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Predictive Factors and Prognostic Relevance of Sunitinib-induced Subclinical and Overt Hypothyroidism in Korean Patients with Metastatic Renal Cell Carcinoma

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ABSTRACT

Background: Sunitinib, commonly used for metastatic renal cell carcinoma (mRCC), often induces hypothyroidism, affecting 27 to 85% of patients. There are clues suggesting an association between sunitinib-induced hypothyroidism and improved survival outcomes. This study aims to identify the predictive factors of sunitinib-induced hypothyroidism and evaluate whether the occurrence of overt or subclinical hypothyroidism predicts tumor outcome in patients with mRCC. **Methods:** Patients administered to sunitinib for mRCC was included in this retrospective study. Log-rank test and Cox proportional hazards model were conducted to identify predictive factors of hypothyroidism and prognostic factors of progression-free survival (PFS) and overall survival (OS). **Results:** A total of 156 patients with mRCC treated with sunitinib were included. Predictive factors of sunitinib-induced hypothyroidism were female (odds ratio (OR), 2.77), sunitinib-induced hypertension (OR, 2.99) and dose reduction of sunitinib due to intolerance (OR, 3.57). Sunitinib-induced overt hypothyroidism was a significant prognostic factor in predicting PFS and OS (hazard ratio, 0.38 and 0.23, respectively). Thyroid hormone replacement did not have an influence on PFS and OS. **Conclusions:** Female patients, patients who experienced sunitinib-induced hypertension and sunitinib dose reduction are at higher risk of hypothyroidism and need close monitoring. Overt hypothyroidism is a strong prognostic factor of sunitinib treatment outcome in mRCC patients and thyroid hormone replacement does not have a negative effect on tumor outcome.

KEYWORDS: Hypothyroidism; metastatic renal cell carcinoma; overall survival; progression-free survival, sunitinib

Sunitinib, a tyrosine kinase inhibitor (TKI) that targets multiple receptor tyrosine kinases including vascular endothelial growth factor (VEGF), significantly transformed the prognosis of metastatic renal cell carcinoma (mRCC) upon its introduction in 2005.[1)] It was recommended as a first line therapy for mRCC patients in various guidelines, including those from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), until newer generations of TKIs and immunotherapy were introduced. However, in Korea, due to the reimbursement issues, treatment options for mRCC patients are limited, and sunitinib is still recommended as a first-line therapy and a viable option for patients who cannot tolerate immunotherapy. Hypothyroidism is a common sunitinib-induced side effect with an incidence of 27 to 85%.[2-4)] More recently, genetic factors such as single nucleotide polymorphisms in the thyroid-stimulating hormone (TSH) receptor and the major histocompatibility complex, Class II, DQ Alpha-1 (HLA-DQA1), have been found to be associated with an

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approximately 2-fold increase in the risk of hypothyroidism,[5] underscoring the need to validate these findings in the Korean population. However, hypothyroidism has been considered as minor importance than other side effects such as hypertension and clinical thyroid screening has not been routinely performed.

Hypothyroidism and elevated TSH levels are associated with diverse comorbidities, including coagulopathy, dyslipidemia, hypertension and coronary heart disease which potentially contribute to increased mortality.[6] A meta-analysis[7] of 12 case-control studies showed an association between hypothyroidism and increased mortality, although heterogeneity and potential genetic confounding were noted. A cohort study[8] utilizing data from the National Health and Nutrition Examination Survey (2001-2012) with follow-up through 2015 found that US adults with subclinical hypothyroidism or high-normal TSH concentrations had increased all-cause mortality compared to those with middle-normal TSH levels, as indicated by hazard (HRs) ratios of 1.90 and 1.36, respectively.

Contrary to the typical association between hypothyroidism and increased mortality, real-world evidence suggests that sunitinib-induced hypothyroidism may correlate with improved therapeutic outcomes of sunitinib in mRCC patients, proposing its role as a predictive marker for sunitinib efficacy. In a study[9] of 41 patients with clear cell mRCC treated with sunitinib in the first-line setting, significantly improved progression-free survival (PFS) was observed (25.3 months vs. 9.0 months, p=0.042), though no difference in overall survival (OS) was noted. Another research involving 81 mRCC patients treated with sunitinib indicated that those who developed hypothyroidism experienced notably better outcomes, including higher remission rates (46.7 vs 13.7%, respectively; p=0.001) and extended overall survival (39 vs. 20 months, p=0.019) compared to euthyroid patients.[8] Bolzacchini *et al*.[10] observed an association between early TSH increase and clinical benefit and proposed that an increase in TSH levels after two weeks of sunitinib could be a predictive factor. However, these studies were constrained by limited number of patients and infrequent monitoring of thyroid function.

Although the precise mechanism of hypothyroidism remains unclear, sunitinib-induced hypothyroidism is thought to occur due to inhibition of the VEGF-signaling pathway or activation of the anticancer immune system.[11] Additionally, since thyroid hormone itself stimulates cancer growth, it is logical that hypothyroidism could prolong PFS and OS. Identifying factors that influence hypothyroidism and managing them effectively can help patients maintain sunitinib treatment and improve outcomes. Moreover, early management of patients with subclinical hypothyroidism may enhance outcomes. The objectives of this study are to identify the predictive factors for sunitinib-induced hypothyroidism and to assess whether the occurrence of overt of subclinical hypothyroidism predicts tumor outcomes in patients with mRCC.

Materials and Methods

Study subjects

This retrospective study utilized electronic medical records (EMRs) to include patients diagnosed with any pathologic subtype of mRCC who completed at least one cycle of sunitinib treatment from January 2007 to June 2014 at Seoul National University Hospital. All participants initially received sunitinib at a starting dose of 50 mg, taken daily for 4 weeks, followed by a 2-week break, continuing a 6-week cycle. Doses were adjusted based on the presence of hematological and non-hematological adverse events. Individuals with uncontrolled thyroid disease or prior VEGF therapy were excluded from the study. Ethical approval for the study was granted by the Institutional Review Board (IRB) of Seoul National University Hospital (SNUH IRB 1706-075-859).

Study outcomes

The study aimed to identify risk factors for sunitinib-induced hypothyroidism and prognostic factors affecting the survival outcomes, specifically PFS and OS. PFS was defined as the duration from treatment initiation to either disease progression or death, while OS was measured from treatment initiation to death. Tumor responses and disease progression were evaluated every two cycles based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria employing either computed tomography scans or magnetic resonance imaging. Bone scans were performed when clinically indicated.

Thyroid function assessment

Thyroid function was evaluated at baseline and periodically during sunitinib treatment, measuring serum free thyroxine and TSH. Definitions of overt and subclinical hypothyroidism were based on criteria from the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE), and the Endocrine Society.[12] Overt hypothyroidism was characterized by below-normal free thyroxine levels and a TSH above the upper limit of normal (ULN), set at 4.1 μIU/mL

by our institutional laboratory, where the normal free thyroxine range is 0.7 to 1.8 ng/dL. Subclinical hypothyroidism involved elevated TSH with normal free thyroxine levels. Thyroid hormone replacement commenced when TSH exceeded 10 μIU/mL, adhering to protocols from previous study.[3] Patients with normal TSH levels were categorized as the euthyroid group.

Statistical analysis

To compare the characteristics between the hypothyroid and the euthyroid groups, categorical values were assessed using Pearson's chi-squared test or Fisher's exact test, and numerical variables were evaluated with either Mann-Whitney U test or the independent samples t-test based on the results of Kolmogorov-Smirnov Test. Logistic regression analysis was used to identify predictive factors for sunitinib-induced hypothyroidism.

To mitigate time-related biases in our analysis, two distinct approaches were employed. Firstly, hypothyroidism status was incorporated as a time-dependent covariate, where initially all patients were considered non-responders, transitioning to responders upon manifestation of hypothyroidism. Secondly, we utilized the landmark analysis technique, setting predetermined times (landmarks) at 3, 6, 9, and 12-months post-initiation of sunitinib treatment to assess responses. Survival analyses and subsequent statistical evaluations were then performed based on the status at these landmark times, excluding any patients who deceased prior to each landmark.

The relationship between hypothyroidism and both PFS and OS was examined using the Kaplan-Meier method, with the log-rank test for univariate analysis and the Cox proportional hazards model for multivariable evaluation. PFS was defined from the date of treatment initiation to radiologically confirmed disease progression or death, and OS was defined as time from sunitinib initiation to death. Prognostic factors included baseline characteristics (age, sex, Heng risk category,[13] Karnofsky Performance Score (KPS), histology, metastasis, prior therapy, time to systemic treatment, lactate dehydrogenase (LDH), serum calcium) and treatment-related factors (sunitinib-induced hypothyroidism, hypertension, proteinuria, renal injury). To address the bias of survival requirement for developing hypothyroidism, hypothyroidism was analyzed as a time-varying covariate and through landmark analysis at 3, 6, 9, and 12 months following sunitinib treatment.

A two-tailed p value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 156 patients were included in the study, of which 86 (55.1%) patients developed hypothyroidism following sunitinib treatment; overt hypothyroidism accounted for 59.3% of these cases. Table 1 presents the baseline characteristics of the hypothyroid and the euthyroid groups. Most baseline characteristics did not differ significantly between the groups. Male patients were predominant in both groups, with a larger proportion in euthyroid group (87.1% vs. 69.8%, p=0.012). The median age was 58 years in both groups, with a similar frequency of geriatric patients (38.4% in the hypothyroid group vs. 42.9% in the euthyroid group, p=0.624). Similar numbers of patients were categorized as having a poor prognosis for mRCC based on Heng risk criteria. Among the patients with overt hypothyroidism, 47 started thyroid hormone replacement therapy, and 33 returned to a euthyroid state after completing sunitinib treatment. None of the patients with either overt or subclinical hypothyroidism discontinued or reduced their sunitinib dosage due to hypothyroidism.

Predictive factors of hypothyroidism

The distribution of factors associated with sunitinib-induced hypothyroidism in patients with mRCC are outlined in Table 2. Univariable analysis identified several predictive factors for sunitinib-induced hypothyroidism (Table 3): being female (OR 2.94; 95% CI, 1.27-6.79), sunitinib-induced hypertension (OR 4.05; 95% CI, 1.87-8.77), sunitinib-induced proteinuria (OR 2.50; 95% CI, 1.28-4.88), number of sunitinib cycles (OR 1.12; 95% CI, 1.04-1.21), and sunitinib dose reduction due to toxicities other than hypothyroidism (OR 4.02; 95% CI, 2.06-7.85). Multivariable analysis confirmed that being female (OR 2.77; 95% CI, 1.03-7.50), sunitinib-induced hypertension (OR 2.99; 95% CI, 1.10-8.15), and dose reduction for reasons other than hypothyroidism (OR 3.57; 95% CI, 1.50-8.53) remained significant predictive factors. Other factors did not show a significant association. In patients with overt hypothyroidism, the initial elevated TSH level was significantly higher than in those with subclinical hypothyroidism (33.14 μIU/mL vs. 7.17 μIU/mL, p=0.045). Although not statistically significant, the cumulative dose of sunitinib (5,271 mg vs. 3,740 mg, p=0.132) and the number of sunitinib cycles (4.1 vs. 3.0, p=0.202) were higher in the group with overt hypothyroidism.

Table 1. Baseline characteristics of subjects

Characteristics	Hypothyroid (n=86)	Euthyroid (n=70)	*p*
Age ≥65, n (%)	33 (38.4)	30 (42.9)	0.624
Male, n (%)	60 (69.8)	61 (87.1)	0.012
BMI (kg/m^2) ≥25, n (%)	19 (22.9)	16 (24.6)	0.934
Heng risk criteria, n (%)			0.406
Favorable	16 (18.6)	18 (25.7)	
Intermediate	58 (67.4)	40 (57.1)	
Poor	12 (14.0)	12 (17.1)	
Past nephrectomy, n (%)	75 (87.2)	60 (85.7)	0.817
Clear cell histology, n (%)	85 (95.3)	66 (94.3)	1.000
Metastatic sites ≥2, n (%)	52 (60.5)	44 (62.9)	0.869
Lung metastasis, n (%)	61 (70.9)	53 (75.7)	0.587
Liver metastasis, n (%)	11 (12.8)	11 (15.7)	0.648
Bone metastasis, n (%)	20 (23.3)	18 (25.7)	0.851
Past systemic therapy, n (%)	22 (25.6)	19 (27.1)	0.856
Underlying HTN, n (%)	54 (37.2)	44 (37.1)	1.000
Underlying CKD, n (%)	15 (17.4)	14 (20.0)	0.685
Underlying proteinuria, n (%)	15 (17.4)	12 (17.1)	1.000
LDH >ULN, n (%)	2 (4.2)	2 (6.5)	0.643
Serum calcium >ULN, n (%)	7 (8.1)	11 (15.7)	0.207

BMI: body mass index, CKD: chronic kidney disease; HTN: hypertension, LDH: lactate dehydrogenase, ULN: upper limit of normal

Table 2. Distribution of factors associated with overt and subclinical hypothyroidism in patients treated with sunitinib

Characteristics	Overt hypothyroidism (N=51)	Subclinical hypothyroidism (N=35)	*p*
Age ≥ 65 (%)	45.1	28.6	0.176
Female (%)	29.4	31.4	1.000
BMI < 25 (%)	72.5	77.1	0.338
Time to TSH elevation after sunitinib initiation (days)	176.2	140.1	0.329
TSH elevation within the first 3 cycles of sunitinib (%)	52.9	74.3	0.070
Cumulative dose of sunitinib (mg)	5271.1	3740.0	0.132
Level of first elevated TSH (uIU/mL)	33.1	7.2	0.045
Number of sunitinib cycles	4.1	3.0	0.202
Dose reduction of sunitinib due to other intolerance (%)	74.5	54.3	0.065

BMI: body mass index, TSH: thyroid stimulating hormone

Survival Outcomes

Patients in the hypothyroid group exhibited significantly longer PFS and OS compared to those in the euthyroid group, with PFS at 10.5 months versus 6.1 months and OS at 23.5 months versus 9.4 months (both $p<0.001$). When hypothyroidism was analyzed as a time-varying covariate, the difference in PFS was not significant ($p=0.105$), although the difference in OS remained significant ($p=0.011$). Despite not reaching statistical significance, the hypothyroid group tended to have longer PFS than the euthyroid group. Landmark analysis at three months showed significant differences in PFS between the two groups, whereas OS differed significantly at three and 12 months but not at six and nine months.

The median PFS in the overt hypothyroid group was 12.2

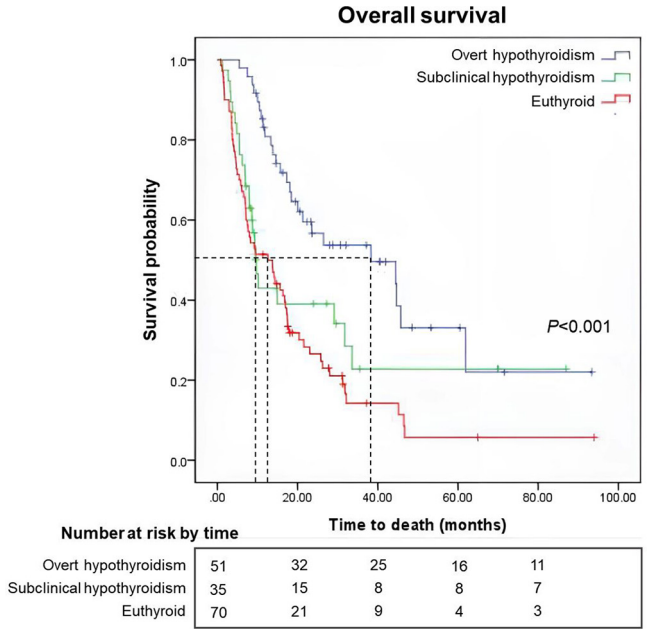

Fig. 1. Kaplan-Meier curves for overall survival among subclinical hypothyroidism, overt hypothyroidism, and euthyroid groups

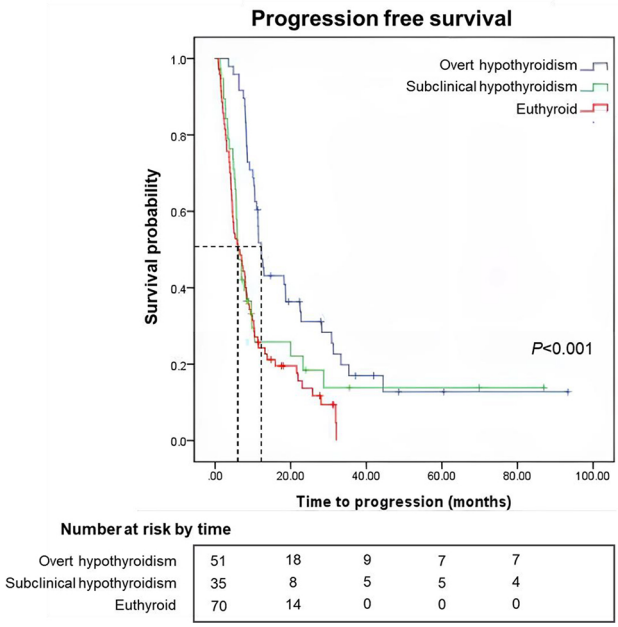

Fig. 2. Kaplan-Meier curves for progression free survival among subclinical hypothyroidism, overt hypothyroidism, and euthyroid groups

months, compared to 6.1 months in both the subclinical hypothyroid and euthyroid groups (p<0.001). A similar pattern was observed for OS, with the overt hypothyroid group achieving a median of 38.3 months, versus 9.7 months in the subclinical group and 12.6 months in the euthyroid group (p<0.001) (Figs. 1 and 2).

Multivariable analysis identified the development of overt hypothyroidism as a significant prognostic factor for improved PFS and OS, with HR of 0.38 (95% CI, 0.16-0.88) and 0.23 (95% CI, 0.09-0.64), respectively (Table 3). Other prognostic factors affecting PFS included Karnofsky Performance Score (KPS) <80% (HR 3.46; 95% CI, 1.18-10.12) and time from diagnosis to systemic treatment of less than one year (HR 2.48; 95% CI, 1.10-5.60). For OS, significant factors were age >65 years (HR 3.40; 95% CI, 1.05-11.04), KPS <80% (HR 4.11; 95% CI, 1.27-13.35), time from diagnosis to systemic treatment less than one year (HR 4.43; 95% CI, 1.71-11.47), and hypercalcemia (HR 5.34; 95% CI, 1.53-18.65). The development of subclinical hypothyroidism was not identified as a favorable prognostic factor for either PFS or OS.

Discussion

In this study, we identified predictive factors for sunitinib-induced hypothyroidism as well as favorable prognostic factors for PFS and OS in Korean patients with mRCC. The incidence of sunitinib-induced hypothyroidism was reported more frequently in retrospective studies, at 53-85%, compared to 36-46% in prospective studies.[14] More recent studies[7-10,15-17] based on real-world data reported that the incidence of sunitinib-induced hypothyroidism as 29.3-59.1%. In our research, the prevalence of hypothyroidism was similar to these previous studies, as 55.1% of patients developed hypothyroidism following sunitinib treatment in our study. Additionally, Kust *et al*.[9] reported median peak TSH values reaching 34.4 mIU/L in 29.3% of patients who developed hypothyroidism, which is comparable to the 33.1 mIU/L observed in our study. A cross-sectional analysis[18] conducted at a single institution in Korea reported an occurrence of approximately 28% for any grade of hypothyroidism in sunitinib administered patients. Sunitinib-induced hypothyroidism is often underdiagnosed due to its nonspecific symptoms such as fatigue; thus, identifying readily accessible predictive factors is crucial to pinpoint patients at high risk.

Our findings indicate that female patients are at a higher risk of developing hypothyroidism, a result consistent with previous studies.[9,19,20] The epidemiological study also indicated a higher prevalence and incidence of subclinical hypothyroidism in Korean female compared to Korean male.[21] Consequently, for women undergoing sunitinib therapy, baseline and periodic thyroid examinations during treatment are necessary. Additional

Table 3. Predictive factors of sunitinib-induced hypothyroidism

Variables	Unadjusted analysis			Multivariable analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Age ≥65	1.21	0.63-2.29	0.573	0.82	0.35-1.96	0.656
Female	2.94	1.27-6.79	0.007	2.77	1.03-7.50	0.044
Heng risk						
Favorable	1.13	0.40-3.20	0.829	8.43	0.92-77.22	0.059
Intermediate	0.69	0.28-1.69	0.415	1.45	0.28-7.59	0.657
Poor	1.00	-	-	1.00	-	-
BMI[a)]						
<25	1.15	0.19-7.14	0.879	0.20	0.02-2.38	0.202
25-29.9	1.31	0.19-9.02	0.782	0.16	0.01-2.16	0.168
≥30	1.00	-	-	1.00	-	-
Past nephrectomy	0.88	0.35-2.21	0.787	0.91	0.25-3.25	0.882
Sunitinib-induced HTN	4.05	1.87-8.77	0.008	2.99	1.10-8.15	0.032
Sunitinib-induced proteinuria	2.50	1.28-4.88	0.007	2.11	0.90-4.95	0.085
Sunitinib-induced renal injury	2.63	0.98-7.08	0.063	1.52	0.44-5.29	0.513
Number of cycles	1.12	1.04-1.21	0.008	0.91	0.82-1.01	0.064
Dose reduction due to other side effects	4.02	2.06-7.85	0.002	3.57	1.50-8.53	0.004

BMI: body mass index, CI: confidence interval, HTN: hypertension, OR: odds ratio
[a)]Evaluated in 148 patients

predictive factors identified include sunitinib-induced hypertension and dose reduction due to toxicity. A previous study found that patients who develop hypothyroidism commonly underwent one or two dose reductions for grade 3-4 hematological or non-hematological toxicities,[3)] indicating that susceptibility to one side effect may increase vulnerability to others, such as hypertension. Interestingly, some research[22,23)] has associated side effects like hypertension and neutropenia with a good prognosis, suggesting that these complications, when managed effectively, could potentially benefit patients. However, contrasting findings were observed in a study[24)] conducted at a single center in Helsinki, Finland, which found no association between hypertension and hypothyroidism in 64 patients with mRCC treated with sunitinib. In contrast, our study identified a clear association between hypertension and hypothyroidism after sunitinib treatment for mRCC, highlighting the variability in clinical responses and the need for further investigation into these interrelated side effects. Therefore, patients who develop hypertension and experience dose reductions due to other intolerances should be closely monitored with additional thyroid function tests to manage these side effects proactively. Furthermore, using blood pressure as an index is not only more convenient but also cost-effective compared to routine thyroid function tests. This approach ensures that potential adverse effects are managed promptly, potentially turning a risk into a prognostic advantage.

Consistent with previous studies conducted in Europe,[25,26)] the hypothyroid group exhibited longer PFS and OS compared to the euthyroid group. This finding aligns with a meta-analysis[27)] that reported similar outcomes (HR, 0.52; 95% CI, 0.31-0.87). However, only overt hypothyroidism emerged as a significant prognostic factor for favorable PFS and OS, while subclinical hypothyroidism did not significantly affect PFS and OS. Existing meta-analyses have indicated a trend toward increased PFS in patients with hypothyroidism, although this was not statistically significant (HR, 0.82; 95% CI, 0.59-1.13). By differentiating between overt and subclinical hypothyroidism, this study confirmed that PFS was significantly prolonged in patients with overt hypothyroidism. Historically, thyroid hormone has been considered a stimulant for tumor growth in cancer patients.[28)] In our study, nearly all patients who developed overt hypothyroidism underwent thyroid hormone replacement therapy, with levothyroxine restoring 72.5% of patients to a euthyroid state. Thus, the improvement in PFS and OS observed in the overt hypothyroid group is likely not due to the hypothyroid state but rather the direct anticancer effects of sunitinib. Thyroid hormone replacement did not negatively impact tumor outcomes,

Table 4. Prognostic factors of progression-free survival (PFS)

Variables	Univariate analysis (Log rank test)			Multivariable analysis (Cox proportional hazard model)		
	Number of patients (Progressed/ Total)	Median PFS (months)	*p*	HR	95% CI	*p*
Age, years						
<65	76/93	8.27	0.250			
≥65	55/63	8.40				
Sex						
Male	103/121	8.40	0.563			
Female	28/35	8.27				
KPS[a]						
<80%	12/12	10.00	<0.001	3.46	1.18-10.12	0.023
≥80%	87/108	2.90				
Nephrectomy						
Yes	112/135	9.10	0.066			
No	19/21	6.17				
Histology						
Non-clear cell	7/8	5.70	0.185			
Clear cell	124/148	8.40				
Prior therapy						
Yes	34/41	8.87	0.298			
No	97/115	8.23				
Time from diagnosis to systemic treatment						
<1 year	84/94	7.47	0.004	2.48	1.10-5.60	0.028
≥1 years	46/61	11.33				
Number of metastases						
1	47/60	11.33	0.013			
≥2	84/96	7.70				
Anemia						
Yes	77/87	10.97	0.049			
No	54/69	7.83				
Thrombosis						
Yes	14/16	6.07	0.118			
No	117/140	9.00				
Neutrophilia						
Yes	8/10	4.33	0.775			
No	123/146	8.40				
Hypercalcemia						
Yes	16/18	3.73	0.003			
No	115/138	9.43				
Elevated LDH[b]						
Yes	3/4	1.97	0.810			
No	64/75	8.03				
Pre-treatment NLR						
≥3	92/113	9.80	0.001			
>3	39/43	5.30				
Sunitinib-induced hypothyroidism						
Overt	40/51	12.20	0.001	0.38	0.16-0.88	0.024
Subclinical	28/35	6.17				
Euthyroid	63/70	6.07				
Sunitinib-induced hypertension						
Yes	35/48	12.60	<0.001			
No	96/108	7.00				
Sunitinib-induced proteinuria						
Yes	50/63	10.47	0.042			
No	81/93	7.83				
Sunitinib-induced renal insufficiency						
Yes	19/23	10.50	0.107			
No	112/133	8.23				

CI: confidence interval, HR: hazard ratio, KPS: Karnofsky performance score, LDH: lactate dehydrogenase, NLR: neutrophil lymphocyte ratio, PFS: progression-free survival

[a]Evaluated in 120 patients, [b]Evaluated in 79 patients

Table 5. Prognostic factors of overall survival (OS)

Variables	Univariate analysis (Log rank test)			Multivariable analysis (Cox proportional hazard model)		
	Number of patients (Progressed/ Total)	Median OS (months)	Log-rank *p*	HR	95% CI	*p*
Age, years						
<65	59/93	17.50	0.026	3.40	1.05-11.04	0.042
≥65	49/63	13.30				
Sex						
Male	87/121	15.63	0.259			
Female	21/35	17.27				
KPS[a)]						
<80%	12/12	3.27	<0.001	4.11	1.27-13.35	0.019
≥80%	66/108	17.50				
Nephrectomy						
Yes	90/135	17.43	0.026			
No	18/21	8.23				
Histology						
Non-clear cell	6/8	9.70	0.326			
Clear cell	102/148	16.80				
Prior therapy						
Yes	26/41	18.03	0.108			
No	82/115	14.60				
Time from diagnosis to systemic treatment						
<1 year	73/94	11.37	<0.001	4.43	1.71-11.47	0.002
≥1 years	36/61	31.23				
Number of metastases						
1	40/-60	25.80	0.033			
≥2	68/96	9.70				
Anemia						
Yes	69/87	11.37	0.003			
No	39/69	25.80				
Thrombosis						
Yes	9/16	11.83	0.983			
No	99/140	16.80				
Neutrophilia						
Yes	8/10	5.83	0.194			
No	100/146	17.27				
Hypercalcemia						
Yes	16/18	4.67	<0.001	5.34	1.53-18.65	0.009
No	92/138	17.50				
Elevated LDH[b)]						
Yes	2/4	6.90	0.649			
No	50/75	13.77				
Pre-treatment NLR						
≥3	71/113	18.43	<0.001			
>3	37/43	7.47				
Sunitinib-induced hypothyroidism						
Overt	25/51	38.27	<0.001	0.23	0.09-0.64	0.005
Subclinical	24/35	9.70				
Euthyroid	59/70	12.60				
Sunitinib-induced hypertension						
Yes	25/48	32.13	<0.001			
No	83/108	12.60				
Sunitinib-induced proteinuria						
Yes	38/63	21.30	0.049			
No	70/93	13.30				
Sunitinib-induced renal insufficiency						
Yes	15/23	23.50	0.121			
No	93/133	14.93				

CI: confidence interval, HR: hazard ratio, KPS: Karnofsky performance score, LDH: lactate dehydrogenase, NLR: neutrophil lymphocyte ratio, OS: overall survival

[a)]Evaluated in 120 patients, [b)]Evaluated in 79 patients

indicating that the administration of levothyroxine need not be delayed.

The limitations of this study stem from its retrospective nature. The study lacks data on drug compliance, which could significantly impact the results. In response to the inherent challenges of the retrospective design, we implemented several strategies to minimize potential bias. Firstly, we ensured a homogeneous patient population relevant to the study's objectives as we included only those patients who received a complete cycle of sunitinib and excluded those with uncontrolled thyroid conditions or previous VEGF therapies to avoid confounding treatment effects. Furthermore, to counter information bias, data were extracted from EMRs, which provided a consistent source of comprehensive patient information, and the data were collected based on consistent protocol. Considering time-related bias due to the adoption of newer generation targeted therapies and immune checkpoint inhibitors, as well as the follow-up period, we limited the inclusion of patients to those treated from 2007 to 2014. However, to control time-related bias, we used time-dependent covariate and landmark method.

Conclusion

Female patients, as well as those who experience sunitinib-induced hypertension or dose reductions, are at an increased risk of developing hypothyroidism; therefore, close monitoring is strongly recommended. Furthermore, overt hypothyroidism has been identified as a strong prognostic factor for favorable treatment outcomes in mRCC patients, and thyroid hormone replacement therapy does not adversely affect tumor outcomes.

Conflict of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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