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Investigation of Predictive and Prognostic Factors in Metastatic Renal Cell Carcinoma (mRCC) Patients Receiving First-line Treatment: A Retrospective Single-center Experience

Birinci Basamak Tedavi Alan Metastatik Renal Hücreli Karsinom (mRCC) Hastalarında Prediktif ve Prognostik Faktörlerin Araştırılması: Retrospektif Tek Merkez Deneyimi

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Abstract

Objective: We conducted this study to assess the efficacy and identify prognostic factors associated with immunotherapy (IO) combination therapies—including IO+IO and IO+tyrosine kinase inhibitor (TKI) regimens—in patients with metastatic renal cell carcinoma (RCC).

Method: We examined 24 patients with metastatic RCC who received first-line IO+IO or IO+TKI combination therapy at Department of Medical Oncology, İstanbul Medipol University between 2022 and 2025. Demographic and clinicopathological characteristics of the patients, along with their treatment responses, were evaluated. An analysis of progression-free survival (PFS) and overall survival (OS) was conducted using Kaplan-Meier and Cox regression models. We also analyzed various prognostic factors to see how they impacted survival.

Results: Most patients were male (79.2%), and the median age was 56 years. The most common metastatic sites were lymph nodes (63%) and lungs (50.3%). The majority of patients had clear cell carcinoma histology (83.3%). Treatment responses observed were 16.7% complete response, 62.5% partial response, 12.5% stable disease, and 8.3% progressive disease. Thus, the overall response rate was found to be 79.2%. The median OS was 41.8 months, and the median PFS was 25.87 months. In the univariate analysis, the stage at diagnosis,

Öz

Amaç: Bu retrospektif, tek merkezli çalışma, metastatik renal hücreli karsinom (RCC) tanılı hastalarda immünoterapi (İO) ve İO kombinasyonu veya İO ile tirozin kinaz inhibitörü (TKİ) tedavilerinin (İO+İO veya İO+TKİ) etkinliğini ve prognostik faktörleri değerlendirmeyi amaçlamıştır.

Yöntem: 2022-2025 yılları arasında İstanbul Medipol Üniversitesi Tıbbi Onkoloji Kliniği'nde metastatik RCC tanısı ile birinci basamakta İO+İO veya İO+TKİ kombinasyon tedavisi alan 24 hasta incelendi. Hastaların demografik ve klinikopatolojik özellikleri ile tedavi yanıtları değerlendirildi. Progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) analizleri Kaplan-Meier ve Cox regresyon modelleri kullanılarak yapıldı. Sağkalımlar üzerine etkili prognostik faktörler analiz edildi.

Bulgular: Hastaların çoğu erkekti (%79,2) ve ortanca yaş 56 yıldı. En sık metastaz bölgeleri lenf nodu (%63) ve akciğer (%50,3) idi. Hastaların büyük çoğunluğu berrak hücreli karsinom histolojisine sahipti (%83,3). Tedavi yanıtları %16,7 tam yanıt, %62,5 kısmi yanıt, %12,5 stabil hastalık ve %8,3 progresif hastalık (PD) olarak gözlendi. Böylece, objektif yanıt oranı %79,2 olarak bulundu. Medyan genel sağkalım (OS) 41,8 ay, medyan PFS 25,87 ay olarak hesaplandı. Tek değişkenli analizde tanı evresi, histoloji, ve nefrektomi varlığı PFS

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Abstract

histology, and presence of nephrectomy were found to be significant for PFS, whereas in the multivariate analysis, only the stage at diagnosis was identified as an independent prognostic factor (p=0.03, hazard ratio: 5.64). For OS, while the stage at diagnosis, histology, and presence of nephrectomy were significant in the univariate analysis, no independent prognostic factors were identified in the multivariate analysis.

Conclusion: IO+IO or IO+TKI combination therapies in metastatic RCC are associated with high response rates and long survival durations. The stage at diagnosis is an independent prognostic factor for PFS. This factor is of critical importance in evaluating patient prognosis and personalizing treatment decisions.

Keywords: First-line treatment, immunotherapy, metastatic renal cell carcinoma, side effects, survival, tyrosine kinase inhibitors

Öz

için anlamlı bulunurken, çok değişkenli analizde sadece tanı evresi bağımsız prognostik faktör olarak belirlendi (p=0,03, tehlike oranı: 5,64). OS için tek değişkenli analizde ise, tanı evresi, histoloji ve nefrektomi varlığı anlamlı iken, çok değişkenli analizde herhangi bir bağımsız prognostik faktör bulunamadı.

Sonuç: Metastatik RCC'de İO+İO veya İO+TKİ kombinasyon tedavileri yüksek yanıt oranları ve uzun sağkalım süreleri ile ilişkilidir. Tanı anındaki evre PFS için bağımsız prognostik faktördür. Bu faktör, hastaların prognozunu değerlendirmede ve tedavi kararlarını kişiselleştirmede kritik öneme sahiptir.

Anahtar kelimeler: Birinci basamak tedavi, immünoterapi, metastatik renal hücreli karsinom, sağkalım, tirozin kinaz inhibitörleri, yan etkiler

Introduction

Renal cell carcinoma (RCC) is a significant global health issue. In 2022, there were 434,840 new cases, and in 2020, it was the 15th leading cause of cancer-related deaths, resulting in over 179,000 fatalities (1,2). The disease is most prevalent in those aged 60 to 70 and is more common in men, with about three male cases for every two in women (3).

Risk factors associated with RCC include systolic hypertension [relative risk (RR) 1.4], diastolic hypertension (RR: 2.3), smoking (RR: 1.6), kidney disease (up to RR: 12.3 in dialysis patients), environmental exposures, and obesity (RR 1.9), which accounts for over 16% of global cases. Obese patients are less likely to present with advanced-stage disease compared to patients with a normal weight (4-9).

RCC starts in the epithelial cells of the kidney's outer layer, the renal cortex. It is diagnosed by examining a tissue sample's appearance and through immunohistochemistry (10). Based on the World Health Organization classification, there are over 20 subtypes of malignant renal cell tumors (11). The three most common are clear cell RCC (75-80%), papillary RCC (10-15%), and chromophobe RCC (5%) (11).

Most cases of clear cell RCC—up to 90%—are associated with a loss of the Von Hippel-Lindau (VHL) tumor suppressor gene (12). While the majority of RCC cases are sporadic (not inherited), 5% to 16% of advanced (Stage III or IV) cases are due to hereditary syndromes (13). VHL disease accounts for 2% of all cases (13).

The classic signs of kidney cancer—flank pain, a lump in the abdomen, and blood in the urine—are rarely seen together, appearing in less than 10% of new RCC diagnoses (14).

Additionally, paraneoplastic syndromes, which are symptoms caused by the cancer's effect on other organs, occur in 10% to 40% of patients (15). These can include fever, high blood calcium, anemia, an increase in platelets, an increase in red blood cells, and high blood pressure (16-18).

When RCC is diagnosed, 70% of cases are in Stage I, while 11% are already in Stage IV (19-21). The prognosis is closely tied to both the tumor's stage and grade (22). Approximately 10% of new RCC patients have metastatic disease at the time of diagnosis (23). The cancer most commonly spreads to the lungs (70%), followed by the lymph nodes (45%), bones (32%), liver (18%), adrenal gland (10%), and the brain (8%) (24,25).

According to the International Metastatic RCC Database Consortium (IMDC), a patient's chances of survival are lower if they have any of the following six risk factors: an elevated neutrophil-to-lymphocyte ratio (NLR), a high platelet count, low hemoglobin, high calcium, a Karnofsky performance score below 80%, or if they required systemic treatment less than a year after their diagnosis (26). In patients with metastatic RCC receiving modern systemic combination therapies, 18-month overall survival (OS) rates have been reported to be 90% to 93% in the favorable risk group, 78% to 83% in the intermediate-risk group, and 50% to 74% in the poor-risk group (26). In a study of 645 patients with metastatic RCC, the median OS was found to be 22 months, with a 95% CI ranging from 20.2 to 26.5 months (27). These rates show a significant improvement compared to the period before the use of immune checkpoint therapies.

Cytotoxic chemotherapy is typically not effective for metastatic RCC (28). Instead, the main treatments are

immunotherapy (IO) and tyrosine kinase inhibitors (TKIs) (28). Current IOs work by blocking specific protein interactions, such as those involving progressive disease (PD)-1/PD-L1/PD-L2 and CTLA-4/CD80/CD86 (28). For advanced and metastatic RCC, the initial treatment is a combination of therapies that use IOs (28). For patients with metastatic clear cell RCC who have an intermediate or poor risk score based on the IMDC criteria, the approved initial treatment is a combination of ipilimumab and nivolumab (28). When patients with metastatic RCC achieve a complete response to IO or have oligometastatic disease, they may become disease-free. A three-year disease-free survival rate of approximately 22% to 27% can be achieved (29). A striking example of this success is seen with high-dose interleukin-2-based IO. While only 5% of patients had a complete response, 59% of those who did remained alive and cancer-free for a median of 10.5 years without needing further treatment (30,31).

The regimen demonstrated a superior OS profile compared to sunitinib, yielding a 5-year OS probability of 43% (32,33). While direct head-to-head comparisons of different IO+TKI combinations are lacking, these regimens consistently achieve higher overall response rate (ORR)—ranging from 55% to 71%—than the ipilimumab plus nivolumab combination (34-36). However, most patients experience side effects such as hypertension and diarrhea with TKI treatment (34). Treatment decisions should be individualized, considering the patient's risk tolerance. Based on the results of the CARMENA study, for most patients with advanced or metastatic disease, cytoreductive nephrectomy is no longer recommended (37).

In RCC patients receiving systemic treatment, potential immune-related side effects should be managed by a multidisciplinary team. Clinically useful predictive biomarkers to guide RCC treatment have not yet been identified. While molecular subtypes based on gene expression profiling have been reported, they have not been prospectively validated for clinical use (38).

Therefore, we retrospectively evaluated the data of patients who received IO+IO or IO+TKI as first-line treatment at our center between 2022 and 2025 and investigated the predictive and prognostic factors that may influence response and survival.

Materials and Methods

Ethics Committee Approval

All patients or their immediate family members provided informed consent to participate in the study. The İstanbul Medipol University Ethics Committee approved the study on August 6, 2025 (decision no: E-10840098-202.3.02-5070).

Patients

Between 2022 and 2025, 200 patients who received treatment for metastatic RCC at the Medical Oncology Department of İstanbul Medipol University were retrospectively screened, and data from 24 patients who received IO+IO or IO+TKI therapy as first line treatment were analyzed. Patients who received single IO or TKI were not included in the study. In addition, patients with missing information were excluded from the analysis. Patients receiving adjuvant IO were also excluded from the study. Early-stage patients receiving adjuvant therapy were not included in the study. Patients receiving post-first-line therapy were also excluded from the study.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), and categorical variables as frequencies and percentages.

Survival analyses, including progression-free survival (PFS) (time from metastatic diagnosis to progression or death) and OS (time from metastatic diagnosis to death), were performed with the Kaplan-Meier method and compared using the log-rank test.

We used univariate analysis to screen for potential prognostic factors, followed by multivariate Cox proportional hazards modeling to identify independent predictors for both PFS and OS. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to express the RR.

Data are reported as mean (standard deviation), median (min-max), 95% CI, and percentages. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

In the study of 24 patients, the demographic and clinical characteristics showed that 79.2% (19 patients) were male, and 20.8% (5 patients) were female. The median age was 56.00 years, ranging from 28 to 76 years. Thirteen patients (54.2%) were under 60 years of age, while 45.8% (n=11) were 60 years or older. At the time of diagnosis, 50.0% (n=12) of the patients were staged as Stage IV, 33.3% (n=8) as Stage II, 12.5% (n=3) as Stage III, and 4.2% (n=1) as Stage I. According to the Eastern cooperative oncology group (ECOG) performance status (PS), 79.2% (n=19) of the

patients had an ECOG PS of 0, while the remaining 20.8% (n=5) had an ECOG PS of 1.

Regarding metastasis sites, the most common site was the lymph node, found in 62.5% of patients. Additionally, lung metastasis was detected in 50%, bone in 33.3%, liver in 12.5%, and adrenal metastasis in 12.5%. It should be noted that one patient could have more than one metastatic site.

None of the patients had received prior adjuvant therapy. Histologically, the vast majority of patients (83.3%, n=20) had clear cell carcinoma histology, while 12.5% (n=3) had papillary and 4.2% (n=1) had chromophobe histology. Two patients (8.3%) had a sarcomatoid component. 62.5% (n=15) of the patients were in the IMDC intermediate-risk group, and 37.5% (n=9) were in the IMDC poor-risk group. There were no patients in the favorable-risk group.

Eleven patients (45.8%) had undergone nephrectomy, while 54.2% (n=13) had not. The mean NLR was 4.49 (median: 2.99), and the mean platelet-to-lymphocyte ratio (PLR) was 183.20 (median: 161.56).

Regarding the treatments administered, 50% (n=12) of the patients received nivolumab-cabozantinib, 25% (n=6) received pembrolizumab-axitinib, and 25% (n=6) received nivolumab-ipilimumab. Treatment responses were evaluated according to RECIST 1.1 criteria: Four patients (16.7%) showed complete response (CR), 15 patients (62.5%) showed partial response, three patients (12.5%) had stable disease (SD), and two patients (8.3%) had PD. The ORR was calculated as 79.2%. As of the time of data analysis, progression was observed in 54.2% (n=13) of patients under these treatments, while no progression was observed in 45.8% (n=11). The mean duration of treatment was 16.6 months (median: 17.10 months).

When survival data were examined, The median OS was 41.8 months, with a 95% CI of 10-115.6. On the other hand, the median PFS was 25.87 months, with a 95% CI of 12.89-38.83. PFS durations differed according to age groups; the median PFS was 21.2 months in patients under 60 years (<60), and 62.8 months in patients aged 60 and over (≥60) (p=0.5).

In the univariate analysis for PFS, only the stage at initial diagnosis (p=0.004), histology (p=0.04), and presence/absence of nephrectomy (p=0.038) were statistically significant prognostic factors. In other words, patients diagnosed at an earlier stage (stage 1 and stage 2) had significantly longer PFS durations compared to patients at a more advanced stage (stage 3 and stage 4). Other factors examined, such as age (p=0.503), gender (p=0.339), ECOG PS (p=0.216), NLR (p=0.57), PLR (p=0.6), presence of sarcomatoid component (p=0.885), and IMDC score (p=0.698) did not show a statistically significant effect on PFS. The treatment modality showed a borderline non-significance (p=0.067).

Multivariate models were constructed using factors significantly associated with outcomes in univariate analysis. For PFS, the model included stage at initial diagnosis, histology, nephrectomy status, and IMDC score. The OS analysis was further adjusted for treatment modality in addition to these factors.

In the multivariate Cox regression analysis for PFS, only the stage at initial diagnosis was found to be a statistically significant and independent prognostic factor (p=0.03, HR: 5.64, 95% CI: 1.18-26.96). A more advanced stage significantly increased the risk of progression. Histology, the presence of nephrectomy, and the IMDC score were not found to be influential factors for PFS in this model.

According to the univariate analysis for OS, the stage at initial diagnosis (p=0.005), histology (p=0.006), and presence or absence of nephrectomy (p=0.017) were statistically significant variables affecting OS. In other words, the median OS durations of patients diagnosed at an earlier stage were significantly longer than those of patients at a more advanced stage (p=0.005). Patients with clear cell histology had significantly longer OS durations than those with papillary and especially chromophobe histology (p=0.006). The presence or absence of nephrectomy also significantly affected OS (p=0.017). Patients who underwent nephrectomy had longer OS durations than those who did not.

For OS, while the stage at diagnosis, histology, and presence of nephrectomy were significant in the univariate analysis, no independent prognostic factors were identified in the multivariate analysis. Factors, such as stage at initial daignosis (p=0.075, HR: 4.0, 95% CI: 0.87-18.36) histology (p=0.55, HR: 1.5, 95% CI: 0.38-5.94), nephrectomy (p=0.87, HR: 0.82, 95% CI: 0.079-8.54), and the treatment received (p=0.76, HR: 0.90, 95% CI: 0.47-1.72), did not show a statistically significant independent effect on OS in this model.

The most common side effects included hypothyroidism (6 patients, 25.0%), diarrhea (5 patients, 20.8%), and hepatitis (5 patients, 20.8%). Additionally, pruritus was observed in two patients (8.3%), Grade 2 hypertension related to axitinib in one patient, Grade 3 orthohyperkeratosis in one patient, and IO-related bullous pemphigoid in

one patient. When the grades of the side effects were examined, 77.8% (n=14) were reported as Grade 2, 16.7% (n=3) as Grade 3, and 5.6% (n=1) as Grade 1. Three patients experienced Grade 3 immune-related adverse events (hepatitis, orthohyperkeratosis, bullous pemphigoid) required steroid intervention. Importantly, no patient discontinued treatment as a result of these side effects.

The results of univariate and multivariate analyses for OS and PFS are summarized in Tables 1 and 2. Toxicity type, grade, and number of patients affected (Grade 1-2 vs. ≥3) is summarized in Table 3.

Kaplan-Meier survival curves for PFS and OS are presented in Figure 1 and Figure 2.

Table 1. Univariate and multivariate analysis for PFS

Variable	Median PFS (months)	Univariate p-value	HR (95% CI)	Multivariate p-value
Age, years		0.50		
<60	21.23			
>60	32.83			
Gender		0.33		
Female	19.33			
Male	28.23			
Stage at initial diagnosis		0.004	5.64 (1.18-26.96)	0.03
Stage 1 Stage 2 Stage 3	165.43 117.06 25.86			
Stage 4	10.03			
ECOG PS		0.21		
0	62.83			
1	21.23			
Histology		0.04	1.83 (0.67-4.98)	0.23
Clear cell	25.86			
Papiller	28.23			
Chromophobe	6.36			
Sarcomatoid component		0.88		
Present	4.53			
Absent	25.86			
IMDC score		0.698		
Intermediate	28.23			
Poor	21.23			
Nephrectomy		0.038	0.39 (0.03-3.93)	0.42
Present	62.83			
Absent	19.33			
Treatment modality		0.067		
Pembrolizumab-axitinib	10.03			
Nivolumab-cabozantinib Nivolumab-ipilimumab	19.33 117.06			
NLR		0.57		
<2.98	25.86			
≥2.98	19.33			
PLR		0.60		
<161.5	62.83			
≥161.5	21.23			

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ECOG PS: Eastern cooperative oncology group performance status, IMDC: International metastatic RCC database consortium, CI: Confidence interval, HR: Hazard ratio, RCC: Renal cell carcinoma, PFS: Progression-free survival

Table 2. Univariate and multivariate analysis for OS

Variable	Median OS (months)	Univariate p-value	HR (95% CI)	Multivariate p-value
Age, years		0.78		
<60	35.76			
>60	41.80			
Gender		0.086		
Female	19.33			
Male	124.4			
Stage at initial diagnosis		0.005	4.0 (0.87-18.36)	0.075
Stage 1 Stage 2 Stage 3	167.4 124.4 35.76			
Stage 4	16.06			
ECOG PS		0.084		
0	167.4			
1	21.23			
Histology		0.006	1.5 (0.38-5.94)	0.55
Clear cell	124.43			
Papiller	41.80			
Chromophobe	6.36			
Sarcomatoid component		0.61		
Present	7.0			
Absent	41.8			
IMDC score		0.26		
Intermediate	41.8			
Poor	21.23			
Nephrectomy		0.017	0.82 (0.079-8.54)	0.87
Present	124.43			
Absent	21.23			
Treatment modality		0.059	0.90 (0.47-1.72)	0.76
Pembrolizumab-axitinib	16.06			
Nivolumab-cabozantinib Nivolumab-ipilimumab	NR 124.43			
NLR		0.74		
<2.98	35.76			
≥2.98	124.43			
PLR		0.21		
<161.5	167.4			
≥161.5	28.76			

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ECOG PS: Eastern cooperative oncology group performance status, IMDC: International metastatic RCC database consortium, CI: Confidence interval, HR: Hazard ratio, RCC: Renal cell carcinoma, NR: Not reached, OS: Overall survival

Discussion

The main findings of our study show that the stage at initial diagnosis is independent prognostic factors for PFS. In the OS analyses, the univariate analysis showed that the stage at initial diagnosis, histology, and the presence of nephrectomy were significant prognostic factors influencing OS. It is widely accepted that the stage at the time of diagnosis is a critical indicator for prognosis, and our finding was consistent with the literature (22,23). Similarly, it is known that the histological subtype, especially clear cell carcinoma, is associated with a better prognosis (11). Although the significant effect of nephrectomy in the

Table 3. Toxicity type, grade, and number of patients affected (Grade 1-2 vs. ≥3)

Toxicity type	Patients affected (n)	Incidence (%)	Grade 1 (n)	Grade 2 (n)	Grade ≥3 (n)	Key notes/association
Hypothyroidism	6	25.0%	Included in n=1 (total Grade 1)	Included in n=14 (total Grade 2)	0	Most common side effect.
Diarrhea	5	20.8%	-	Included in n=14	0	-
Hepatitis	5	20.8%	-	Included in n=14	1	One of the Grade 3 events requiring intervention.
Pruritus (itching)	2	8.3%	-	Included in n=14	0	-
Hypertension	1	4.2%	0	1	0	Grade 2; related to axitinib.
Orthohyperkeratosis	1	4.2%	0	0	1	Grade 3.
Bullous pemphigoid	1	4.2%	0	0	1	IO-related Grade 3 event.
Total events graded	-	-	1	14	3	77.8% were Grade 2, and 16.7% were Grade 3.

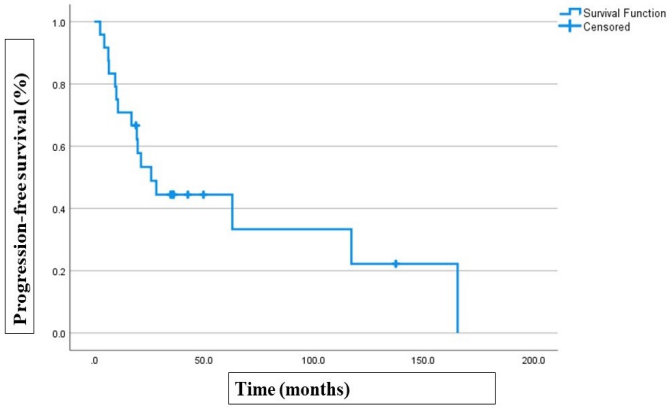

Figure 1. Kaplan-Meier curves for progression-free survival

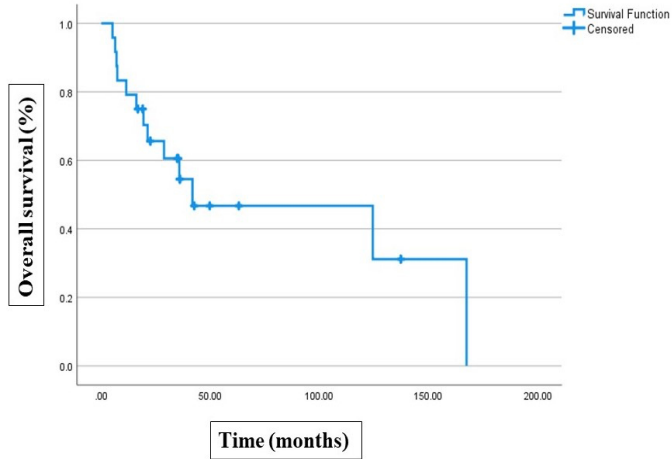

Figure 2. Kaplan-Meier curves for overall survival

univariate analysis highlights the importance of primary tumor control, its failure to be an independent factor in the multivariate analysis supports the existing conflicting literature.

While the stage at diagnosis, histology, and presence of nephrectomy were significant in the univariate analysis for OS, no independent prognostic factors were identified in the multivariate analysis.

Interestingly, factors that appeared significant in the univariate analysis, such as histology and whether a nephrectomy was performed, were not significant in the multivariate OS analysis. This suggests that the prognostic effects of these variables may be partially explained by or are correlated with more powerful prognostic factor included in the model, such as the stage at initial diagnosis. The role of cytoreductive nephrectomy in metastatic kidney cancer is changing with the development of modern systemic therapies, and it is no longer routinely recommended for some patient groups based on the results of the CARMENA study (37). Our study's finding suggests that the independent prognostic effect of nephrectomy may be overshadowed by other clinical prognostic factors in a multivariate model. This may be related to the small number of patients in our study.

In the PFS analyses, the univariate analysis found the stage at initial diagnosis and histology to be significant, while only the stage at initial diagnosis was identified as an

independent prognostic factor for PFS in the multivariate analysis. This indicates that the initial stage of the disease plays a critical and independent role in determining the risk of progression. The lack of significance for histology in the multivariate PFS analysis may again be due to the influence of other strong factors. Other factors such as ECOG PS, NLR, PLR, and the presence of a sarcomatoid component did not show a significant prognostic effect in the univariate analyses for both PFS and OS. The lack of statistical significance for these factors, which have been shown to be prognostic in larger cohorts (NLR, PLR), is primarily attributed to the limited sample size (n=24). The low statistical power prevented these factors from reaching the threshold of significance. Additionally, the NLR and PLR values were treated as continuous variables, but defining a specific cut-off point (e.g., NLR >3 or 5) might have revealed prognostic value. Although some studies have shown the prognostic importance of these markers (26), this significance may not have been reached in our small patient group.

Due to the relatively small sample size, inclusion of multiple covariates in the multivariable Cox model may have introduced a risk of overfitting, potentially affecting the stability of HR estimates. Therefore, multivariable findings should be interpreted cautiously.

The median OS of 41.8 months and the median PFS of 25.87 months observed under treatment reflect a significant improvement compared to the period before the use of immune checkpoint therapies in metastatic RCC patients (26,27). The observed side effects (such as hypothyroidism, diarrhea, and hepatitis) also overlap with the known toxicity profiles of IO and TKI combinations (28). The treatment response rates of the patients included in the study appear to be consistent with the high ORR reported in the literature for modern immuno-oncology-based combination therapies (rates ranging from 55% to 71% have been reported) (34-36).

Study Limitations

Our study has some important limitations. The most notable limitation is the small sample size of only 24 patients. This may have reduced the statistical power, causing some clinically important factors to fail to reach statistical significance. Since this was a retrospective study conducted at a single center, its findings may not apply to a wider patient population and introduces potential biases in data collection. The presentation of multi-categorical variables (such as histology, treatment modality) with a single degree of freedom (df=1) in the multivariate analysis prevented us from providing detailed results for specific subcategory comparisons.

Conclusion

Our findings re-emphasize that the stage at initial diagnosis is critically important independent prognostic factor for predicting PFS in metastatic RCC patients. This factor maintain its place in clinical practice for evaluating patient prognosis and individualizing treatment strategies. Future research should validate these findings in larger, multi-center, and prospective patient cohorts. Additionally, the investigation of new and validated biomarkers to further guide RCC treatment will help us predict treatment response and survival more accurately. Such studies will contribute to the development of personalized medicine approaches.

Ethics

Ethics Committee Approval: The İstanbul Medipol University Ethics Committee approved the study on August 6, 2025 (decision no: E-10840098-202.3.02-5070).

Informed Consent: All patients or their immediate family members provided informed consent to participate in the study.

Footnotes

Authorship Contributions

Concept: J.H., E.K., Ö.F.Ö., Ö.Y., A.B., Design: J.H., E.K., Ö.A., A.B., Data Collection or Processing: J.H., E.K., Ö.A., Analysis or Interpretation: J.H., E.K., Ö.F.Ö., Ö.Y., A.B., Literature Search: J.H., Ö.A., Ö.F.Ö., Ö.Y., Writing: J.H., A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17-48.
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. (2024). Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today.
3. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of renal cell carcinoma. Eur Urol. 2019;75(1):74-84.
4. Cheung CY, Chan GC, Chan SK, Ng F, Lam MF, Wong SS, et al. Cancer incidence and mortality in chronic dialysis population: a multicenter cohort study. Am J Nephrol. 2016;43(3):153-159.

5. Chow WH, Gridley G, Fraumeni JF, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 2000;343(18):1305-1311.

6. Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC study group. Multicenter urothelial and renal cancer study. Int J Epidemiol. 2000;29(6):1014-1024.

7. Henschler D, Vamvakas S, Lammert M, Dekant W, Kraus B, Thomas B, et al. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. Arch Toxicol. 1995;69(5):291-299.

8. Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G, et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. J Natl Cancer Inst. 2013;105(24):1862-1870.

9. Arnold M, Pandeya N, Byrnes G, Renehan PAG, Stevens GA, Ezzati PM, et al. Global burden of cancer attributable to high bodymass index in 2012: a population-based study. Lancet Oncol. 2015;16(1):36-46.

10. Al-Ahmadie HA, Alden D, Qin LX, Olgac S, Fine SW, Gopalan A, et al. Carbonic anhydrase IX expression in clear cell renal cell carcinoma: an immunohistochemical study comparing 2 antibodies. Am J Surg Pathol. 2008;32(3):377-382.

11. Moch H, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, et al. The 2022 World Health Organization classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol. 2022;82(5):458-468.

12. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol. 2004;22(24):4991-5004.

13. Carlo MI, Mukherjee S, Mandelker D, Vijai J, Kemel Y, Zhang L, et al. Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma. JAMA Oncol. 2018;4(9):1228-1235.

14. Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF. Diagnosis and management of renal cell carcinoma: a clinical and pathologic study of 309 cases. Cancer. 1971;28(5):1165-1177.

15. Loughlin KR. The great masquerader's new wardrobe in the modern era: the paraneoplastic manifestations of renal cancer. Urol Clin North Am. 2023;50(2):305-310.

16. Moldovan T, Boynton D, Kuperus J, Parker J, Noyes SL, Brede CM, et al. Incidence and clinical relevance of paraneoplastic syndromes in patients with renal cell carcinoma. Urol Oncol. 2023;41(9):392.e11-392.e17.

17. Pallagani L, Choudhary GR, Himanshu P, Madduri VKS, Singh M, Gupta P, et al. Epidemiology and clinicopathological profile of renal cell carcinoma: a review from tertiary care referral centre. J Kidney Cancer VHL. 2021;8(1):1-6.

18. Kim HL, Belldegrun AS, Freitas DG, Bui MH, Han KR, Dorey FJ, et al. Paraneoplastic signs and symptoms of renal cell carcinoma: implications for prognosis. J Urol. 2003;170(5):1742-1746.

19. Patel HD, Gupta M, Joice GA, Srivastava A, Alam R, Allaf ME, et al. Clinical stage migration and survival for renal cell carcinoma in the United States. Eur Urol Oncol. 2019;2(4):343-348.

20. Cheaib JG, Patel HD, Johnson MH, Gorin MA, Haut ER, Canner JK, et al. Stage-specific conditional survival in renal cell carcinoma after nephrectomy. Urol Oncol. 2020;38(1):6.e1-6.e7.

21. Ficarra V, Righetti R, Pilloni S, D'amico A, Maffei N, Novella G, et al. Prognostic factors in patients with renal cell carcinoma: retrospective analysis of 675 cases. Eur Urol. 2002;41(2):190-198.

22. Palumbo C, Pecoraro A, Knipper S, Rosiello G, Luzzago S, Deuker M, et al. Contemporary age-adjusted incidence and mortality rates of renal cell carcinoma: analysis according to gender, race, stage, grade, and histology. Eur Urol Focus. 2021;7(3):644-652.

23. Pierorazio PM, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. Eur Urol. 2015;68(3):408-415.

24. Dudani S, de Velasco G, Wells JC, Gan CL, Donskov F, Porta C, et al. Evaluation of clear cell, papillary, and chromophobe renal cell carcinoma metastasis sites and association with survival. JAMA Netw Open. 2021;4(1):e2021869.

25. Duarte C, Hu J, Beuselinck B, Panian J, Weise N, Dizman N, et al. Metastatic renal cell carcinoma to the pancreas and other sites-a multicenter retrospective study. EClinicalMedicine. 2023;60:102018.

26. Ernst MS, Navani V, Wells JC, Donskov F, Basappa N, Labaki C, et al. Outcomes for international metastatic renal cell carcinoma database consortium prognostic groups in contemporary first-line combination therapies for metastatic renal cell carcinoma. Eur Urol. 2023;84(1):109-116. Erratum in: Eur Urol. 2023;83(6):e166-e167.

27. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794-5799.

28. Rose TL, Kim WY. Renal cell carcinoma: a review. JAMA. 2024;332(12):1001-1010.

29. Appleman LJ, Kim SE, Harris WB, Pal SK, Pins MR, Kolesar J, et al. Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease after metastasectomy: ECOG-ACRIN E2810. J Clin Oncol. 2024;42(17):2061-2070.

30. Buchbinder EI, Dutcher JP, Daniels GA, Curti BD, Patel SP, Holtan SG, et al. Therapy with high-dose interleukin-2 (HD IL-2) in metastatic melanoma and renal cell carcinoma following PD1 or PDL1 inhibition. J Immunother Cancer. 2019;7(1):49.

31. Fishman M, Dutcher JP, Clark JI, Alva A, Miletello GP, Curti B, et al. Overall survival by clinical risk category for high dose interleukin-2 (HD IL-2) treated patients with metastatic renal cell cancer (mRCC): data from the PROCLAIM^{SM} registry. J Immunother Cancer. 2019;7(1):84.

32. Albiges L, Tannir NM, Burotto M, McDermott D, Plimack ER, Barthélémy P, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open. 2020;5(6):e001079.

33. Tannir NM, Escudier B, McDermott DF, Burotto M, Choueiri TK, Hammers HJ, et al. Nivolumab plus ipilimumab (NIVO+IPI) vs sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC): long-term follow-up data from the phase 3 CheckMate 214 trial. J Clin Oncol. 2024;42(4):363.

34. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med. 2021;384(14):1289-1300.

35. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2021;384(9):829-841.

36. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1116-1127.

37. Méjean A, Ravaud A, Thezenas S, Colas S, Beauval JB, Bensalah K, et al. Sunitinib alone or after nephrectomy in metastatic renalcell carcinoma. N Engl J Med. 2018;379(5):417-427.

38. Motzer RJ, Banchereau R, Hamidi H, Powles T, McDermott D, Atkins MB, et al. Molecular subsets in renal cancer determine outcome to checkpoint and angiogenesis blockade. Cancer Cell. 2020;38(6):803-817.e4.