

1. Introduction

Renal cell carcinoma accounts for 3–5% of all adult malignancies, with increasing worldwide incidence [1]. In Morocco, it is the 4th most common urological cancer [2]. Approximately 30% of patients present with de novo metastatic disease, and 20–30% of localized cases will progress to metastatic stage after surgical treatment [3].

The therapeutic landscape of metastatic renal cell carcinoma (mRCC) has undergone major advances. In the 2000s, cytokines (interferon-alpha, interleukin-2) were used with modest efficacy. The advent of anti-angiogenic targeted therapies, including tyrosine kinase inhibitors (TKIs) such as sunitinib and pazopanib, as well as the monoclonal antibody bevacizumab (often combined with interferon), improved median survival to approximately 12–15 months [4]. More recently, the combination of an immune checkpoint inhibitor (pembrolizumab) with a TKI (axitinib) has demonstrated overall survival exceeding 45 months in pivotal trials [5,6].

However, most trials have been conducted in high-income countries. Real-world data from North Africa and the Middle East are scarce, where access to new drugs is often limited and multiple strategies (watchful waiting, bevacizumab, TKIs alone, immuno-TKIs) coexist [7].

The primary objective of this study is to describe the epidemiological, histoprognostic, and therapeutic characteristics of patients followed for mRCC in a Moroccan reference university center. The secondary objective is to identify prognostic factors influencing overall survival and progression-free survival.

2. Patients and methods

2.1. Study design and setting

This is a retrospective, observational, single-center study conducted in the Department of Medical Oncology at Hassan II University Hospital of Fez (Morocco). This institution is the main cancer center of the Fez-Meknès region (about 4.5 million inhabitants). The study was approved by the local ethics committee (ref. CE-CHU-Fès-2023/45).

2.2. Population

All patients aged ≥18 years with histologically proven metastatic renal cell carcinoma (stage IV according to TNM 8th edition) managed in the department between January 1, 2016 and June 30, 2023, were included. Patients lost to follow-up before the first response assessment or with incomplete medical records were excluded.

2.3. Data collection

Data were extracted from electronic and paper medical records using a standardized data collection form. The following variables werecollected:

- **Epidemiological**: age, sex, smoking history, arterial hypertension (AHT), diabetes.

- **Clinical and biological**: WHO performance status, IMDC score (number of risk factors: hemoglobin < lower limit of normal, corrected calcium > upper limit, Karnofsky<80%, time from diagnosis to treatment <1 year, neutrophilia, thrombocytosis), presence of vascular invasion (tumor thrombus or venous invasion on imaging).
- **Pathological**: histological type (WHO 2016 classification), Fuhrman nuclear grade.
- **Therapeutic**: type of initial surgery (total nephrectomy, partial nephrectomy, or none), first-line systemic treatment. Four categorieswereredefined:
    - Watchful waiting only (no systemic therapy, indolent disease or unfit patient)
    - Bevacizumab
    - TKI alone (sunitinib or pazopanib)
    - Immunotherapy + TKI: all patients in this group received pembrolizumab + axitinib, the only such combination administered in our center during the study period.

2.4. Statistical analysis

Quantitative variables are expressed as mean ± standard deviation or median (interquartile range) after Shapiro-Wilk normality testing. Qualitative variables are reported as counts and percentages.

Overall survival (OS) was defined as the time from metastasis diagnosis to death (any cause) or last follow-up (living patients censored at last news).

Progression-free survival (PFS) was defined as the time from initiation of first systemic treatment to radiological progression (RECIST 1.1) or death. For patients under watchful waiting, PFS was not calculated.

Survival curves were estimated using the Kaplan–Meier method, with comparisons performed using the log-rank test. Prognostic factors were assessed by univariate analysis using the chi-square test or Fisher's exact test for categorical variables. The significance threshold was set at $p < 0.05$ (two-sided). Variables with $p < 0.10$ in univariate analysis, along with clinically relevant variables, were included in the multivariate Cox proportional hazards model. Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Population characteristics

Of 112 screened patients, 95 met the inclusion criteria. The 17 excluded patients had incomplete records (n=11) or immediate loss to follow-up (n=6).

Median age was 62 years (range: 34–84). Sixty-one patients (64.2%) were male, giving a male/female ratio of 1.8. Arterial hypertension was present in 47 patients (49.5%) and current or former smoking in 34 (35.8%). A WHO

performance status ≥2 wasnoted in 41 patients (43.2%). Table 1 summarizes these data.

Table 1: Baseline clinical characteristics of the 95 patients

Age	
>60years	**62(65.3%)**
<60years	**33(34.7%)**
sex	
Male	**61(64.2%)**
Female	**34(35.8%)**
Comorbidities	
Smokinghistory	**34(35.8%)**
Hypertension	**47(49.5%)**
ESRD (end-stage renal disease)	**3(3.2%)**
Nephrectomy	
Totalnephrectomy	**58(61.1%)**
Partialnephrectomy	**14(14.7%)**
No surgery	**23(24.2%)**
Performance status	
0-1	**54(56.8%)**
>2	**41(43.2%)**

3.2. Pathologicalcharacteristics

Clear cell carcinoma was the predominant histologic type, observed in 80 patients (84.2%). Papillary carcinoma affected 9 patients (9.5%), chromophobe carcinoma 3 patients (3.2%), and other rare types (sarcomatoid, unclassified) 3 patients (3.2%).

High Fuhrman grade (grades 3–4) was found in 62 patients (65.3%).

3.3. IMDC score

The distribution according to the IMDC prognostic score was:

- Favorable risk (0 factors): 12 patients (12.6%)
- Intermediaterisk (1–2 factors): 48 patients (50.5%)
- High risk (≥3 factors): 35 patients (36.8%)

3.4. Treatmentsreceived

Regarding surgery, 58 patients (61.1%) underwent total nephrectomy, 14 patients (14.7%) partial nephrectomy, and 23 patients (24.2%) had no surgical resection (biopsy only or radiological diagnosis).

First-line systemic treatments are detailed in Table 2. Eighty patients received systemic treatment (bevacizumab, TKI, or immuno-TKI), while 15 patients were managed with watchful waiting because of indolent disease, advanced age, or comorbidities.

Table 2: First-line systemic treatment (N=95)

Treatment type	**Number of patients(%)**
Watchfulwaiting	**15 (15.8%)**
Bevacizumab	**16 (16.8%)**
TKI alone (sunitinib or pazopanib)	**26 (27.4%)**

Pembrolizumab + axitinib	**38 (40.0%)**

3.5. Prognostic factors

Univariate analysis (chi-square test) identified several factors significantly associated with poorer overall survival (Table 3):

Table 3. Univariate analysis of prognostic factors for overall survival

Variable	p-value
WHO PS ≥3	<0.001
High-risk IMDC	<0.001
Vascular invasion	<0.001
Partial nephrectomy	<0.001
Non-clearcellhistology	<0.001
Age	0.37
Hypertension	0.64
smoking	0.28
Fuhrman grade	0.09

3.6. Survival outcomes

Median overall survival (OS) for the entire cohort was 18.0 months (95% CI: 15.0–21.0). The 12-month and 24-month OS rates were 68% and 40%, respectively, reflecting a relatively poor prognosis in this population.

Among patients who received systemic treatment, median progression-free survival (PFS) was 10.0 months (95% CI: 7.0–13.0). PFS was not assessed in patients managed with watchful waiting, which should be considered when interpreting these results.

Survival outcomes varied substantially according to prognostic groups. Patients with high-risk IMDC scores had significantly worse survival compared to those with favorable or intermediate risk (log-rank $p < 0.001$), confirming the robustness of this classification in our cohort.

In exploratory analyses, patients treated with pembrolizumab plus axitinib demonstrated the most favorable outcomes, with a median OS of approximately 35 months and a median PFS of 14 months, compared to 14 months (TKIs alone), 10 months (bevacizumab), and 8 months (watchful

waiting). However, these comparisons should be interpreted with caution due to the absence of statistical testing and potential selection bias.

3.7. Multivariate analysis

A multivariate analysis was performed using a Cox proportional hazards regression model to identify independent prognostic factors associated with overall survival.

After adjustment for potential confounding variables, WHO performance status ≥3 and high-risk IMDC score remained independently associated with poorer overall survival. Patients with WHO PS ≥3 had a significantly increased risk of death (HR = 2.45, 95% CI: 1.45–4.12, p = 0.001), while those classified as high-risk according to IMDC had an even higher risk (HR = 2.87, 95% CI: 1.68–4.90, p < 0.001).

Vascular invasion also remained an independent adverse prognostic factor (HR = 1.98, 95% CI: 1.20–3.25, p = 0.007).

In contrast, histological subtype and type of nephrectomy were not significantly associated with overall survival after adjustment, suggesting that their effect observed in univariate analysis may be explained by confounding factors.

Table 4: Multivariate Cox regression analysis for overall survival

Variable	HR	95% CI	p-value
WHO PS ≥3	2.45	1.45-4.12	0.001
High-risk IMDC	2.87	1.68-4.90	<0.001
Vascular invasion	1.98	1.20-3.25	0.007
Non-clearcellhistology	1.32	0.78-2.21	0.29
Partial nephrectomy	1.21	0.70-2.08	0.48

4. Discussion

4.1. Comparison with contemporary literature

The therapeutic landscape of metastatic renal cell carcinoma (mRCC) has evolved considerably with the emergence of immune checkpoint inhibitor (ICI)-based combinations, which are now considered the standard of care in first-line treatment [5,6,17].

Long-term follow-up of pivotal trials such as KEYNOTE-426 has confirmed the sustained survival benefit of pembrolizumab plus axitinib over sunitinib, reinforcing its role as a cornerstone therapy [20]. However, outcomes observed

in clinical trials are often superior to those reported in routine practice due to strict patient selection criteria.

Recent real-world studies have provided valuable complementary data. A large multicenter analysis demonstrated that immunotherapy-based regimens significantly improve survival outcomes compared to targeted therapy alone, particularly in intermediate- and poor-risk patients [14]. Similarly, other real-world cohorts have reported median progression-free survival approaching 19–24 months with ICI–TKI combinations, compared to approximately 10 months with TKI monotherapy [15,16].

Moreover, contemporary observational studies confirm that immunotherapy combinations are associated with improved progression-free survival and longer time to treatment failure compared to TKI-based strategies [19]. These findings are further supported by meta-analyses showing consistent survival benefits of ICI-based combinations across different patient subgroups [17].

In our study, patients treated with pembrolizumab plus axitinib achieved a median overall survival of 35 months, which is slightly lower than that reported in clinical trials but remains consistent with real-world evidence. This discrepancy likely reflects differences in patient characteristics, including poorer performance status, higher comorbidity burden, and limited access to subsequent treatment lines.

4.2. Prognostic factors

The prognostic factors identified in our study are consistent with established models such as the IMDC classification, which remains a robust tool in both clinical trials and real-world settings [4,18].

Recent analyses from international databases have confirmed the continued prognostic relevance of IMDC risk groups in the immunotherapy era, even with the introduction of combination strategies [18]. In addition, real-world evidence suggests that histological subtype and clinical characteristics continue to play a major role in survival outcomes [14,19].

The negative prognostic impact of vascular invasion observed in our cohort is supported by recent literature, which identifies tumor thrombus as a marker of aggressive disease biology and increased metastatic potential.

Our multivariate analysis confirmed that performance status and IMDC risk classification remain the strongest independent prognostic factors in metastatic renal cell carcinoma, even in the era of immunotherapy. These findings are consistent with contemporary real-world studies, which continue to demonstrate the robustness of these clinical parameters across different treatment settings [18].

Although vascular invasion remained independently associated with poorer survival, histological subtype and type of surgery lost statistical significance after adjustment, suggesting that their apparent impact in univariate analysis may be influenced by underlying disease severity and patient selection. This

finding may reflect selection bias, as patients undergoing partial nephrectomy could represent a subgroup with specific clinical characteristics not fully captured in our analysis.

4.3. Therapeutic implications

Our findings highlight the persistent gap between clinical trial efficacy and real-world effectiveness, particularly in low- and middle-income countries. While immunotherapy-based combinations have become the global standard [17], access remains uneven across regions.

Real-world studies consistently demonstrate that ICI-based combinations outperform TKI monotherapy in terms of survival outcomes [15,19]. However, their implementation in routine practice is often limited by economic constraints, reimbursement policies, and healthcare infrastructure.

In our cohort, only 40% of patients received pembrolizumab plus axitinib, which likely contributed to the intermediate survival outcomes observed. This emphasizes the need for improved access to innovative therapies and optimized treatment strategies in resource-limited settings.

4.4. Study limitations

This study has several limitations. First, its retrospective and single-center design introduces potential selection bias and limits the generalizability of the findings. Second, the relatively small sample size (n=95) reduces statistical power, particularly for subgroup analyses and for the multivariate Cox model, which may lead to overfitting or wide confidence intervals.

Third, although a multivariate analysis was performed, the limited number of events and the modest cohort size restrict the number of variables that could be reliably included. Therefore, the independent prognostic factors identified should be considered exploratory and require validation in larger independent cohorts.

Furthermore, the lack of detailed data on treatment toxicity, dose modifications, and subsequent therapy lines may have influenced survival outcomes. Finally, heterogeneity in treatment strategies reflects real-world practice but complicates direct comparisons between therapeutic groups.

4.5. Future perspectives

Future research should focus on prospective multicenter cohorts and the development of national registries to better characterize mRCC epidemiology and treatment outcomes in Morocco.

In addition, recent advances highlight the emergence of new therapeutic combinations (e.g., pembrolizumab–lenvatinib) and the growing importance of personalized treatment strategies based on clinical and molecular profiling.

The identification of predictive biomarkers and optimization of treatment sequencing remain key challenges in the immunotherapy era.

Conclusion

This study confirms the prognostic value of IMDC score, performance status, vascular invasion, and non-clear cell histology in metastatic renal cell carcinoma. With a median overall survival of 18 months and 40% of patients receiving first-line pembrolizumab-axitinib, our results reflect real-world outcomes in a limited-resource setting. Broader access to immunotherapy combinations and earlier diagnosis remain the main challenges to improve survival in Morocco.

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