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Genitourinary Cancer: Renal, Bladder, and Testicular

Active Smoking May Negatively Affect Response Rate, Progression-Free Survival, and Overall Survival of Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Active smoking • Metastatic renal cell carcinoma • Outcome • Sunitinib treatment

Abstract

Background. Obesity, smoking, hypertension, and diabetes are risk factors for renal cell carcinoma development. Their presence has been associated with a worse outcome in various cancers. We sought to determine their association with outcome of sunitinib treatment in metastatic renal cell carcinoma (mRCC).

Methods. An international multicenter retrospective study of sunitinib-treated mRCC patients was performed. Multivariate analyses were performed to determine the association between outcome and the pretreatment status of smoking, body mass index, hypertension, diabetes, and other known prognostic factors.

Results. Between 2004 and 2013, 278 mRCC patients were treated with sunitinib: 59 were active smokers, 67 were obese, 73 were diabetic, and 165 had pretreatment hypertension. Median progression-free survival (PFS) was 9 months, and overall survival (OS) was 22 months. Factors associated with PFS were smoking status (past and active smokers: hazard ratio [HR]: 1.17, $p = .39$; never smokers: HR: 2.94, $p < .0001$), non-clear cell histology (HR: 1.62, $p = .011$), pretreatment neutrophil-to-lymphocyte ratio >3 (HR: 3.51, $p < .0001$), use of angiotensin system inhibitors (HR: 0.63, $p = .01$), sunitinib dose reduction or treatment interruption (HR: 0.72, $p = .045$), and Heng risk (good and intermediate risk: HR: 1.07, $p = .77$; poor risk: HR: 1.87, $p = .046$). Factors associated with OS were smoking status (past and active smokers: HR: 1.25, $p = .29$; never smokers: HR: 2.7, $p < .0001$), pretreatment neutrophil-to-lymphocyte ratio >3 (HR: 2.95, $p < .0001$), and sunitinib-induced hypertension (HR: 0.57, $p = .002$).

Conclusion. Active smoking may negatively affect the PFS and OS of sunitinib-treated mRCC. Clinicians should consider advising patients to quit smoking at initiation of sunitinib treatment for mRCC. ***The Oncologist*** 2014;19:1–10

Implications for Practice: Smoking is a risk factor for kidney cancer development. A recent international study sought to determine its association with outcome of treatment in metastatic disease. The study included 278 patients from 7 medical centers, who were treated with sunitinib (an approved standard biologic treatment for metastatic kidney cancer). The study revealed that ongoing smoking may negatively impact the response to therapy (decrease of disease burden) as well as the progression free survival (time period without disease progression) and overall survival (longevity of patients). Thus, clinicians should consider advising patients to quit smoking at initiation of therapy for metastatic kidney cancer.

Introduction

Renal cell carcinoma (RCC) is the most common cancer of the kidney [1]. Thirty percent of patients present with metastatic disease [2, 3], and recurrence develops in 40% of patients treated for a localized tumor [2, 4]. An understanding of the pathogenesis of RCC at the molecular level and randomized clinical trials have established the standard role of the orally administered vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor inhibitor sunitinib for the treatment of advanced RCC [5].

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Smoking, obesity, diabetes, and hypertension are risk factors for RCC development [6–8]. Their presence has been associated with a worse outcome of therapy in various cancers. In patients with RCC, a history of smoking was associated with worse pathologic features and survival outcomes [9]. Smoking history and active smoking may be associated with shorter survival of patients with prostate cancer [10], advanced non-small cell lung cancer [11, 12], limited small cell lung cancer [13], bladder cancer [14], and upper tract urothelial carcinoma [15]. The effect of smoking may be mediated through inflammation, oxidative tissue damage, or immune suppression that act on cancer progression [9, 11]. Smoking-induced activated macrophages may generate reactive oxygen species that promote angiogenesis, tumor invasion, and metastasis [9, 13]. Furthermore, smoking may increase blood carboxyhemoglobin, producing relative hypoxia [13], and hypoxia-inducible factor has been shown to contribute to the RCC tumorigenesis process [16]. The presence of diabetes was found to be associated with poorer prognosis of patients with ovarian cancer [17], prostate cancer [18], and oral squamous cell carcinoma [19]. Body mass index (BMI) was found to be a predictive factor in patients treated with hormonal therapy for breast cancer and a prognostic factor in patients with colorectal cancer receiving chemotherapy [20, 21].

In the present study, we sought to determine the association of pretreatment obesity, smoking, hypertension, and diabetes with response rate, progression-free survival (PFS), and overall survival (OS) of patients treated with sunitinib for metastatic RCC (mRCC).

Materials and Methods

Study Group

The study group was composed of consecutive patients with mRCC who were treated with sunitinib between February 1, 2004, and March 31, 2013, in seven centers across two different countries: the U.S. (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland) and Israel (Institute of Oncology, Meir Medical Center, Kfar Saba; Department of Oncology, Asaf Harofe Medical Center, Zerifin; Department of Oncology, Rambam Medical Center, Haifa; Department of Oncology, Sheba Medical Center, Tel Hashomer; Department of Oncology, Wolfson Medical Center, Holon; Department of Oncology, Soroka University Medical Center, Beer-Sheva). Patient data were retrospectively and personally collected by the investigator (D.K.) from electronic medical records and paper charts, including the following clinicopathologic information: age; gender; presunitinib treatment status of smoking (active, past, never); BMI (obese: BMI $\geq$30; overweight: BMI 25–29.9; normal weight: BMI $<$25); hypertension; diabetes; clear cell versus non-clear cell histology; past nephrectomy; the time interval from initial diagnosis to sunitinib treatment initiation; metastases sites; presence of lung, liver, or bone metastases; Eastern Cooperative Oncology Group performance status; hemoglobin level; corrected (for albumin) calcium level; alkaline phosphatase (AP) level; pretreatment neutrophil-to-lymphocyte ratio (NLR); sunitinib-induced hypertension; prior treatments for RCC; and sunitinib dose reduction or treatment interruption. Data on the concomitant use of medications, including angiotensin system inhibitors (ASIs; angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and bisphosphonates, were gathered from patients' electronic medical records and paper charts documenting baseline patient intake and regular on-treatment follow-ups, pharmacy records, and contact of patients and other treating physicians as needed. Outcome data were last updated on March 31, 2013, including objective response rate, PFS, and OS.

Sunitinib Treatment

All patients had objective disease progression on scans before starting sunitinib treatment. Sunitinib was prescribed as a part of standard treatment or clinical trial. It was administered orally, usually at a starting dose of 50 mg once daily, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. On-treatment dose reduction or treatment interruption was done for the management of adverse events, depending on their type and severity, according to standard guidelines. Treatment was continued until evidence of disease progression on scans, unacceptable adverse events, or death. Patient follow-up generally consisted of regular physical examinations and laboratory assessments (hematologic and serum chemical measurements) every 4–6 weeks, and imaging studies were performed every 12–18 weeks.

Treatment Outcomes

Follow-up time was defined as the time from sunitinib treatment initiation to March 31, 2013. For the evaluation of response, the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was applied [22]. In patients with only bone metastases, only complete response, stable disease, or progressive disease were noted, not partial response [23]. The response was assessed by independent radiologists and treating physicians (while the patients were on treatment in each center, as part of standard patient follow-up) and personally reviewed by the investigator (D.K.). PFS was determined by the investigator (D.K.) and defined as the time from the initiation of sunitinib treatment until evidence of disease progression on scans or death from any cause. OS was defined as the time from the initiation of sunitinib treatment to death from any cause.

Statistical Analysis

We analyzed presunitinib treatment obesity, smoking, hypertension, and diabetes and potential (previously reported) factors associated with outcome [24–30], including past nephrectomy; clear cell versus non-clear cell histology; the presence of more than two metastatic sites; lung, liver, or bone metastasis; sunitinib-induced hypertension; past cytokines and/or targeted treatments; sunitinib dose reduction or treatment interruption; the use of ASIs before or within 1 month after initiation of sunitinib treatment; use of bisphosphonates; the risk according to the Heng prognostic model; and the presunitinib treatment NLR. Patients without available data on pretreatment NLR and those with baseline comorbidity such as chronic lymphocytic leukemia and with recent ($\leq$1 month) treatment (surgery, steroids, tyrosine kinase inhibitors,

cytokines) known to be associated with a change of blood counts were excluded from the NLR analysis [30]. A univariate analysis (unadjusted) of association between each clinicopathologic factor and clinical outcome was performed using logistic regression for response rate and Cox regression model for survival outcomes (PFS and OS). Factors with significant association in the univariate analysis were included in a multivariate Cox proportional hazards regression model to determine their independent effects. In addition, we performed two multivariate backward elimination analyses of all variables, including those that were not significant in the previous analysis, and after excluding the factors with missing data. Finally, to better elucidate the effect of active smoking, we performed a subgroup analysis comparing the response rate, PFS, and OS between active smokers and an individually matched cohort of nonsmokers selected from the general cohort of nonsmokers. The subgroups were matched by age, gender, Heng risk, prior nephrectomy, histology, presence of two or more metastases sites, pretreatment NLR, treatment line, sunitinib-induced hypertension, sunitinib dose reduction or treatment interruption, and the use of ASIs.

In all tests, a two-tailed p value of $<.05$ was considered statistically significant. Patients who did not progress or die by March 31, 2013, were censored in PFS analysis or OS analysis, respectively. Survival probabilities and median survival times were estimated from Kaplan-Meier curves. Data were analyzed using S-Plus 8.0 for Windows Enterprise Developer.

Regulatory Considerations

The research was carried out in accordance with the approval by the institutional review boards of our institutions.

Results

Patient Characteristics

Two hundred and seventy eight patients (median age: 63 years [mean: 62 $\pm$ 11.3 years; range: 22–87]; male 67%, n = 186) with mRCC were treated with sunitinib between February 1, 2004, and March 31, 2013. Sixty-seven patients (24%) had non-clear cell histology. The distribution of clinicopathologic and prognostic factors is shown in Tables 1–3. Overall, 124 patients (45%) never smoked, 95 (34%) were past smokers, and 59 (21%) were active smokers. Sixty-seven patients (24%) were obese, 82 (29%) were overweight, 82 (30%) were normal weight, and 47 (17%) had no data on pretreatment BMI. Seventy-three patients (26%) were diabetic, and 165 (59%) had pretreatment hypertension. A total of 244 patients (88%) were included in the pretreatment NLR analysis, from which were excluded 34 patients without available data on pretreatment NLR (n = 16) and those with baseline comorbidity (chronic lymphocytic leukemia, n = 1) and recent ($\leq$1 month) treatment (steroids, n = 5; interferon, n = 3; sorafenib, n = 5; surgery, n = 2; radiation, n = 2) known to be associated with a change of blood counts [30].

Fifty patients were treated with bisphosphonates (initiated before or with sunitinib therapy).

Sunitinib Treatment Outcomes

Median follow-up time was 55 months (55 $\pm$ 21 mean $\pm$ SD, range 12-109). Objective response at first imaging evaluation within the first three months of sunitinib treatment initiation was complete response 3% (n = 9), partial response 36% (n = 99), stable disease 39% (n = 109), and progressive disease 22% (n = 61). Median PFS was 9 months (15.3 $\pm$ 16 mean $\pm$ SD, range 1-90). Median OS was 22 months (25 $\pm$ 20 mean $\pm$ SD, range 1-90). 245 patients (88%) have progressed, and 203 patients (73%) died.

Univariate Analysis of Factors Associated With Response Rate, PFS, and OS

The following factors were individually associated with response to sunitinib (complete response, partial response, or stable disease vs. disease progression) at first imaging evaluation within the first 3 months of treatment initiation: smoking status (never vs. active smokers: odds ratio [OR]: 5.3, $p < .0001$; past vs. never smokers: OR 1.37, p = .03), Heng risk (favorable vs. poor risk: OR: 1.7, p = .001; intermediate vs. poor risk: OR: 4.1, p = .01), BMI (normal and overweight: OR: 2.3, p = .03; obese: OR: 0.8, p =.57), diabetes (OR: 0.48, p = .047), use of ASIs (nonusers vs. users: OR: 0.32, p = .001), past nephrectomy (no vs. yes; OR: 0.4, p = .008), clear cell histology (OR: 2.4, p = .005), absence of liver metastases (OR: 2, p = .02), low presunitinib treatment NLR $\leq$3 (OR: 2.4, p = .004), sunitinib-induced hypertension (OR: 2.3, $p < .0001$), and sunitinib dose reduction or treatment interruption (OR: 0.36, p = .001).

The following factors were individually associated with PFS (Table 1): smoking status (active vs. never smokers: hazard ratio [HR]: 2.24, $p < .0001$; past vs. never smokers: HR: 1.02, p = .89), Heng risk (favorable vs. poor risk: HR: 1.45, p = .026; intermediate vs. poor risk: HR: 2.7, $p < .0001$), BMI (normal and overweight: HR: 0.74, p = .064; obese: HR: 0.6, p = .004), the use of ASIs (no vs. yes: HR: 1.7, $p < .0001$), the use of bisphosphonates (yes vs. no: HR: 0.64, p = .008), nephrectomy (yes vs. no: HR: 0.62, p = .04), sunitinib-induced hypertension (yes vs. no: HR: 0.72, p = .01), sunitinib dose reduction or treatment interruption (no vs. yes: HR: 0.78, p = .049), non-clear cell histology (vs. clear cell histology; HR: 1.8, $p < .0001$), elevated AP (yes vs. no: HR: 1.67, p = .002), presunitinib treatment NLR $>$3 ($>$3 vs. $\leq$3: HR: 2.42, $p < .0001$), and female gender (female vs. male: HR: 0.76, p = .043).

The following factors were individually associated with OS (Table 2): smoking status (active vs. never smokers: HR: 2.6, $p < .0001$; past vs. never smokers: HR: 1.17, p = .33), Heng risk (favorable vs. poor risk: HR: 1.55, p = .019; intermediate vs. poor risk: HR: 2.9, $p < .0001$), the use of ASIs (no vs. yes: HR: 1.55, p = .003), the use of bisphosphonates (yes vs. no: HR: 0.59, p = .008), sunitinib-induced hypertension (yes vs. no: HR: 0.59, $p < .0001$), sunitinib dose reduction or treatment interruption (no vs. yes: HR: 0.67, p = .005), elevated AP (yes vs. no: HR: 2.1, $p < .0001$), presunitinib treatment NLR $>$3 ($>$3 vs. $\leq$3: HR: 2.64, $p < .0001$), non-clear cell histology (vs. clear cell histology: HR: 1.79, $p < .0001$), past nephrectomy (yes vs. no: HR: 0.53, $p < .0001$), and BMI (normal and overweight: HR: 1.6, p = .014; obese: HR: 1.18, p = .38).

Multivariate Analysis of Factors Associated With Response Rate, PFS, and OS

The following factors were independently associated with response to sunitinib (complete response, partial response,

Table 1. Distribution of clinicopathologic and prognostic factors and univariate and multivariate analysis of their association with progression-free survival

Factor	Distribution	Univariate analysis: *p*, HR (95% CI)	Multivariate analysis: *p*, HR (95% CI)
Age, yr, median (mean ± SD, range) ($n = 278$)	63 (62 ± 11, 22–87)	.164, 0.992 (0.981–1.003)	
Gender ($n = 278$)	Female: 33% ($n = 92$); Male: 67% ($n = 186$)	.043, 0.762 (0.585–0.992) (female vs. male)	.08, 1.38 (0.96–1.99)
Tumor histology ($n = 278$)	Clear cell histology: 76% ($n = 211$); non-clear cell: 24% ($n = 67$)	<.0001, 1.8 (1.35–2.4) (non-clear vs. clear)	.011, 1.62 (1.12–2.34)
Past nephrectomy ($n = 278$)	82% ($n = 228$)	.04, 0.62 (0.45–0.86) (yes vs. no)	.39, 0.83 (0.55–1.26)
Prior systemic treatment ($n = 278$)	27% ($n = 75$)	.56, 1.1 (0.78–1.6)	
Lung metastasis ($n = 278$)	72% ($n = 201$)	.129, 0.8 (0.6–1.07)	
Liver metastasis ($n = 278$)	26% ($n = 73$)	.32, 1.16 (0.87–1.54)	
Bone metastasis ($n = 278$)	39% ($n = 109$)	.36, 0.89 (0.69–1.15)	
≥2 metastatic sites ($n = 278$)	82% ($n = 227$)	.47, 1.13 (0.82–1.55)	
Elevated pretreatment alkaline phosphatase ($n = 245$)	21% ($n = 51$)	.002, 1.67 (1.2–12.3) (yes vs. no)	.69, 1.09 (0.72–1.65)
Sunitinib-induced HTN ($n = 278$)	49% ($n = 136$)	.01, 0.72 (0.56–0.92) (yes vs. no)	.51, 0.89 (0.64–1.25)
Sunitinib dose reduction/treatment interruption ($n = 278$)	50% ($n = 140$)	.049, 0.78 (0.6–0.99) (no vs. yes)	.045, 0.72 (0.52–0.992)
Users of angiotensin system inhibitors ($n = 278$)	38% ($n = 106$)	<.0001, 1.7 (1.3–2.2) (no vs. yes)	.01, 0.63 (0.44–0.89)
Users of bisphosphonates ($n = 278$)	18% ($n = 50$)	.008, 0.64 (0.46–0.9) (yes vs. no)	.99, 0.99 (0.66–1.51)
Heng risk stratification ($n = 278$)	Favorable risk: 22% ($n = 60$); intermediate risk: 59% ($n = 163$); poor risk: 19% ($n = 55$)	.026, 1.45 (1.05–1.99), vs. poor risk; <.0001, 2.7 (1.8–4), vs. poor risk	.77, 1.07 (0.67–1.73); .046, 1.87 (1.012–3.46)
Pretreatment neutrophil-to-lymphocyte ratio >3 ($n = 244$)	46% ($n = 113$)	<.0001, 2.42 (1.83–3.19) (>3 vs. ≤ 3)	<.0001, 3.51 (2.4–5.1)
Smoking status ($n = 278$)	Never: 45% ($n = 124$)		
	Past: 34% ($n = 95$)	.893, 1.02 (0.76–1.36), vs. never smoking	.39, 1.17 (0.82–1.68), vs. never smoking
	Active: 21% ($n = 59$)	<.0001, 2.24 (1.62–3.1), vs. never smoking	<.0001, 2.94(1.89–4.58), vs. never smoking
Body mass index ($n = 231$)	Normal (<25): 35% ($n = 82$)		
	Overweight (25–29.9): 35% ($n = 82$)	.064, 0.74 (0.54–1.09), vs. obese	.89, 1.03 (0.71–1.48)
	Obese (≥30): 30% ($n = 67$)	.004, 0.6 (0.43–0.85), vs. obese	.77, 0.94 (0.62–1.43)
Diabetes ($n = 278$)	26% ($n = 73$)	.19, 1.2 (0.91–1.62)	
Pretreatment HTN ($n = 278$)	59% ($n = 165$)	.75, 0.96 (0.74–1.24)	

Abbreviations: CI, confidence interval; HR, hazard ratio; HTN, hypertension; *n*, number of patients with data available.

or stable disease, versus disease progression) at first imaging evaluation within the first 3 months of treatment initiation: smoking status (never vs. active smokers: OR: 4.6, $p = .006$; past vs. never smokers: OR: 1.24, $p = .65$), clear cell histology (OR: 2.5, $p = .035$), absence of liver metastases (OR: 2.5, $p = .042$), low presunitinib treatment NLR ≤3 (OR: 2.65, $p = .029$), and sunitinib-induced hypertension (OR: 3.7, $p = .006$).

The following factors were independently associated with PFS (Table 1): smoking status (active and past smokers: HR: 2.94, $p < .0001$; never smokers: HR: 1.17, $p < .39$; median PFS was 4 months for active smokers, 10 months for past smokers, and 12 months for never smokers), non-clear cell histology (vs. clear cell histology: HR: 1.62, $p = .011$), pretreatment NLR >3 (>3 vs. ≤3: HR: 3.51, $p < .0001$), the use of ASIs (yes vs. no: HR: 0.63, $p = .01$), sunitinib dose reduction or treatment interruption (no vs. yes: HR: 0.72, $p = .045$), and Heng risk (good risk vs. poor risk: HR: 1.07, $p = .77$; intermediate risk vs. poor risk: HR:1.87, $p = .046$).

The following factors were independently associated OS (Table 2): smoking status (active and past smokers: HR: 1.25,

Table 2. Distribution of clinicopathologic and prognostic factors and univariate and multivariate analysis of their association with overall survival

Factor	Distribution	Univariate analysis: *p*, HR (95% CI)	Multivariate analysis: *p*, HR (95% CI)
Age, yr, median (mean ± SD, range) ($n = 278$)	63 (62 ± 11, 22–87)	.13, 0.99 (0.98–1.003)	
Gender ($n = 278$)	Female: 33% ($n = 92$); male: 67% ($n = 186$)	.47, 0.9 (0.67–1.2)	
Tumor histology ($n = 278$)	Clear cell histology: 76% ($n = 211$); non clear cell: 24% ($n = 67$)	<.0001, 1.79 (1.3–2.4) (non-clear vs. clear)	.053, 1.48 (0.99–2.2)
Past nephrectomy ($n = 278$)	82% ($n = 228$)	<.0001, 0.53 (0.37–0.74) (yes vs. no)	.56, 0.66 (0.43–1.012)
Prior systemic treatment ($n = 278$)	27% ($n = 75$)	.09, 1.38 (0.95–2.1)	
Lung metastasis ($n = 278$)	72% ($n = 201$)	.31, 0.85 (0.62–1.16)	
Liver metastasis ($n = 278$)	26% ($n = 73$)	.11, 1.28 (0.94–1.74)	
Bone metastasis ($n = 278$)	39% ($n = 109$)	.59, 0.93 (0.7–1.23)	
≥2 metastatic sites ($n = 278$)	82% ($n = 227$)	.8, 1.05(0.74–1.48)	
Elevated pretreatment alkaline phosphatase ($n = 245$)	21% ($n = 51$)	<.0001, 2.1 (1.49–2.98) (yes vs. no)	.1, 1.43 (0.93–2.2)
Sunitinib induced HTN ($n = 278$)	49% ($n = 136$)	<.0001, 0.59 (0.45–0.78) (yes vs. no)	.002, 0.57 (0.4–0.81)
Sunitinib dose reduction/treatment interruption ($n = 278$)	50% ($n = 140$)	.005, 0.67(0.51–0.88) (no vs. yes)	.32, 0.81 (0.54–1.23)
Users of angiotensin system inhibitors ($n = 278$)	38% ($n = 106$)	.003, 1.55 (1.16–2.07) (no vs. yes)	.57, 0.89 (0.62–1.31)
Users of bisphosphonates ($n = 278$)	18% ($n = 50$)	.008, 0.59 (0.4–0.87) (yes vs. no)	.052, 0.63 (0.39–1.004)
Heng risk stratification ($n = 278$)	Favorable risk: 22% ($n = 60$)		
	Intermediate risk: 59% ($n = 163$)	.019, 1.55 (1.07–2.24), vs. poor risk	.77, 1.08 (0.66–1.8), vs. poor risk
	Poor risk: 19% ($n = 55$)	<.0001, 2.9 (1.87–4.53), vs. poor risk	.22, 1.5 (0.78–2.9), vs. poor risk
Pretreatment neutrophil-to-lymphocyte ratio >3 ($n = 244$)	46% ($n = 113$)	<.0001, 2.64 (1.96–3.56) (>3 vs. ≤ 3)	<.0001, 2.95 (2–4.34)
Smoking status ($n = 278$)	Never: 45% ($n = 124$)		
	Past: 34% ($n = 95$)	.33, 1.17 (0.85–1.62), vs. never smoking	.29, 1.25 (0.83–1.86), vs. never smoking
	Active: 21% ($n = 59$)	<.0001, 2.6 (1.83–3.7), vs. never smoking	<.0001, 2.7 (1.7–4.3), vs. never smoking
Body mass index ($n = 231$)	Normal (<25): 35% ($n = 82$)		
	Overweight (25–29.9): 35% ($n = 82$)	.014, 1.6 (1.1–2.33), vs. obese	.75, 0.94 (0.63–1.4), vs. obese
	Obese (≥30): 30% ($n = 67$)	.38, 1.18 (0.81–1.73), vs. obese	.7, 0.91 (0.58–1.45), vs. obese
Diabetes ($n = 278$)	26% ($n = 73$)	.18, 1.24 (0.9–1.71)	
Pretreatment HTN ($n = 278$)	59% ($n = 165$)	.14, 0.81 (0.61–1.07)	

Abbreviations: CI, confidence interval; HR, hazard ratio: HTN, hypertension; *n*, number of patients with data available.

$p = .29$; never smokers: HR: 2.7, $p < .0001$; median OS was 11 months for active smokers, 22 months for past smokers, and 25 months for never smokers), pretreatment NLR >3 (>3 vs. ≤3: HR: 2.95, $p < .0001$), and sunitinib-induced hypertension (yes vs. no: HR: 0.57, $p = .002$).

The primary results for the association between smoking status and treatment outcome are further supported by model selection using backward elimination of all variables, including those that were not significant in the previous analysis (Table 3), and by model selection using backward elimination after excluding the factors with missing data (Table 4). In contrast to the primary analysis, in the analysis of all variables (Table 3), the presence of lung and liver metastases was associated with PFS, whereas the Heng risk was not, and factors associated with OS included sunitinib dose reduction or treatment interruption, histology, past nephrectomy, prior

Table 3. Model selection using backward elimination of the association between all variables and progression-free survival and overall survival

Factor	Distribution	Progression-free survival: *p*, HR (95% CI)	Overall survival: *p*, HR (95% CI)
Age, yr, median (mean ± SD, range) ($n = 278$)	63 (62 ± 11, 22–87)	.8, 0.998 (0.985–1.012)	.73, 0.98 (0.98–1.01)
Gender ($n = 278$)	Female: 33% ($n = 92$); male: 67% ($n = 186$)	.12, 1.3 (0.93–1.85)	.53, 1.12 (0.78–1.62)
Tumor histology ($n = 278$)	Clear cell histology: 76% ($n = 211$); non clear cell: 24% ($n = 67$)	.002, 1.76 (1.24–2.5) (non-clear vs. clear)	.002, 1.77 (1.23–2.56)
Past nephrectomy ($n = 278$)	82% ($n = 228$	.37, 0.84 (0.56–1.24)	.01, 0.59 (0.39–0.89) (yes vs. no)
Prior systemic treatment ($n = 278$)	27% ($n = 75$)	.25, 1.3 (0.82–2.2)	.026, 1.77 (1.07–2.92) (yes vs. no)
Lung metastasis ($n = 278$)	72% ($n = 201$)	.019, 1.5 (1.07–2.12) (yes vs. no)	.028, 1.53 (1.05–2.24)
Liver metastasis ($n = 278$)	26% ($n = 73$)	.026, 1.52 (1.05–2.2) (yes vs. no)	.074, 1.42 (0.97–2.1)
Bone metastasis ($n = 278$)	39% ($n = 109$)	.65, 1.1 (0.78–1.49)	.93, 0.98 (0.65–1.5)
≥2 metastatic sites ($n = 278$)	82% ($n = 227$)	.92, 0.98 (0.62–1.53)	.84, 0.95 (0.6–1.5)
Elevated pretreatment alkaline phosphatase ($n = 245$)	21% (n51)	.89, 0.97 (0.63–1.5)	.085, 1.45 (0.95–2.2)
Sunitinib induced HTN ($n = 278$)	49% ($n = 136$)	.59, 0.91 (0.65–1.28)	.006, 0.61 (0.43–0.87)
Sunitinib dose reduction/treatment interruption ($n = 278$)	50% ($n = 140$)	.044, 0.73 (0.54–0.991) (no vs. yes)	.005, 0.6 (0.43–0.86)
Users of angiotensin system inhibitors ($n = 278$)	38% ($n = 106$	.013, 0.66 (0.48–0.92) (no vs. yes)	.88, 1.03 (0.68–1.58)
Users of bisphosphonates ($n = 278$)	18% ($n = 50$)	.8, 0.94 (0.6–1.49)	.1, 0.69 (0.44–1.08)
Heng risk stratification ($n = 278$)	Favorable risk: 22% ($n = 60$)		
	Intermediate risk: 59% ($n = 163$)	.77, 1.07 (0.7–1.6), vs. poor risk	.927, 1.02 (0.63–1.7), vs. poor risk
	Poor risk: 19% ($n = 55$)	.15, 1.47 (0.88–2.48), vs. poor risk	.48, 1.25 (0.68–2.29), vs. poor risk
Pretreatment neutrophil-to-lymphocyte ratio >3 ($n = 244$)	46% ($n = 113$)	<.0001, 3.95 (2.78–5.6) (>3 vs. ≤ 3)	<.0001, 3.14 (2.16–4.56)
Smoking status ($n = 278$)	Never: 45% ($n = 124$)		
	Past: 34% ($n = 95$)	.66, 1.08 (0.76–1.54), vs. never smoking	.68, 1.09 (0.73–1.63), vs. never smoking
	Active: 21% ($n = 59$)	<.0001, 2.71 (1.8–4.1), vs. never smoking	<.0001, 2.52 (1.6–3.96), vs. never smoking
Body mass index ($n = 231$)	Normal (<25): 35% ($n = 82$)		
	Overweight (25–29.9): 35% ($n = 82$)	.44, 0.86 (0.58–1.26), vs. obese	.75, 0.93 (0.6–1.4)
	Obese (≥30): 30% ($n = 67$)	.31, 0.81 (0.53–1.2), vs. obese	.63, 0.89 (0.54–1.46)
Diabetes ($n = 278$)	26% ($n = 73$	.51, 0.87 (0.58–1.32)	.26, 0.8 (0.54–1.18)
Pretreatment HTN ($n = 278$)	59% ($n = 165$)	.26, 1.21 (0.87–1.68)	.61, 0.91 (0.65–1.29)

Abbreviations: CI, confidence interval; HR, hazard ratio: HTN, hypertension; *n*, number of patients with data available.

systemic therapy, and the presence of lung metastases. In contrast to the primary analysis, in the analysis after excluding the factors with missing data (Table 4), male gender, use of bisphosphonates, and pretreatment hypertension were associated with PFS, whereas sunitinib dose reduction or treatment interruption was not, and factors associated with OS included histology, sunitinib dose reduction or treatment interruption, prior systemic therapy, use of bisphosphonates, Heng risk, and the use of ASIs.

Active Smokers Versus Past Smokers and Nonsmokers

To better elucidate the effect of active smoking, we performed a subgroup analysis comparing response rates, PFS, and OS of active smokers ($n = 59$) and a matched cohort of nonsmokers

Table 4. Model selection using backward elimination of the association between clinicopathologic and prognostic factors and progression-free survival and overall survival, after excluding the factors with missing data

Factor ($n = 278$)	Distribution	Progression free survival: *p*, HR (95% CI)	Overall survival: *p*, HR (95% CI)
Age, yr, median (mean ± SD, range)	63 (62 ± 11, 22–87)	.77, 1.002 (0.99–1.014)	.47, 1.005 (0.99–1.018)
Gender	Female: 33% ($n = 92$); male: 67% ($n = 186$)	.01, 1.44 (1.09–1.9) (male vs. female)	.28, 1.19 (0.87–1.6)
Tumor histology	Clear cell histology: 76% ($n = 211$); non clear cell: 24% ($n = 67$)	.008, 1.5 (1.12–2) (non clear vs. clear)	.02, 1,47 (1.06–2.03)
Past nephrectomy	82% ($n = 228$)	.84, 0.96 (0.65–1.42)	.074, 0.72 (0.49–1.03)
Prior systemic treatment	27% ($n = 75$)	.14, 1.34 (0.9–1.9)	.01, 2.1 (1.34–3.1) (yes vs. no)
Lung metastasis	72% ($n = 201$)	.32, 1.16 (0.86–1.56)	.17, 1.25 (0.91–1.73)
Liver metastasis	26% ($n = 73$)	.8, 0.96 (0.69–1.3)	.53, 1.12 (0.8–1.57)
Bone metastasis	39% ($n = 109$)	.072, 1.33 (0.98–1.8)	.26, 1.21 (0.87–1.7)
≥2 metastatic sites	82% ($n = 227$)	.78, 1.05 (0.74–1.5)	.67, 0.92 (0.6–1.4)
Sunitinib induced HTN	49% ($n = 136$)	.14, 0.82 (0.62–1.07)	.002, 0.63 (0.47–0.84) (yes vs. no)
Sunitinib dose reduction/treatment interruption	50% ($n = 140$)	.074, 0.78 (0.6–1.024)	.055, 0.75 (0.56–1.006)
Users of angiotensin system inhibitors	38% ($n = 106$)	<.0001, 0.48 (0.35–0.65) (yes vs. no)	.022, 0.7 (0.52–0.95)
Users of bisphosphonates	18% ($n = 50$)	.012, 0.595 (0.39–0.89) (yes vs. no)	.009, 0.596 (0.4–0.88)
Heng risk stratification	Favorable risk: 22% ($n = 60$)		
	Intermediate risk: 59% ($n = 163$)	.089, 1.34 (0.96–1.87), vs. poor risk	.161, 1.31 (0.9–1.9), vs. poor risk
	Poor risk: 19% ($n = 55$)	<.0001, 2.26 (1.47–3.46), vs. poor risk	<.0001, 2.46 (1.53–3.95), vs. poor risk
Smoking status	Never: 45% ($n = 124$)		
	Past: 34% ($n = 95$)	.44, 1.13 (0.83–1.53), vs. never smoking	.26, 1.21(0.87–1.7), vs. never smoking
	Active: 21% ($n = 59$)	<.0001, 2.27 (1.6–3.2), vs. never smoking	<.0001, 2.76(1.9–3.9), vs. never smoking
Diabetes	26% ($n = 73$)	.52, 1.12 (0.8–1.57)	.51, 1.13 (0.79–1.6)
Pretreatment HTN	59% ($n = 165$)	.032, 1.4 (1.03–1.9) (yes vs. no)	.83, 1.04 (0.74–1.46)

Abbreviations: CI, confidence interval; HR, hazard ratio: HTN, hypertension; *n*, number of patients with data available.

Table 5. Subgroup analysis stratified by smoking status

Characteristic	Active smokers ($n = 59$)	Matched past smokers and nonsmokers ($n = 59$)	*p*
Response rate			
CR	0% ($n = 0$)	5% ($n = 3$)	
PR	24% ($n = 14$)	46% ($n = 27$)	
SD	30% ($n = 18$)	37% ($n = 22$)	<.0001
CR/PR/SD	54% ($n = 32$)	88% ($n = 52$)	
Disease progression within 12 weeks of	46% ($n = 27$)	12% ($n = 7$)	
Progression-free survival, mo, median (mean ± SD, range)	4 (8 ± 7, 1–41)	11 (19 ± 17, 2–77)	<.0001
Overall survival, mo, median (mean ± SD, range)	11 (14 ± 13, 1–54)	26 (29 ± 20, 3–78)	<.0001

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

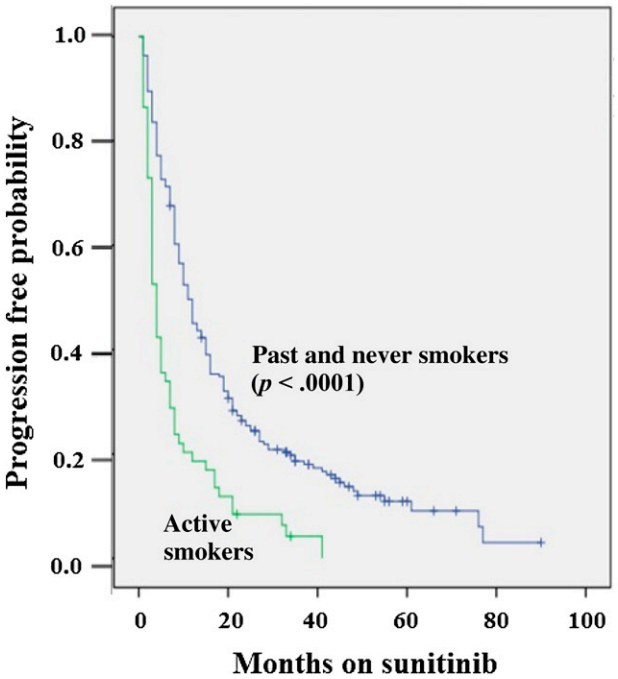

Figure 1. Kaplan-Meier curves showing progression-free survival, stratified by smoking status.

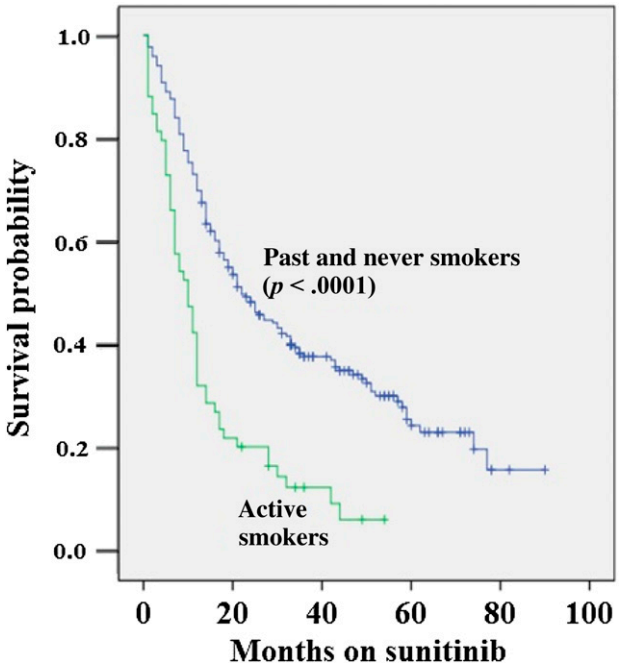

Figure 2. Kaplan-Meier curves showing overall survival, stratified by smoking status.

and past smokers ($n = 59$) selected from the general cohort of nonsmokers and past smokers ($n = 219$) (Table 5). The two subgroups were matched by Heng risk, the use of ASIs, gender, age, prior nephrectomy, histology, the presence of two or more metastatic sites, presunitinib treatment NLR, treatment line, sunitinib-induced hypertension, and sunitinib dose reduction or treatment interruption. Objective response in active smokers versus past smokers and nonsmokers was partial response or stable disease in 54% ($n = 32$) versus 88% ($n = 52$) and progressive disease at first imaging evaluation within the first 2 months in 46% ($n = 27$) versus 12% ($n = 7$) ($p < .0001$). The median PFS of past smokers and nonsmokers was more than double that of active smokers (11 months vs. 4 months, $p < .0001$; Fig. 1). Median OS was 11 months in active smokers versus 26 months in past smokers and nonsmokers ($p < .0001$; Fig. 2). The respective incidence of diarrhea and hand and foot syndrome in active smokers versus past smokers and nonsmokers was 31% ($n = 18$) in both groups ($p = 1$) and 17% ($n = 10$) versus 22% ($n = 13$) ($p = .49$). The groups were balanced with regard to the presence of lung, liver, or bone metastases; the use of bisphosphonates; and AP level.

Discussion

Smoking, obesity, hypertension, and diabetes are risk factors for RCC development [6–8]. Although their presence has been associated with a worse outcome of therapy in various cancers [9–13, 17–21], their influence on the efficacy of modern targeted agents for mRCC is currently unknown. The present study suggests that active smoking may decrease the PFS and OS of sunitinib-treated mRCC patients, whereas BMI, diabetes mellitus (DM),and pretreatment hypertension were not found to be associated with outcome. In this retrospective study, after adjustment for other known outcome-associated factors, patients actively smoking had significantly lower PFS, by 7 months (4 months vs. 11 versus, $p < .0001$), and OS, by 15 months (11 months vs. 26 months, $p < .0001$) than past smokers and nonsmokers. Active smoking was also associated with less clinical benefit (response plus stable disease in 54% versus 88%) and a higher risk of disease progression at first imaging evaluation within the first 3 months (46% vs. 12%, $p < .0001$). The association between smoking status and treatment outcome is further supported by univariate and multivariate analysis of the entire patient cohort; by model selection using backward elimination of all variables, including those that were not significant in the previous analysis; and by model selection using backward elimination after excluding the factors with missing data.

In patients with RCC, a history of smoking is associated with worse pathologic features and survival outcomes [9]; however, the mechanisms of negative impact of continued cigarette smoking on treatment outcome is complex and remains to be elucidated. The effect of smoking may be mediated through inflammation, oxidative tissue damage, or immune suppression that acts on cancer progression [9, 11]. Smoking-induced activated macrophages may generate reactive oxygen species that promote angiogenesis, tumor invasion, and metastasis [9, 13]. Tobacco exposure also can alter multiple immunologic functions, including the innate and adaptive immune system [9]. Smoking induces changes in natural killer cell activity and cell-mediated immunity and may lead to accelerated tumor progression [31]. Furthermore, nicotine has been shown to protect cancer cells from apoptosis induced by diverse stimuli and to exert proangiogenic activities [13]. Smoking may increase blood carboxy-hemoglobin, producing relative hypoxia [13], and hypoxia-inducible factor has been shown to contribute to the RCC tumorigenesis process [16]. Preclinical data suggest that resistance to VEGFR inhibitors may be mediated via elements upstream of receptor blockade, such as hypoxia-inducible factor, that can drive tumor growth despite target blockade [16].

Our study has some limitations. First, this is a multicenter retrospective study represents an unselected heterogeneous cohort of patients that were treated with sunitinib, including all histologic variants of RCC, and patients who were treatment naïve and those with a history of prior therapy. Nonetheless, the outcomes of the present study's patient population (i.e., median PFS of 9 months and median OS of 22 months) are similar to previously published data on patients with mRCC that were treated with sunitinib [32]. Second, we are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. Third, the total number of patients that actively smoked ($n = 59$) is relatively small. Other clinicopathologic factors that were not found to be significantly associated with disease progression in the present study might have been important in a larger patient cohort. Fourth, whether our findings are specific to sunitinib or generalizable to other tyrosine kinase inhibitors is not known. Fifth, time-dependent models were not used in analyzing the association between postbaseline clinicopahtologic factors and sunitinib treatment outcome. Finally, smoking has the potential to induce metabolism of some drugs mainly through CYP2C induction. Although it is unlikely to affect sunitinib metabolism (mainly CYP3A4), a reduction of sunitinib exposure secondary to smoking may be associated with treatment outcome. In the present study, active smoking was associated with numerically less hand and foot syndrome. Although this difference was not statistically significant at a .05 significance level in our relatively small cohort, we are not able to exclude the effects of smoking on metabolism.

Despite these limitations, our clinical observation that active smoking may negatively affect the outcome of sunitinib treatment in RCC may contribute to treatment decisions, patient selection, and clinical trial design. Given this evidence, clinicians should ask their patients about smoking status before starting treatment and may consider advising them to quit smoking and provide the necessary support to do so. Further studies may be warranted to test and confirm our hypothesis-generating observation in larger patient cohorts, to elucidate the underlying molecular mechanisms, to define the association between smoking status and outcome in different subgroups of patient (e.g., according to risk by prognostic models, clear cell vs. non-clear cell histology, and first-line vs. advanced-line treatment), and to test the association between postbaseline clinicopathologic factors and treatment outcome in time-dependent models. These may include retrospective subgroup analysis of previously completed large randomized trials of sunitinib or other VEGFR inhibitor therapy in mRCC as well as prospective observational studies of targeted therapies.

Conclusion

Active smoking may negatively affect the PFS and OS of sunitinib-treated mRCC patients. BMI, DM, and pretreatment hypertension were not found to be associated with outcome. Clinicians should consider advising patients to quit smoking at initiation of sunitinib treatment for mRCC.

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Disclosures

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