Scientific Reports

https://doi.org/10.1038/s41598-026-35435-3

Article in Press

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Received: 25 March 2025

Accepted: 6 January 2026

Published online: 17 January 2026

Cite this article as: Bolek H., Sertesen Camoz E., Kuzu O.F. *et al.* Prognostic role of smoking in metastatic renal cell carcinoma in real-world data from the Turkish Oncology Group Kidney Cancer Consortium (TKCC). *Sci Rep* (2026). https://doi.org/10.1038/s41598-026-35435-3

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Prognostic role of smoking in metastatic renal cell carcinoma in real-world data from the Turkish Oncology Group Kidney Cancer Consortium (TKCC)

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Abstract

Smoking has been implicated as a potential factor influencing cancer progression and outcomes in various malignancies, including metastatic renal cell carcinoma (mRCC). This study aimed to evaluate the effect of smoking status on treatment outcomes in mRCC patients, with a focus on metastatic sites. This retrospective cohort study utilized data from the Turkish Oncology Group Kidney Cancer Consortium (TKCC). The primary endpoint of the study was overall survival (OS) across metastatic sites. A total of 779 patients were included, of whom 464 (58.1%) were former/current smokers. Smoking status did not significantly affect OS in the overall cohort. However, in the bone metastatic subgroup, former/current smokers exhibited worse OS compared to never smokers (33.9 months vs. 22.1 months; p = 0.005). Multivariate Cox regression analysis showed that former/current smoking was an independent predictor for OS in patients with bone metastasis (former/current smoker vs never smoker HR 1.44, 95%CI 1.05-1.99; p = 0.026) and bone-only metastasis (former/current smoker vs never smoker HR 4.44; 95%CI 1.27-15.55; p = 0.020) after adjusting for confounding factors. Smoking is an independent predictor of poor survival in mRCC patients with bone metastases, highlighting the organ-specific effects of smoking on cancer progression. Further research is needed to explore underlying mechanisms and evaluate outcomes in the context of modern therapies.

Keywords

Renal cell carcinoma

Smoking

Bone metastasis

Overall survival

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Introduction

Kidney cancer remains a significant global health burden, with an annual incidence of approximately 434,419 cases and 155,702 deaths [1]. While cigarette smoking is a well-established risk factor for renal cell carcinoma (RCC), its role in disease progression and prognosis is less well-defined. Previous studies have reported inconsistent findings regarding the impact of smoking on overall survival (OS) in RCC patients [2, 3]. Studies supporting a causal relationship highlight a clear dose-response correlation, and the benefits of cessation on risk have been consistently demonstrated [2-5]. In epidemiologic studies cigarette smoking is associated with higher incidence of lymph node involvement and metastatic stage in patients with RCC [6]. Smoking has been linked to various biological processes, such as angiogenesis,

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migration, invasion, and resistance to cell death, which contribute to the aggressive behavior of many cancers and may explain its association with advanced clinicopathological features in RCC.

Given that smokers often present with more advanced disease, smoking may be linked to disease progression and poorer clinical outcomes. Smokers with clear cell RCC display more aggressive pathological features and higher aberrant p53 expression, which may contribute to poorer survival outcomes compared to nonsmokers [7]. Multiple studies showed that smoking negatively impacts the renal cancer specific survival and overall survival in patients with RCC, but results are inconsistent [6-10]. The effect of smoking on treatment responses could be influenced by the physiology of specific organs and metastatic sites. Variations in the tumor microenvironment, immune system interactions, and vascular architecture in different organs and metastatic locations may modulate how smoking influences treatment outcomes. Furthermore, the influence of smoking on treatment outcomes may vary based on the affected metastatic sites, given the unique tumor microenvironments of different organs. Bone metastases, which occur in about 30–40% of mRCC cases, are associated with particularly poor outcomes and represent a distinct biological and clinical challenge. Despite this, limited research has examined how smoking impacts survival specifically in patients with bone metastases.

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This study aims to address this gap by investigating the prognostic role of smoking status in mRCC patients, with a specific focus on metastatic sites, particularly the bone, to provide insights into organ-specific effects and guide future therapeutic approaches.

Method

Patient population

We performed a retrospective cohort study using patient data sourced from the Turkish Oncology Group Kidney Cancer Consortium (TKCC) Database, which includes patients with mRCC who are 18 years of age or older from different cancer centers in Turkey The study included patients who had a diagnosis of mRCC, were older than 18 years of age, and received TKI or IO-based combination systemic treatment as first-line treatment. The study excluded patients with missing data on smoking status or metastatic sites, as well as those with incomplete data required for overall survival analysis.

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Demographic information (e.g., age, gender), smoking status, nephrectomy history, sites of metastasis, first-line treatment details, pathological characteristics (e.g., histological subtype, presence of sarcomatoid features), the initiation date of systemic treatment for metastatic disease, the date of the last follow-up, and mortality status were retrieved from the TKCC database.

End points and statistical analysis

The primary endpoint of the study was to investigate the effects of smoking status on overall survival (OS) in the overall cohort and across metastatic site subgroups. OS was defined as the time from the initiation of first-line therapy to death from any cause. Progression free survival defined as the time from the initiation of first-line therapy to progression or death from any cause. Objective response rate (ORR) was defined as the proportion of patients who achieved a complete response or partial response according to RECIST 1.1. Disease control rate (DCR) was defined as the proportion of patients who achieved complete response, partial response, or stable disease according to RECIST 1.1.All statistical analyses were conducted using IBM SPSS Statistics version 24.0 for Mac (IBM Corp., Armonk, NY). Continuous variables were expressed as medians with interquartile ranges (IQR), while categorical variables were presented as percentages. Comparisons of categorical variables were performed using the Chi-square test, and continuous variables were compared using either the Mann-Whitney U test or the Student's T-test. Survival outcomes were estimated using the Kaplan-Meier method. Multivariate analyses were performed using variables with a p value of ≤ 0.20 in the univariate analyses. Multivariable Cox regression analysis was employed to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). All p-values were two-sided, with statistical significance defined as $p < 0.05$.

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Mthics approval

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ankara University Medical Faculty Ethics Committee (Approval Number: I09-701-24). Due to the retrospective design of the study, informed consent to participate was waived by the Ankara University Medical Faculty Ethics Committee

Results

A total of 1,415 patients diagnosed with mRCC were screened for the study. Of these, 117 patients were excluded for not receiving treatment for metastatic disease, 54 patients were

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excluded for receiving nonstandard treatments, 299 patients were excluded due to unknown smoking status, 153 patients were excluded due to missing data on metastatic sites, and 13 patients were excluded due to missing data required for overall survival calculations (Fig. 1). The study included a total of 779 patients. The median age was 61.2 years (IQR: 14.1). Among the patients, 597 (74.7%) were male, and 669 (83.7%) had an ECOG performance status of 0-1. A total of 464 patients (58.1%) were current or former smokers, while 335 (41.9%) were never smokers. Among the patients, 635 (79.5%) patients had clear cell histology. Regarding the IMDC risk groups, 112 patients (14%) were in the favorable-risk category, 385 (48.2%) in the intermediate-risk category, and 168 (21%) in the poor-risk category. The most common metastatic site was the lung (n=561, 70.2%), followed by lymph node/soft tissue metastases (n=485, 60.7%) and bone metastases (n=332, 41.6%) (Table 1).

Median OS was 36.3 months (95%CI 31.1-41.5) for the overall population. Median OS was 37.6 months (95%CI 28.1-47.1) and 34.3 months (95%CI 27.4-41.2) for never smokers and former/current smokers, respectively (p = 0.373) (Fig. 2). There was no significant difference in median OS between never smokers and former/current smokers among patients with lung metastasis, lymph node/soft tissue metastasis, liver metastasis, or CNS metastasis. (Supplementary Figure 1). In patients with bone metastases, the median OS was longer in never smokers [33.9 months (95%CI 23.1-44.79)] compared to former/current smokers [22.1 months (95%CI 16.1-28.2)] (p = 0.005) (Fig. 3A). Among patients without bone metastases, there was no significant difference in median overall survival based on smoking status. Former/current smokers had a median OS of 57.2 months (95% CI 39.9-74.6), compared to 45.3 months (95% CI 33.6-57.0) for never smokers (p = 0.238) (Fig. 3B).

In the bone metastatic subgroup, the proportion of male patients was significantly higher among former/current smokers (90.4%) compared to never smokers (51.5%) (p < 0.001). Additionally, patients with ECOG performance status 2-3 were more prevalent in the former/current smoker group (25.2%) compared to the never smoker group (16.4%) (p = 0.046). While the frequency of metastatic sites was generally similar between the two groups, lung metastases were significantly more common in former/current smokers (66.2%) compared to never smokers (55.2%) (p = 0.044). There were no differences in other clinicodemographic characteristics between the former/current smoker and never smoker groups (Table 2).

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In the bone metastatic subgroup, in addition to former/current smoking (HR1.51, 95%CI 1.13-2.01; p = 0.005), ECOG performance status 2-3 (HR 2.85, 95%CI 2.07-3.92; p <0.001), IMDC poor risk group (HR 3.45, 95%CI 2.03-5.84; p <0.001), presence of lung metastasis (HR 1.65, 95%CI 1.23-2.20; p = 0.001) and presence of liver metastasis (HR 1.96, 95%CI 1.45-2.66; p <0.001) were associated with shorter OS in univariate analysis (Table 3). Multivariate Cox regression analysis showed that former/current smoking was an independent predictor for OS in patients with bone metastasis (former/current smoker vs never smoker HR 1.44, 95%CI 1.05-1.99; p = 0.026) after adjusting for confounding factors, such as age, ECOG performance status, previous nephrectomy, IMDC risk groups, lung metastasis, liver metastasis and CNS metastasis (Table 3). Disease progression occurred in 256 patients (77.1%), and 221 of these (86.3%) received at least one line of systemic therapy after progression. Details of post-progression second-line treatments are provided in Supplementary table 1. There was no difference in median progression free survival (PFS) between never smokers and former/current smokers among the bone metastatic subgroup [7.39 months (95%CI 5.28-9.50 and 7.23 months (5.66-8.79), respectively] (Supplementary Figure-2).

In the subgroup of patients with bone-only metastasis (n=51), the median OS was 86.7 months (95% CI: 35.9-137.6) in never smokers and 55.3 months (95% CI: 18.2-92.3) in former/current smokers (p = 0.169), with no significant differences in baseline clinicodemographic characteristics between the groups (Supplementary table 2). Yet, multivariate Cox regression analysis showed that former/current smoking was an independent predictor for OS in patients with bone-only metastasis (former/current smoker vs never smoker HR 4.44; 95%CI 1.27-15.55; p = 0.020) after adjusting for confounding factors, such as ECOG performance status, previous nephrectomy, histologic subtype, IMDC risk groups (Table 4).

Radiologic response was assessable in 508 patients. In the overall population, ORR and DCR were 40.9 vs 37.2% and 74.9 vs 75.8% for never smokers and former/current smokers, respectively. In the bone metastasis subgroup, radiologic response was assessed in 118 patients, and ORR and DCR were 41.3 vs 33.4% and 70.0% vs 69.4% for never smokers and former/current smokers, respectively.

Discussion

Our study demonstrates that smoking status significantly impacts the prognosis of patients with mRCC, particularly those with bone metastases. While smoking did not affect OS in the general mRCC cohort, former and current smokers with bone metastases had significantly shorter OS

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compared to never smokers. Multivariate analysis confirmed that smoking was an independent predictor of poor OS in both the bone metastatic and bone-only metastatic subgroups. These findings underscore the organ-specific impact of smoking, particularly on the bone microenvironment, which may influence disease progression and survival outcomes in this subgroup.

Additionally, our analysis showed that former/current smokers with bone metastases were more likely to present with poor ECOG performance status and concomitant lung metastases compared to never smokers. Additionally in bone metastatic subgroup ORR was higher (41.3% vs 33.4%) in never smokers, although assessing the radiologic response in bone metastasis is challenging. These factors may further contribute to the worse survival outcomes observed in smokers with bone metastases. Interestingly, no significant differences in OS were observed between smoking groups for other common metastatic sites, including lung, liver, lymph nodes, or CNS.

Studies provide inconsistent findings regarding the impact of smoking on mRCC prognosis. For instance, an analysis of the IMDC database revealed no significant differences in OS, time to treatment failure (TTF), or objective response rate (ORR) among patients with mRCC receiving first-line IO-based combination therapies, regardless of smoking status [10]. However, a non-prespecified subgroup analysis of the phase-III JAVELIN Renal 101 trial indicated that current/former smokers appeared to derive greater benefit from avelumab and axitinib treatment compared to never smokers [11]. In patients treated with VEGF-TKI, no significant difference in PFS was observed among current, former, and never smokers. However, OS was shorter in current smokers, and the intensity of smoking was identified as an independent predictor of OS [12]. Depending on the microenvironment and physiology of the organs that are affected, smoking may have different effects on treatment responses at different metastatic sites.

Bone metastases are a common site of disease in patients with mRCC, occurring in approximately 30% of cases, though the prevalence was slightly higher in our cohort (41.6%) [13, 14]. Patient and disease characteristics including age, gender, histological subtype, and the distribution of IMDC risk categories were aligned with the general literature [15, 16]. Bone metastases have been identified as a poor prognostic factor for patients with mRCC. [17]. Studies have shown that bone-only metastases are associated with better outcomes compared

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to bone plus extraosseous metastases, and the number of bone metastases correlates with disease prognosis [13, 18, 19]. Similarly, in our cohort, patients with bone-only disease had longer OS compared to the overall bone metastatic group (86.7 months and 33.9 months for never smokers and 55.3 months and 22.1 months for former/current smokers, respectively).Cigarette smoking causes aberrant regulation of various signal transduction mechanisms and is associated with genetic abnormalities and tumor progression. Cigarette smoking affects the cells responsible for bone remodeling and alters the bone microenvironment. Smoking impairs the proliferation and differentiation of osteoblasts via various mechanisms. Smoking also affects osteoclast differentiation by increasing precursor numbers, promoting their proliferation, and inhibiting apoptosis [20]. Furthermore, levels of IL-1, IL-6, and TNF are elevated in current and former smokers compared to nonsmokers, resulting in increased inflammatory and osteoclastogenic cytokines, which further exacerbate bone destruction [21]. Additionally, smoking induces alterations in the bone microenvironment and architecture [21]. These changes may influence the progression and characteristics of bone metastases, creating a favorable environment for tumor growth and metastatic spread. In patients with lung cancer, IL-6 and RANKL levels were elevated in smokers. Smoking was shown to enhance IL-6-dependent cell migration through the activation of PI3K, Akt, and NF-κB signaling pathways. Additionally, IL-6 contributes to smoking-induced osteoclastogenesis in lung cancer, promoting osteolytic bone metastasis [22]. Osteopontin, another critical protein involved in malignant transformation and metastasis, has been found at higher levels in smokers [23-25]. Metastatic tumor cells with reduced osteopontin expression have demonstrated a significant loss of metastatic activity. Melanoma model has shown that bone metastasis is significantly reduced in osteopontin-deficient mice compared to wild-type mice [26]**.** The pathophysiology of bone metastases and the impact of smoking on bone metabolism are highly complex, highlighting the need for comprehensive translational research to elucidate the influence of smoking on the tumor microenvironment and its effects on organ-specific antitumor responses.

Our study has several limitations. First, as a retrospective analysis, it is inherently subject to biases, including selection bias and missing data, which may have influenced the outcomes. Second, data on smoking status and the number of pack-years of tobacco exposure were obtained through self-reported patient interviews, lacking detailed information such as the timing of smoking cessation and cumulative tobacco exposure. This limitation is particularly relevant, as previous studies have identified smoking as an independent prognostic factor for

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renal cell carcinoma survival, and some reports suggest that current smokers have a poorer prognosis than former smokers, with smoking cessation after diagnosis potentially improving survival [8, 12, 27]. Additionally, Moreover, cancer-specific survival could not be calculated in our cohort, so we cannot exclude the possibility that part of the observed effect of smoking on OS is driven by non–cancer-related mortality. Furthermore, only a minor portion of patients received IO-based combination therapies, which represent the current standard of care. Finally, organ-specific radiologic responses could not be assessed. Despite limitations, this study is among the largest to examine smoking's prognostic impact in mRCC, with a novel focus on metastatic sites. Robust multivariate analyses highlight smoking as an independent predictor in bone metastases, offering clinically significant insights for future research and therapies.

In conclusion, our study highlights that smoking is associated with poorer overall survival in mRCC patients with bone metastases. These findings underscore the organ-specific effects of smoking on cancer progression, particularly in the bone microenvironment. Future prospective studies and translational research should focus on understanding the biological mechanisms linking smoking and bone metastases. Additionally, evaluating the impact of smoking on patients receiving modern immunotherapy-based regimens could guide more personalized treatment strategies.

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Acknowledgments

We extend our heartfelt gratitude to all members of the Turkish Oncology Group Kidney Cancer Consortium (TKCC) for their invaluable contributions. We would like to express special thanks to Ozlem Ustundag for her outstanding administrative support and assistance in data collection.

Author contributions

Conceptualization: Hatice Bolek, Emre Yekeduz, and Yuksel Urun. Methodology: Hatice Bolek, Deniz Tural, Cagatay Arslan, Sema Sezin Goksu, Ozlem Nuray Sever, Nuri Karadurmus, Cengiz Karacin, Mehmet Ali Nahit Sendur, Mustafa Ozguroglu, Emre Yekeduz, and Yuksel Urun. Formal analysis: Hatice Bolek and Emre Yekeduz. Investigation: Hatice Bolek. Data Curation: Hatice Bolek, Omer Faruk Kuzu, Elif Sertesen Camoz, Saadet Sim, Serhat Sekmek, Hilal Karakas, Selver Isık, Murad Guliyev, Halil Göksel Guzel, and Aysun Fatma Akkus. Visualization: Hatice Bolek. Writing-Original Draft: Hatice Bolek, Emre Yekedüz, Yüksel Urun Writing-Review & Editing: All authors Project administration: Yuksel Urun.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests

Yüksel Ürün: Advisory work —Abdi-İbrahim, Astellas, AstraZeneca, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen ilaç, Gilead, GSK, Janssen, Merck, MSD, Novartis, Pfizer, Roche; travel, honoraria and consultation fees—Abdi-İbrahim, Astellas, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen ilaç, Gilead, GSK, Janssen, Merck, Novartis, Pfizer, Roche-. All remaining authors have declared no conflicts of interest.

Ethical statement

Ethical approval number: Ankara University Faculty Ethics Committee, I09-701-24.

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Table 1 Baseline characteristics of the patients.

Variables		N = 799
Age, years (median, IQR)		61.21 (14.1)
Age	<65	518 (64.8)
	≥ 65	281 (35.2)
Gender	Female	202 (25.3)
	Male	597 (74.7)
Smoking	Never	335 (41.9)
	Former/current	464 (58.1)
ECOG-PS	0-1	669 (83.7)
	2-3	110 (13.8)
	Unknown	20 (2.5)
Nephrectomy		565 (80.7)
Histologic subtype	Clear cell	635 (79.5)
	Non-clear cell	115 (14.4)
	Unknown	49 (6.1)
Sarcomatoid features	Yes	93 (11.6)
	No	484 (60.6)
	Unknown	222 (27.8)
Nuclear grade	1-2	158 (19.8)
	3-4	363 (45.4)
	Unknown	278 (65.2)
IMDC risk group	Favorable	112 (14)
	Intermediate	385 (48.2)
	Poor	168 (21)
	Unknown	134 (16.8)
Bone metastasis	Yes	332 (41.6)
	No	467 (58.4)
Lung metastasis	Yes	561 (70.2)
	No	238 (29.8)
Liver metastasis	Yes	159 (19.9)
	No	640 (80.1)
LN or soft tissue metastasis	Yes	485 (60.7)
	No	314 (39.3)
CNS metastasis	Yes	69 (8.6)
	No	730 (91.4)
First line treatment	TKI monotherapy	754 (94.4)
	IO-based combination	45 (5.6)

CNS = central nervous system, ECOG = Eastern cooperative oncology group, IMDC = international metastatic renal cell carcinoma database consortium, IO = immunotherapy, IQR

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= interquartile range, LN= lymph node, PS = performance status, TKI = tyrosine kinase inhibitor.

Table 2 Baseline characteristics of patients by smoking status in bone metastasis group.

Variables		All (N = 332)	Current-ex smokers (N = 198)	Never smokers (N = 134)	p
Age, years (median, IQR)		61.03 (13.8)	60.88 (13.5)	61.46 (14.3)	
Age	<65	213 (64.2)	129 (65.2)	84 (62.7)	0.646
	≥ 65	119 (35.8)	69 (34.8)	50 (37.3)	
Gender	Female	84 (25.3)	19 (9.6)	65 (48.5)	**<0.001**
	Male	248 (74.7)	179 (90.4)	69 (51.5)	
ECOG-PS	0-1	252 (75.9)	142 (71.7)	110 (82.1)	**0.046**
	2-3	72 (21.7)	50 (25.2)	22 (16.4)	
	Unknown	8 (2.4)	6 (3)	2 (1.5)	
Nephrectomy		208 (62.7)	120 (60.6)	88 (65.7)	0.349
Histologic subtype	Clear cell	266 (80.1)	157 (79.3)	109 (81.3)	0.388
	Non-clear cell	44 (13.3)	29 (14.6)	15 (11.2)	
	Unknown	22 (6.6)	12 (6.1)	10 (7.5)	
Sarcomatoid features	Yes	38 (11.5)	25 (12.6)	13 (9.7)	0.460
	No	197 (59.3)	117 (59.1)	80 (59.7)	
	Unknown	97 (29.2)	56 (28.3)	41 (30.6)	
Nuclear grade	1-2	61 (18.4)	31 (15.6)	30 (22.4)	0.166
	3-4	143 (43.1)	88 (44.4)	55 (41.0)	
	Unknown	128 (38.5)	79 (39.9)	49 (36.6)	
IMDC risk group	Favorable	32 (9.6)	20 (10.1)	12 (8.9)	0.228
	Intermediate	163 (49.1)	92 (46.5)	71 (52.9)	
	Poor	89 (26.8)	60 (30.3)	29 (21.6)	
	Unknown	48 (14.5)	26 (13.1)	22 (16.4)	
Lung metastasis	Yes	205 (61.7)	131(66.2)	74 (55.2)	**0.044**
	No	127 (38.2)	67 (33.8)	60 (44.8)	
Liver metastasis	Yes	76 (22.9)	49 (24.7)	27 (20.1)	0.328

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	No	256 (77.1)	149 (75.3)	107 (79.9)	
LN or soft tissue metastasis	Yes	202 (60.8)	123 (62.1)	79 (59)	0.562
	No	130 (39.2)	75 (37.9)	55 (41)	
CNS metastasis	Yes	38 (11.4)	21 (10.6)	17 (12.7)	0.559
	No	294 (88.6)	177 (89.4)	117 (87.3)	
First line treatment	TKI	313 (94.3)	186 (93.9)	127 (94.8)	0.747
	IO-based combination	19 (5.7)	12 (6.1)	7 (5.2)	

CNS = central nervous system, ECOG = Eastern cooperative oncology group, IMDC = international metastatic renal cell carcinoma database consortium, IO = immunotherapy, IQR = interquartile range, LN= lymph node, PS = performance status, TKI = Tyrosine kinase inhibitor.

Table 3 Univariate and multivariate analysis for predictors of overall survival in patients with bone metastasis.

Variable		**Univariate HR (95%CI)**	**p**	**Multivariate HR (95%CI)**	**p**
Age	<65	1		1	
	≥ 65	1.24 (0.93-1.66)	0.146	1.17 (0.83-1.66)	0.363
Gender	Female	1		-	
	Male	0.90 (0.66-1.23)	0.521	-	-
Smoking	Never	1		1	
	Ex/Current	1.51 (1.13-2.01)	**0.005**	1.44 (1.05-1.99)	**0.026**
ECOG-PS	0-1	1		1	
	2-3	2.85 (2.07-3.92)	**<0.001**	1.89 (1.28-2.79)	**0.001**
Nephrectomy	No	1		1	
	Yes	0.58 (0.44-0.77)	**<0.001**	0.82 (0.58-1.16)	0.263
Histologic subtype	Clear cell	1		-	
	Non-clear cell	1.25 (0.81-1.94)	0.313	-	-
Sarcomatoid features	No	1		-	
	Yes	1.23 (0.80-1.87)	0.343	-	-
Nuclear grade	1-2	1		-	
	3-4	1.02 (0.69-1.50)	0.936	--	-
IMDC risk group	Favorable	1		1	
	Poor	3.45 (2.03-5.84)	**<0.001**	2.28 (1.24-4.17)	**0.008**
Lung metastasis	No	1		1	
	Yes	1.65 (1.23-2.20)	**0.001**	1.71 (1.24-2.37)	**0.001**
Liver metastasis	No	1		1	
	Yes	1.96 (1.45-2.66)	**<0.001**	1.75 (1.26-2.43)	**0.001**
LN or soft tissue metastasis	No	1		-	
	Yes	1.19 (0.89-1.58)	0.228	-	-

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CNS metastasis	No	1		1	
	Yes	1.42 (0.95-2.14)	0.090	1.15 (0.73-1.82)	0.549

CI = confidence interval, CNS = central nervous system, ECOG = Eastern cooperative oncology group, HR = hazard ratio, IMDC = international metastatic renal cell carcinoma database consortium, LN= lymph node, PS = performance status.

Table 4 Univariate and Multivariate analysis for predictors of overall survival in patients with bone only metastasis.

Variable		**Univariate HR (95% CI)**	**p**	**Multivariate HR (95% CI)**	**p**
Age	<65	1		-	
	≥ 65	1.27 (0.63-2.96)	0.434	-	-
Gender	Female	1		-	
	Male	0.98 (0.33-2.92)	0.982	-	-
Smoking	Never	1		1	
	Ex/current	1.76 (0.78-3.97)	0.174	4.44 (1.27-15.55)	**0.020**
ECOG-PS	0-1	1		1	
	2-3	2.65 (1.02-6.90)	**0.045**	2.64 (0.83-8.39)	0.099
Nephrectomy	No	1		1	
	Yes	0.46 (0.19-1.12)	0.086	0.11 (0.83-8.39)	**0.005**
Histologic subtype	Clear cell	1		1	
	Non-clear cell	3.66 (1.18-1.37)	**0.025**	3.98 (0.67-23.67)	0.129
Sarcomatoid features	No	1		-	
	Yes	1.03 (0.29-3.66)	0.964	-	-
Nuclear grade	1-2	1			
	3-4	1.93 (0.70-5.34)	0.203		
IMDC risk group	Favorable	1		1	
	Poor	3.87 (0.85-17.62)	0.080	1.90 (0.35-10.43)	0.459

CI = confidence interval, ECOG = Eastern cooperative oncology group, HR = hazard ratio, IMDC = international metastatic renal cell carcinoma database consortium, PS = performance status.

Fig. 1 CONSORT diagram.

Fig. 2 Kaplan-Meier curves for overall survival for all population.

Fig. 3 Overall survival for patients with bone metastasis (**A**) and without bone metastasis (**B**).