JBUON 2021; 26(4): 1628-1634
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Real-life data on first-line Sunitinib and Pazopanib therapy in metastatic renal cell carcinoma patients: a single center experience

Alper Topal[1], Sezin Sayın[2], Ali Gokyer[3], Ahmet Kucukarda[3], Osman Kostek[3], Muhammet Bekir Hacıoglu[3], Sernaz Uzunoglu[3], Bulent Erdogan[3], Irfan Cicin[3]

[1]Trakya University School of Medicine, Department of Internal Medicine, Edirne, Turkey. [2]Trakya University School of Medicine, Medical Student, Edirne, Turkey. [3]Trakya University School of Medicine, Department of Internal Medicine, Division of Medical Oncology, Edirne, Turkey.

Summary

Purpose: *In this study, we aimed to compare the data of sunitinib and pazopanib used in the first-line treatment of metastatic renal cell carcinoma (RCC) cases and to evaluate the effective factors in terms of survival.*

Methods: *The records of 125 patients with metastatic RCC admitted between January 2005 and February 2018 were retrospectively analyzed and 63 patients who received pazopanib or sunitinib were included in the study while 62 patients were excluded due to insufficient data. Clinical and histological characteristics, treatment responses, progression-free survival (PFS), and overall survival (OS) of the patients were compared.*

Results: *Patients with metastatic RCC who received pazopanib or sunitinib as tyrosine kinase inhibitors (TKI) in first-line treatment were analyzed; 45 (71.4%) were male while 18 (28.6%) were female, and the median age was 60. 43 (68.3%) patients were treated with sunitinib and 20 (31.7%) with pazopanib. PFS of pazopanib and sunitinib were 10.6 and 7.2 months, respectively. Median OS was 14.5 months in patients receiving pazopanib and 13.6 months in those receiving sunitinib. There was no statistical difference in PFS and OS between both treatments. The median OS of clear-cell RCC was 15.2 months, while of non-clear-cell RCC was 7.7months.*

Conclusions: *High ECOG score, non-clear-cell histology, presence of liver metastasis in metastatic RCC patients were found to be associated with shorter OS and PFS. Sunitinib and pazopanib produced similar OS and PFS rates in first-line treatment of metastatic RCC.*

Key words: *renal cell carcinoma, sunitinib, pazopanib, overall survival*

Introduction

Renal cell carcinoma (RCC) forms 2-3% of all cancers [1]. RCC, the most common form of kidney cancer, constitutes 90% of the cases and is almost twice as common in men than women [2]. 30% of RCCs are metastatic at the time of diagnosis and approximately 30% of organ-limited RCCs become metastatic after local treatment [3]. 5-year survival in RCC is 92.6% in the disease localized to the kidney, 64.2% in patients with regional lymph node involvement, and 11.6% in metastatic patients [4].

Metastatic RCC is one of the treatment-resistant tumors and the antitumor effect of cytotoxic chemotherapy on RCC is very low [5]. Response to interferon-alpha (IFN-α), interleukin-2 (IL-2), or combined cytokine treatments is limited and

Corresponding author: Ali Gokyer, MD. Trakya University School of Medicine, Department of Internal Medicine Division of Medical Oncology, Edirne, 22030, Turkey.
Tel: +90 5536376360; Email: aligkyer@hotmail.com
Received: 10/02/2021; Accepted: 27/03/2021

has serious side effects [5]. Better response rates and longer progression-free survival (PFS) have been shown with targeted therapies [2]. The main approach in targeted therapy is the use of agents (sunitinib, sorafenib, pazopanib, axitinib, cabozantinib) that inhibit tyrosine kinases, which are the intracellular part of the vascular endothelial growth factor (VEGF) receptor [6]. Sunitinib, the most commonly used among these drugs, showed a significant difference with a median 11 months PFS versus IFN-α in a phase 3 study conducted in 2007 [7]. Pazopanib was approved in a non-inferiority comparative study versus sunitinib in 2013, with median PFS for 8.4 months and median overall survival (OS) for 28.4 months [8].

Recent randomized studies have shown that various immunotherapy combination therapies (nivolumab plus ipilimumab, avelumab plus axitinib, pembrolizumab plus axitinib) have longer median PFS and median OS in metastatic clear-cell RCC (ccRCC) compared to sunitinib alone. These combinations are currently the first choice in first-line treatment in intermediate and high risk patients [9].

In this study, we compared the data of sunitinib and pazopanib used in the first-line treatment of metastatic RCC cases, and evaluated the factors affecting the prognosis and survival of the patients.

Methods

Participants

All participants provided signed informed consent form.

Patients with metastatic RCC admitted to the Department of Medical Oncology of Trakya University between January 2005 and February 2018 were retrospectively evaluated. The records of 125 patients were examined. Sixty-three patients who received tyrosine kinase inhibitors, pazopanib or sunitinib, were included in the study. Sixty-two patients were excluded from the study due to lack of data. The diagnosis date indicated the date of pathological diagnosis or the operation date in patients without a preoperative diagnosis. The patients' age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, Karnofsky performance status, nephrectomy history, histological examination result, Fuhrman grade, presence of sarcomatoid differentiation, Memorial Sloan-Kettering Cancer Center (MSKCC) score, number and sites of metastases, the duration between the diagnosis and treatment, which drug were used as a first-line tyrosine kinase inhibitor, OS and PFS values were analyzed. The OS indicated the duration from diagnosis to death and the PFS from the initiation of treatment to the date when progression was first detected.

Statistics

Quantitative data were calculated as medians (interquartile range) and compared with the Studenst t-test and Mann-Whitney U-test. Categorical data were compared with the Fisher chi-square test. Kaplan-Meier and Log-Rank tests were used in survival analysis. $P<0.05$ was accepted as statistically significant for all p values. Statistical analysis was performed using SPSS 21.0 (IBM SPSS, New York, USA).

Results

Patient characteristics

Sixty-three patients with metastatic RCC who received pazopanib or sunitinib as tyrosine kinase inhibitors (TKI) in first-line treatment were included in the study. Forty-five (71.4%) of the patients were male and 18 (28.6%) female. The median age of the patients was 60 years (34-85). The ECOG score of the patients at the time of diagnosis was 0-1 in 59 (93.6%) patients, and 2 and above in 4 (6.4%). Nephrectomy was performed in 54 (85.7%) patients, while 9 (14.3%) were not. Histological examination results of the patients were as follows: 50 (79.4%) clear-cell, 10 (15.9%) papillary, 2 (3.2%) chromophobe, 1 (1.6%) unclassifiable histology (Table 1).

Table 1. Classification of the patients included in the study according to their history of nephrectomy, histopathologic features, Fuhrman grade, sarcomatoid differentiation, and metastatic disease

	n (%)
History of nephrectomy	
Yes	54 (85.7)
No	9 (14.3)
Histopathology	
Clear-cell	50 (79.4)
Papillary	10 (15.9)
Chromophobe	2 (3.2)
Unclassifiable	1 (1.6)
Fuhrman grade	
1	3 (4.8)
2	22 (34.9)
3	23 (36.5)
4	10 (15.9)
Unknown	5 (7.9)
Sarcomatoid differentiation	
Yes	8 (12.7)
No	39 (61.9)
Unknown	16 (25.4)
De novo metastatic disease	
Yes	47 (74.6)
No	16 (25.4)

Table 2. Distribution of patient characteristics according to treatment options

	Sunitinib (n=43)	*Pazopanib (n=20)*	*p value*
Age, year			0.20
Mean ± standard deviation	59±13	63±12	
Median (minimum-maximum)	59 (34-85)	64 (44-85)	
Gender, n (%)			0.86
Male	31 (72.1)	14 (70.0)	
Female	12 (27.9)	6 (30.0)	
ECOG-performance score, n (%)			0.09
0-1	42 (97.7)	17 (85.0)	
2	1 (2.3)	3 (15.0)	
History of nephrectomy, n (%)			0.37
Yes	38 (88.4)	16 (80.0)	
No	5 (11.6)	4 (20.0)	
Histopathology, n (%)			0.74
Clear-cell	35 (81.4)	15 (75.0)	
Non-clear-cell	8 (18.6)	5 (25.0)	
Furhman grade, n (%)			0.59
1- 2	19 (45.2)	6 (37.5)	
3-4	23 (54.89)	10 (62.5)	
Sarcomatoid differentiation, n (%)			0.40
Yes	5 (14.3)	3 (25.0)	
No	30 (85.7)	9 (75.0)	
De novo metastatic disease, n (%)			0.75
Yes	31 (72.1)	16 (80.0)	
No	12 (27.9)	4 (20.0)	
MSKCC score, n (%)			0.86
Favorable risk	2 (8.3)	-	
Intermediate risk	14 (58.3)	2 (66.7)	
High risk	8 (33.3)	1 (33.3)	
Number of metastasis sites, n (%)			
1	22 (51.2)	12 (60.0)	
2 and above	21 (48.8)	8 (40.0)	

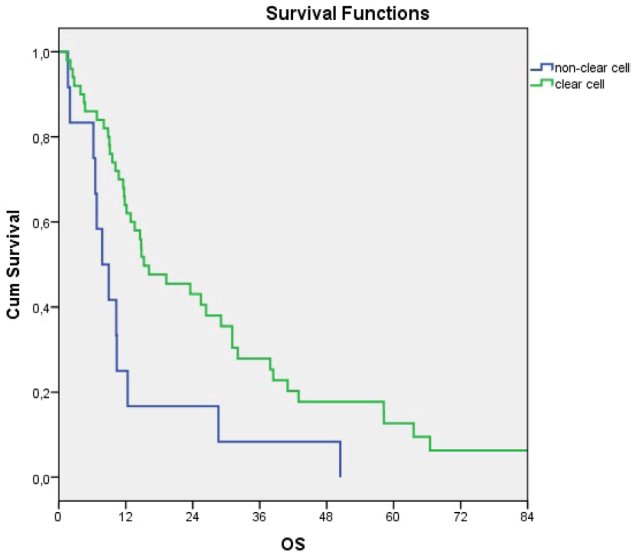

Figure 1. OS curve of RCC histological subtypes (p=0.005).

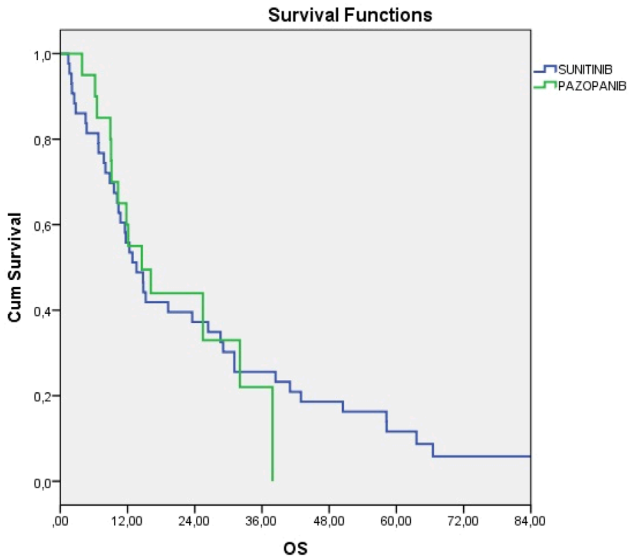

Figure 2. OS curve of Sunitinib and Pazopanib (p=0.96).

Considering the first-line TKI, it was seen that 43 (68.3%) patients were treated with sunitinib and 20 (31.7%) with pazopanib. The mean patiemts' age who received sunitinib was 59 years and 63 was in pazopanib (p=0.2). Thirty-one (72.1%) of the patients who underwent treatment with sunitinib were male and 12 (27.9%) female. Fourteen (70%) of the 20 patients who received pazopanib were male whereas 6 (30%) were female (p=0.86). When the ECOG values were examined, 42 (97.7%) patients who received sunitinib had an ECOG score of 0-1 and one (2.3%) patient had ECOG score of 2 and above. While the ECOG score of 17 (85%) patients who received pazopanib was 0-1, 3 (15%) patients were found to have ECOG 2 and above (p=0.09). Regarding the results of histologic examination, 35 (81.4%) had clear-cell and 8 (18.6%) patients had non-clear-cell histology in

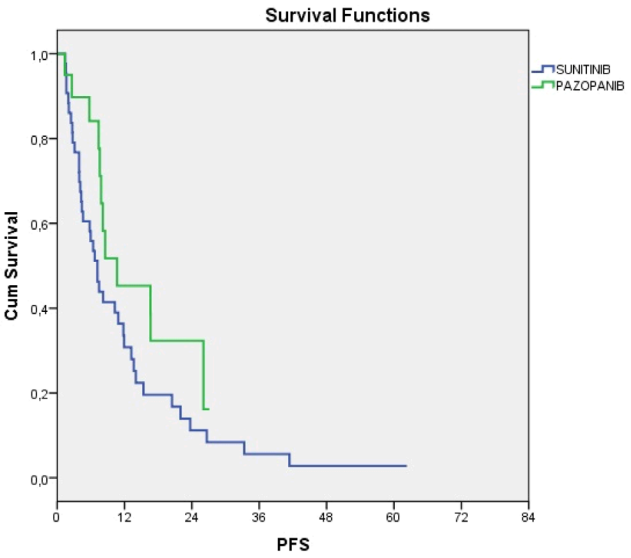

Figure 3. PFS curve of Sunitinib and Pazopanib (p=0.04).

Table 3. PFS rates distribution by patients and RCC characteristics

	PFS *Median (GA % 5-95)*	*p value*
Gender		0.68
Male	7.5 (3.3-11.8)	
Female	8.1 (6.7-9.5)	
ECOG-performance score		0.14
0-1	10.6 (6.1-15.2)	
2	7.1 (4.6-9.7)	
History of nephrectomy		0.16
Yes	8.1 (4.6-11.6)	
No	6,.4 (3.1-9.7)	
Histopathology		0.009
Clear-cell	10.2 (6.8-13.6)	
Non-clear-cell	4.1 (3.4-4.7)	
Fuhrman grade		0.89
1- 2	8.1 (1.8-14.5)	
3-4	7.2 (4.2-10.2)	
Sarcomatoid differentiation		0.97
Yes	8.1 (6.7-9.5)	
No	7.4 (4.8-9.9)	
Number of metastatic sites		0.68
1	8.1 (6.9-9.4)	
2 and above	6.7 (4.3-9.1)	
Duration from diagnosis to treatment		0.65
<1 year	7.8 (6.5-9.1)	
Over 1 year	10.2 (2.2-18.3)	
First-line tyrosine kinase inhibitor		0.09
Pazopanib	10.6 (1.0-21.3)	
Sunitinib	7.2 (5.3-9.1)	

the sunitinib group, whereas 15 (75%) patients had clear-cell and 5 (25%) had non-clear-cell histology in the pazopanib group (p=0.74). Considering the Fuhrman grade of the patients who received sunitinib, it was seen that 19 (45.2%) patients were grade 1-2, and 23 (54.89%) grade 3-4. In the pazopanib group, 6 (37.5%) patients were grade 1-2 and 10 (62.5%) patients were grade 3-4 (p=0.59). Five (14.3%) patients had sarcomatoid differentiation in the sunitinib group and 3 (25%) in the pazopanib group (p=0.40). *De novo* metastatic disease was detected in 31 (72.1%) patients who received sunitinib, while this number was 16 (80%) in the pazopanib group (p=0.75). When the MSKCC scores were analyzed, 1 (2.3%) patient was at favorable risk group, 32 (74.4%) were at intermediate risk group, and 10 (23.3%) were at high risk group in the patients treated with sunitinib. In the patients who received pazopanib, 1 (5%) patient was at favorable risk group, 12 (60%) were at intermediate risk group, and 7 (35%) were at high risk group (p=0.86) (Table 2). When the best radiological responses obtained during TKI treatment were compared, 4 (9.3%) patients had a partial response, 22 (51.2%) had a stable response, and 17 (39.5%) had progression in the sunitinib group. In the pazopanib group, 5 (25%) patients had a partial response, 13 (65%) had a stable response, and 2 (10%) had progression.

Survival analysis

The PFS values of pazopanib and sunitinib were 10.6 months and 7.2 months, respectively (p=0.09). There was no statistically difference in the superiority of the two drugs over PFS (Figure 1). When PFS was evaluated based on gender, the median value was 7.5 months in males and 8.1 months in females (p=0.68). Considering the effect of ECOG score on PFS, the median PFS of patients with a score of 0 was 10.6 months, while it was 7.1 months for patients with 1-2 (p=0.14). Regarding the effect of nephrectomy, the median PFS of patients who underwent nephrectomy was 8.1 months, while it was 6 months in patients

Table 4. OS rates distribution according to patients and RCC characteristics

	OS (95% CI)	*p value*
Gender, n (%)		0.59
Male	14.7 (11.1-18.4)	
Female	10.7 (1.9-19.5)	
ECOG-performance score, n (%)		0.007
0-1	25.4 (11.3-39.5)	
2	10.3 (7.4-13.3)	
History of nephrectomy, n (%)		0.23
Yes	14.7 (10.2-19.2)	
No	11.6 (3.3-20.0)	
Histopathology, n (%)		0.005
Clear-cell	15.2 (5.4-25.1)	
Non-clear-cell	7.7 (4.1-11.4)	
Fuhrman grade, n (%)		0.78
1- 2	14.7 (1.0-34.2)	
3-4	12.1 (10.9-13.2)	
Sarcomatoid differentiation, n (%)		0.89
Yes	10.7 (7.1-14.4)	
No	14.7 (10.9-18.5)	
Number of metastatic sites, n (%)		0.83
1	15.2 (1.1-29.3)	
2 and above	11.6 (6.6-16.7)	
Duration from diagnosis to treatment, n (%)		0.91
<1 year	13.6 (10.1-17.1)	
Over 1 year	15.2 (1.8-42.1)	
First-line tyrosine kinase inhibitor, n (%)		0.96
Pazopanib	14.5 (6.4-22.6)	
Sunitinib	13.6 (9.5-17.6)	

without nephrectomy (p=0.16). Regarding the presence or absence of the clear-cell histologic component of RCC, PFS was 10.2 and 4.1 months, respectively, and was statistically significant (p=0.009) (Table 3).

Median OS was 14.5 months in patients receiving pazopanib and 13.6 months in patients receiving sunitinib. There was no statistical difference between pazopanib and sunitinib in terms of OS (p=0.96) (Figure 2). When evaluated according to gender, the median OS was 14.7 months in males and 10.7 months in females. There was no statistical difference between the genders in terms of OS (p=0.59). The median OS of patients with ECOG score of 0 was 25.4 months, with a score of 1 and above 10.3 (7.4-13.3) months (p=0.07). The median OS of ccRCC was 15.2 (5.4-25.1) months, while non-clear-cell RCC (nccRCC) was 7.7 (4.1-11.4) months. The OS of patients with nccRCC was significantly shorter (p=0.005) (Table 4).

In the univariate analysis of OS, liver metastasis, high ECOG score, and histopathology variables showed statistically significant difference. In the multivariate Cox regression analysis, clear-cell pathology was an independent risk factor for mortality (HR 2.01 95% CI 1.01-4.01) (p=0.04) (Figure 3).

Discussion

RCC is urological cancer with the highest mortality rate of over 40%, based on deaths due to tumors originating from the urinary system. Many variables are effective in the prognosis of disease. In our study, it was revealed that high ECOG score, non-clear-cell pathology and presence of liver metastasis were associated with shorter OS. There was no statistically significant difference in OS and PFS between pazopanib and sunitinib.

In our study, the median OS of pazopanib was 14.5 months, while it was 13.6 months in the sunitinib group, showing similar effects on OS. In the study of Motzer et al [10] pazopanib and sunitinib were compared, and no superiority of the two drugs over OS could be shown, (median OS was 28.4 months in the pazopanib group and 29.3 months in the sunitinib group) (p=0.28). RCC is more common in men than in women, and the male/female ratio is 2/1 in the literature [6,11]. In our study, 45 (71.4%) of the patients were male and 18 (28.6%) female. The male/female ratio was found as 2.5/1, similar to literature. In a study by Rini et al [6], the median age was 60 in the patient group and similarly, in our study, the median age of the patients was 60. When the histopathologic examination results of the patients were evaluated, 50 (79.4%) patients had clear-cell, 10 (15.9%) had papillary, 2 (3.2%) had chromophobe, and 1 (1.6%) had unclassified histopathology. In a multicenter study, including 4063 patients, conducted by Patard et al [12], 87.7% of the patients had clear-cell, 9.7% papillary, and 2.5% chromophobe histopathology. In a retrospective study of Leibovich et al [13] 3062 patients were examined, and it was observed that 80.5% had clear-cell, 14.3% papillary and 5.2% chromophobe histopathology. In the RECORD-1 study conducted by Motzer et al [14], a high performance score was found to be associated with shorter OS. Furthermore, Myung Soo Kim et al [15] compared sunitinib and pazopanib and demonstrated that a high ECOG score was associated with short OS. When we examined the effect of ECOG score on OS in our study, the median OS of patients with an ECOG score of 0 was 25.4 months, while it was 10.3 months in the patients with an ECOG score of 1 and above. Thus, a higher ECOG score was found to be associated with shorter OS. In the study of Kassouf et al [16] from the MD Anderson Cancer Center, the data of 606 metastatic patients were retrospectively analyzed and showed that the survival of nccRCC patients was 9.7 months, while it was 20.3 months in ccRCC patients. In our study, the median OS of ccRCC was 15.2 months, while it was 7.7 months for nccRCC. Considering the effect of the histological type of cancer on PFS, the median PFS was 10.2 months in ccRCC and 4.1 months for nccRCC. Therefore, it was found that non-clear-cell histopathology was associated with shorter PFS and OS. In the literature it was found that OS was statistically shortened in patients with liver and bone metastasis, while other metastatic sites did not have a significant effect on OS [11,17,18]. In our study, while liver metastasis was found to be associated with shorter OS, no statistically significant relationship was found between bone metastasis and other metastatic sites and OS.

The limitations of our study are that it is a retrospective, single-center study and conducted with a small number of patients. It is appropriate to evaluate the obtained results by considering this information.

Conclusion

As a result, we found that high ECOG score, non-clear-cell histopathology and presence of liver metastasis were associated with shorter OS and PFS in metastatic RCC patients. Sunitinib and pazopanib were not superior to each other in terms of OS and PFS.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interests

The authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30. doi: 10.3322/caac.21590. Epub 2020 Jan 8. PMID: 31912902.
2. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. New Engl J Med 2017;376:354-66.
3. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): A literature review. Cancer Treat Rev 2008;34:193-205.
4. Motzer RJ, Hutson TE, Tomczak P et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584-90.
5. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. J Urol 2000;163:408-17.
6. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet 2009;373:1119-32.
7. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24. doi: 10.1056/NEJMoa065044. PMID: 17215529.
8. Motzer RJ, Hutson TE, Cella D et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722-31. doi: 10.1056/NEJMoa1303989. PMID: 23964934.
9. Albiges L, Powles T, Staehler M et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma. Eur Urol 2019;76:151-156. doi: 10.1016/j.eururo.2019.05.022. PMID: 31151678.
10. Motzer RJ, Hutson TE, Cella D et al. Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. New Engl J Med 2013;369:722-31.
11. Motzer RJ, Mazumdar M, Bacik J et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530-40.
12. Patard JJ, Leray E, Rioux-Leclercq N et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005;23:2763-71.
13. Leibovich BC, Lohse CM, Crispen PL et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol 2010;183:1309-15.
14. Motzer RJ, Escudier B, Oudard S et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer 2010;116:4256-65.
15. Kim MS, Chung HS, Hwang EC et al. Efficacy of First-Line Targeted Therapy in Real-World Korean Patients with Metastatic Renal Cell Carcinoma: Focus on Sunitinib and Pazopanib. J Korean Med Sci 2018;33:e325.
16. Kassouf W, Sanchez-Ortiz R, Tamboli P et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma with nonclear cell histology. J Urol 2007;178:1896-900.
17. Motzer RJ, Escudier B, Tomczak P et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552-62.
18. McKay RR, Kroeger N, Xie W et al. Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. Eur Urol 2014;65:577-84.