Prognostic Significance Of Dynamic Inflammatory Indexes in Cases Renal Cell Cancer Treated By Tyrosine Kinase Inhibitor (TKI)

Tirozin Kinaz İnhibitörleri (TKİ) İle Tedavi Edilmiş Böbrek Hücreli Kanser Hastalarında Dinamik İnflamatuar İndekslerin Prognostik Önemi

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ÖZET

GİRİŞ ve AMAÇ: Metastatik böbrek hücreli kanser (MBHK) sıklığı giderek artmaktadır ve temel tedavisi anti-angiogenik tirozin kinaz inhibitörleridir (TKİ). Sistemik inflamasyonun karsinogenezde önemli bir rollerinden biri de pro-angiogenik faktörlerin salınımını arttırmaktır. Biz de bu yazımızda TKİ tedavisi alan MBHK olgularında sistemik inflamatuar indekslerinden nötrofil lenfosit oranı (NLO), sistemik immun-inflamasyon indeksi (SII), prognostik nutrisyonel indeks (PNI) ve tedavi sürecinde değişen SII değerlerinin prognostik önemini ortaya çıkarmayı amaçladık.

YÖNTEM ve GEREÇLER: Çalışmamıza TKİ tedavisi alan 28 MBHK hastası retrospektif olarak dahil edilmiştir. Kaplan–Meier ve log-rank testleri kullanılarak klinikodemografik verilerle yaşam süreleri arasındaki ilişki belirlenmiştir. NLO (2,73), SII (832) ve PNI (39) için en sensitif ve spesifik değerler ROC analizi ile saptanıp prognostik önemleri tekli ve multi faktöriyel analizler yapılarak tespit edilmiştir

BULGULAR: Yüksek NLO (≥2,73) ve SII (≥832) ile düşük PNI (<39) daha kısa progresyonsuz yaşam süresi (PYS) ve genel sağkalım (GS) ile ilişkili olup TKI tedavisinin 1. Ayındaki azalmış SII'ye sahip olan hastaların ise daha uzun PYS ve GS'ye sahip olduğu tespit edilmiştir. GS için yapılan univariate analizlerde ECOG performans durumu, NLR, SII, SII değişimi ve PNI prognostik olmakla beraber multifaktöriyel analizlerde sadece SII değişimi bağımsız prognostik faktördür.

TARTIŞMA ve SONUÇ: TKI tedavisi alan MBHK hastalarında tedavi ile azalmış SII daha uzun GS için tek bağımsız prognostik faktördür.

Anahtar Kelimeler: Böbrek hücreli kanser (BHK), sistemik immun-inflamasyon indeksi (SII), prognostik nutrisyonel indeks (PNI), tirozin kinaz inhibitörü (TKI)

ABSTRACT

INTRODUCTION: The frequency of metastatic renal cell cancer (RCC) is increasing and main drugs in management are anti-angiogenic tyrosine kinase inhibitors (TKI). Systemic inflammation has an important role in carcinogenesis and increase the secretion of pro-angiogenic factors. Here prognostic significance of neutrophil lymphocyte ratio (NLR), systemic immune-inflammation index (SII), prognostik nutritional index (PNI) and also change in SII during TKI therapy have been evaluated in cases with RCC treated with TKI

METHODS: Twenty eight cases with RCC treated with TKI were evaluated retrospectively. Kaplan–Meier and log-rank tests were used to detect the association between clinical/demographic findings and survival times. The most sensitive and specific values were found by ROC analysis: Prognostic significance of NLR (2,73), SII (832), SII changes and PNI (39) were detected.

RESULTS: High NLR (≥2,73) and SII (≥832) and low PNI (<39) were found to be associated with shorter PFS and OS. Decreased SII after TKI therapy was found to be associated with longer PFS and OS. In univariate analyses, ECOG performance status, NLR, SII, SII change and PNI were prognostic for OS, whereas in multivariate analyzes only SII change found to be independent factors for OS

DISCUSSION AND CONCLUSION: Decreased SII after TKI therapy was the only independent prognsotic factor in cases with TKI treated with TKI.

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Keywords: Renal cell cancer (RCC), systemic immune-inflammation index (SII), prognostik nutritional index (PNI), tyrosine kinase inhibitor (TKI)

INTRODUCTION

Renal cell carcinoma (RCC) is the most common renal cancer in adults [1]. The incidence of RCC is increasing in recent years and it is expected to be as high as 35 per 100.000 persons [2]. RCC is seen more frequently in males and is seen in 50-70 years [3]. The majority of renal cancer originates from renal parenchyma and less frequently from renal pelvis. Clear cell cancer originates from tubule epithelium and accounts 80% of RCCs [3]. Inactivation of Von Hippen Lindau (VHL) tumor supressor gene and increase in hypoxia-Inducible Factor-1 alpha (HIF-1a) are critical roles in the development of RCC. Increase in HIF-1a causes increase in vascular endothelial growth factor (VEGF) and also abnormal cell proliferation and angiogenesis [4-6].For this reason anti-angiogenic TKIs such as sunitinib, pazopanib, sorafenib and axitinib are the most frequently used drugs [7]

Inflammation has very important role carcinogenesis. Systemic inflammation induces tumor proliferation and angiogenesis but inhibits apoptosis [8]. Proinflammatory cytokines and circulating immune-inflammatory cells such as neutrophils, platelets and lymphocytes mediate this axis.Immune-inflammation based prognostic indexes including neutrophil-lymphocyte ratio (NLR), platelet- lymphocyte ratio (PLR), prognostic nutritional index (PNI) are predictive for progression and overall survival in various solid tumors including RCC [9-12]. Additionally in recent times it is thought that systemic immune-inflammation index (SII) developed with the combination of platelet, neutrophil and lymphocyte numbers reflects the balance between inflammatory and immune status of the patients. SII is an promising index in cancers such as hepatocellular cancer, pancreas, small and non-small cell lung cancer, gastric and esophagial cancers [13-16].There is limited data about the prognostic value of SII in RCC. Here we wanted to show the prognostic significance of NLR, SII, PNI and also change in SII during TKI treatment in RCC.

METHODS

Twenty eight cases with RCC treated by TKI were evaluated retrospectively. Demographic variables including age, sex, Eastern Co-operative Oncology Group (ECOG) performance status, histopathologic subtype, interferon using, surgical status were taken from patients' files. Hemoglobin, neutrophil, lymphocyte, platelet counts, calcium, albumin, LDH levelsat diagnosis and first month of the TKI treatment were recorded. NLR was calculated bydividing the number of neutrophils by the number of lymphocytes.SII was calculated by division of multiplying platelet and neutrophil to lymphocyte. PNI was calculated by 10x Albumin (g/L) + 5 x total lymphocyte count formula. The most sensitive and specific values were detected by ROC analysis: cut off was 2.73 for NLR, 832 for SII and 39 for PNI. The participants were informed of the study and they provided written consents and Ethics committee approval was not taken as a retrospective study.

Statistics

OS was calculated from the use of TKI to death or last follow up. PFS was calculated from the use of TKI to recurrence, death or last follow up. Kaplan–Meier analysisand log-rank tests were used to compare the association between OS/PFS and clinical/demographic variables. Prognostic significance of NLR, SII, PNI and changes in SII were detected by univariate and multivarite analyses. Odds ratio and 95%confident interval were detected by cox regression analysis. SPSS 21 (SPSS IBM Corp, Armonk, NY, USA) was used for statistical analyses and$p < 0.05$ was accepted as statistically significant.

RESULTS

Median age was 59,5 (range 31-76) and 8 of the 28 cases were female. ECOG performance status was0-1 in 19 cases and $\geq$ 2 in 9 cases. Histologically 22 cases had clear cell histology, papillary in 4 and chromophobe in 2 cases. Sarcomatoid differentiation was detected in 3 cases and Fuhrmann grade was 1, 2, 3 and 4 in 1,1, 17, 9; respectively.Only three cases had goodwhile 21 and 4 cases had intermediate and poor risk disease according to

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the Memorial Sloan Kettering Cancer Center (MSKCC) index. Eleven cases had been treated by pazopanib and 17 cases by sunitinib. Half of the cases had been treated by interferon before TKI. Metastatic sites were more than one in 13 cases while single metastasis had been detected in 15 cases. Nephrectomy had been performed in 25 cases.Clinical and demographic findings have been shown at Table 1.

Table 1. Baseline Clinic And Demographic Characteristics

	n (%)
Age	
Median (range)	59,5 ± 11 (31-76)
Gender	
Female	8 (28,5)
Male	20 (71,5)
ECOG	
0-1	19 (67,9)
≥ 2	9 (32,1)
Histologic subtype	
Clear cell	22 (78,6)
Papiller	4 (14,3)
Chromofob	2 (7,1)
Sarcomatoid differentiation	
Yes	3 (10,7)
No	25 (89,3)
Fuhrmann Histologic Grade	
1-2	2 (7,1)
3	17 (60,7)
4	9 (32,1)
MSKCC	
Favorable	3 (10,7)
Intermediate	21 (75)
Poor	4 (14,3)
Surgery	
Yes	25 (89,3)
No	3 (10,7)
Interferon	
Yes	14 (50)
No	14 (50)
Number of metastatic site	
1	16 (57,1)
≥2	12 (42,9)
TKİ Type	
pazopanib	11 (39,2)
sunitinib	17 (60,8)
First response	
Regression	5 (17,9)
Stable	14 (50)
Progression	9 (32,1)
Progression	
No	7 (25)
Yes	21 (75)
Status	
Alive	10 (35,7)
Death	18 (64,3)

Progression was detected in 21 cases and 18 cases died as of November 2018. Median follow up time was 14 months (range 1-58). Median PFS and OS times were 11 (range 4,6-17,3) and 20 (range 3,8-36,186) months; respectively. The association between clinical and pathological variables and PFS/OS times were shown at Table 2. Sex, histologic subtype, sarcomatoid differantiation, fuhrmann grade, MSKCC status, interferon using, nephrectomy status were not found to be associated with PFS (p:0.975, p:0.615, p:0.469, p:0.544, p:0.285, p:0.504, 0.216, respectively)and OS (p:0.855, p:0.963, p:0.228, p:0.822, p:0.139, p:0.716, p:0.782, respectively).Patients with better ECOG score(ECOG 0-1)had longer median PFS/OS times (36/42 months) as compared with poorer ECOG PS (>2) (5/5 months) (p:0.001, p:0.004, respectively).PFS/OS times were found to be longer in cases with one metastatic site than more than one site(PFS: 19 vs 5 ay, p:0.022, OS: 48 vs 8, p:0.03).

Median PFS was found to be shorter in cases with higher NLR (≥2,73) and SII (≥832) as compared with lower NLR and SII: NLR <2,73 vs ≥2,73: 37 vs 8months (p:0.008), SII <832 vs ≥ 832, 30 vs 5months (p:0.035). Similarly OS was found to be shorter in cases with higher NLR and SII: NLR <2,73 vs ≥2,73: 42 vs 13months (p:0.015), SII:<832 vs ≥ 832, 42 vs 8months (p:0.011) (Figure 1). Decreasing scores for SII during TKI therapy were found to be associated with longer PFS/OS times as compared cases without decreased SII score: 42/30months vs 3/3 months (p:0.000, p:0.000, respectively) (Figure 2).Lower PNI (≥39) was found to be associated with shorter survival times: PFS: 5 vs 36months (p:0.008), OS: 8 vs 42 months (p:0.009) (Figure 1).The association between PFS/OS times and NLR, SII, PNI and SII changes have been shown at Table 3.

Independent prognostic factors for OS were evaluated with Cox regression analysis and for this aim ECOG performance status, the number of metastatic sites, NLR, SII, SII change and PNI were included (Table 4). ECOG performance status, NLR, SII, SII change and PNI have been found to be prognsotic for OS in univariate analyses (p:0,009, p:0,024, p:0,020, p:0,006, p:0,015, respectively). However in multivariate analysis

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only change in SII has been found to be independent prognostic factor (HR: 18,073, %95 CL 2,923-111,753, p: 0,002).

significance of immune-inflammatory indexes in cases with RCC treated with TKIs. We found that change in SII during therapy was independent risk factor for OS. This finding is important to understand the association between inflammatory process and angiogenesis.

Table 2. Overall and Progression-free survival times according to clinical parameters

			PFS		OS	
	Total (n)	Total (%)	Median	p*	Median	p
Gender				0.975		0.855
Female	8	28,5	10		15	
Male	20	71,5	11		30	
ECOG				0.001		0.004
0-1	19	67,8	36		42	
2	9	32,2	5		5	
Histologic subtype				0.615		0.963
Clear cell	22	78,5	11		20	
Non-clear cell	6	21,5	8		11	
Sarkomatoid differentiation				0.469		0.228
No	25	89,2	13		20	
Yes	3	10,8	5		5	
Fuhrmann grade				0.544		0.822
1-2	2	7,1	5		11	
3	17	60,7	19		30	
4	9	32,2	9		13	
MSKCC index				0.285		0,139
Favourable	3	10,7	NR		NR	
Intermediate	21	75	13		30	
Poor	4	14,3	1		1	
Interferon				0.504		0.716
No	14	50	9		18	
Yes	14	50	13		20	
Surgery				0.216		0.782
No	3	10,8	5		NR	
Yes	25	89,2	13		20	
Number of metastatic site				0.022		0.003
1	16	57,1	19		48	
≥2	12	42,9	5		8	
Overall	28	100	11		20	

ECOG: Eastern Co-operative Oncology Group, MSKCC: Memorial Sloan Kettering Cancer Center index

DISCUSSION

Surgery is the main therapeutic option in cases with localized RCC while TKIs are main therapeutic agents in cases with metastatic RCC[17]. Predictive factors determining predictive factors to TKIs are very important in clinical practice to detect rational drug use. In this study we wanted to explore the prognostic

Table 3. Overall and Progression-free survival times according to NLR, SII, PNI and changes of these parameters after therapy (n=28)

			PFS		OS	
	Total (n)	Total (%)	Median	p	Median	p
NLR				0.008		0.015
<2,73	13	46,5	37		42	
≥ 2,73	15	53,5	8		13	
SII				0.035		0.011
<832	15	53,5	30		42	
≥ 832	13	46,5	5		8	
SII Change				0.000		0.000
Decrease	20	71,4	30		42	
Increase	8	18,6	3		3	
PNI				0.008		0.009
<39	14	50	5		8	
≥ 39	14	50	36		42	
Overall	28	100	11		20	

NLR: neutrophil lymhocyte ratio, SII: Systemic immun-inflammation index, PNI: Prognostic Nutrional İndex

Table 4. Univariate and Multivariate Analysis of Potential Prognostic Factors for Overall Survival

Parameters	Univariate		Multivariate	
	HR	p	HR	p
ECOG performance score	4,453 (1,450-13,671)	0,009	3,967 (0,380-41,412)	0,250
Number of metastatic site (0-1 vs ≥2)	1,732 (0,883-3,401)	0,110	-	-
NLR (<2,73 vs ≥2,73)	3,495 (1,183-10,321)	0,024	3,388 (0,631-18,184)	0,155
SII (<832 vs ≥ 832)	4,084 (1,248-13,371)	0,020	1,042 (0,083-13,007)	0,975
SII Change (Decrease vs Increase)	7,627 (1,796-32,384)	0,006	18,073 (2,923-111,753)	0,002
PNI (<39 vs ≥ 39)	0,272 (0,095-0,781)	0,015	0,751 (0,173-3,256)	0,702

ECOG: Eastern Co-operative Oncology Group, NLR: neutrophil lymhocyte ratio, SII: Systemic immun-inflammation index, PNI: Prognostic Nutrional İndex

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Although survival times have been found to be increased according to Surveillance, Epidemiology, and End Results (SEER) data, 5 years OS is 12,3%[18]. Increase in survival times is especially associated with therapies targeting angiogenesis which is main pathway in abnormal angiogenesis causing progression in RCC. Pazopanib and Sunitinib inhibit VEGFR and PDGFR subtypes and main drugs proposed by ESMO and NCCN and used as first line therapy in metastatic RCC[19]. Sunitinib and pazopanib have been found to be beneficial in cases with metastatic RCC and have been approved by FDA[20-21]. We found similar PFS and OS times reported in available literature in cases treated with sunitinib/pazopanib median PFS was 11 months and OS was 20 months.

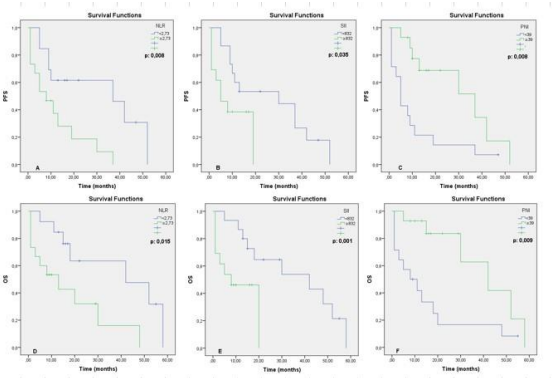

Figure 1:PFS and OS Kaplan-Meier Survival Curves; A-D; NLR, B-E; SII C-F; PNI.

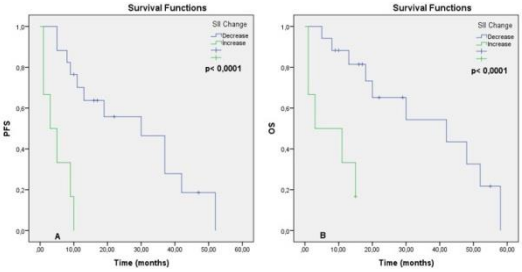

Figure 2:PFS and OS Kaplan-Meier Survival Curves: A-B; SII Change

Synergistic activity between angiogenesis and inflammation has been reported many times[22]. It is very well known that inflammation areas in tumors are hypoxic and this hypoxia causes secretion of some pro-angiogenic factors such as VEGF and FGF. Additionally peripheral blood cells such as neutrophils, platelets, macrophages contribute to secretion of systemic inflammatory cytokines. Lymphocytes are also show anti-tumoral properties[23].It has been shown in many studies that higher NLR, DNLR and PLR and lower LMR are associated with an increase in inflammation and poor prognosis. Inflammatory markers are predictive for poor prognosis also in RCC and with these indexes we may detect the success of inhibition of angiogenesis in RCC with TKI treatment[24]. Higher NLR has been found as poor prognostic indicator and decrease in NLR in early treatment period has been found to be associated with survival advantage by Park et al in 109 cases teated with sunitinib [25]. In another study lower NLR (<3) has been found associated with longer PFS and OS in cases with metastatic RCC treated with sunitinib [26]. We found also longer PFS and OS in cases with lower NLR and our cut off was 2.73.SII is another inflammatory marker and more powerful index due to inclusion of platelet in addition to NLR and this index is found to be more informative for inflammation in recent times. In a metaanalysis covering 15 studies higher SII has been found to be associated with shorter OS in cases with HCC, urinary system cancers, gastrointestinal cancers, small cell cancers and acral melanomas[27].There is only one study exploring the prognostic significance of SII in RCC and higher SII has been found to be associated with shorter PFS and OS: 355 cases treated by sunitinib have been incuded in this study and cases with higher SII at sixth month of TKI therapy had shorter survival[28]. Similar to Lolli's study we found shorter PFS and OS in cases with high SII and cases showing decrease in SII in first month of TKI therapy had longer survival. We also found change in SII as the only independent prognostic factor. With this finding we can say that inflammation status at the beginning of TKI therapy is important but also change in SII at early period of TKI therapy is more predictive for the success of anti-angiogenic effect of the TKI. However this is the first study showing the predictive significance of change in SII at first monthof TKI therapy and it must be confirmed with larger studies.

PNI is a new inflammation index and has been defined by Onodera et al. It includes serum albumin and lymphocyte counts and its

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prognostic significance has been shown in various cancers including HCC, pancreaticcancer, gastriccancer and pleural mesothelioma [29]. Studies about PNI in RCC are limited. Prognostic significance for OS of PNI in RCC has been shown in 125 metastatic RCC cases treated with TKI. Pre-operative PNI has been found to be prognostic for DFS [30]. In our study PNI was found as prognostic for PFS and OS but was not found as independent factor in multivariate analysis. This may be due to the limited number of our cases and also cutoff value of PNI which is different from other studies: it has been found as 44 and 41 in other studies it was 38 in our study. There are highly variable results in literature.

Although our study showed interesting predictive markers in cases with RCC treated by TKI, main limitations of our study is retrospective nature and low number of the patients. For this reason these indexes must be studied and confirmed by larger patient groups.

CONCLUSİON

Systematic inflammation is important in carcinogensis associated with RCC as reported in many malignant tumors. This study is important. Because decreasing SII has been found to be the only prognostic factor as the first time. It seems that SII change in early period of TKI therapy may be predictive for disease recurrence and survival times and must be confirmed in larger studies.

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Conflict of İnterest:

The authors declare that they have no conflict of interest.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015; 65(2), 87-108.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European journal of cancer. 2013; 49(6), 1374-1403.
3. Shanks JH. Pathology of renal cell carcinoma: recent developments. Clin Oncol (R Coll Radiol). 1999; 11(4), 263-268.
4. Leisz S, Schulz K, Erb S, et al. B. Distinct von Hippel-Lindau gene and hypoxia-regulated alterations in gene and protein expression patterns of renal cell carcinoma and their effects on metabolism. Oncotarget 2015; 6(13), 11395.
5. Kaelin WG Jr. The von Hippel-Lindau tumor suppressor gene and kidney cancer. Clin Cancer Res. 2004; 10(18), 6290S-6295S.
6. Piva F, Giulietti M, Occhipinti G, et al. Computational analysis of the mutations in BAP1, PBRM1 and SETD2 genes reveals the impaired molecular processes in renal cell carcinoma. Oncotarget 2015; 6(31), 32161.
7. Dabney R, Devine R, Sein N, George B. New agents in renal cell carcinoma. Target Oncol. 2014; 9(3), 183-193.
8. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol, 2009; 10(11), 1045-1052.
9. Nishijima TF, Muss HB, Shachar SS, Tamura K, Takamatsu Y. Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: a systematic review and meta-analysis. Cancer Treat. Rev. 2015; 41(10), 971-978.
10. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predictssurvival in patients with cancer. Br. J. Cancer. 2012; 107(4), 695.
11. Templeton AJ, Ace O, McNamara MG et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol. Biomarkers Prev. 2014; *23(7); 1204–12*
12. Okada S, Shimada J, Kato D, Tsunezuka H, Teramukai S, Inoue M. Clinical significance of prognostic nutritional index after surgical treatment in lung cancer. Ann Thorac Surg. 2017; 104(1), 296-302.
13. Aziz MH, Sideras K, Aziz NA et al. The systemic-immune-inflammation index independently predicts survival and recurrence in resectable pancreatic cancer and its prognostic value depends on bilirubin levels: a retrospective multicenter cohort study. Ann. Surg. [Epub ahead of print] 2018; doi.org/10.1097/SLA.0000000000002660
14. Geng Y, Shao Y, Zhu D et al. Systemic immune-inflammation index predicts prognosis of patients with esophageal squamous cell carcinoma: a propensity score-matched analysis. Sci. Rep. 2016; 6, 39482.
15. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J. Exp. Med. 2015; 236(4), 297-304.
16. Huang L, Liu S, Lei Y et al. Systemic immune-inflammation index, thymidine phosphorylase and survival of localized gastric cancer patients after curative resection. Oncotarget. 2016; 7(28), 44185.
17. Dutcher JP. Recent developments in the treatment of renal cell carcinoma. Therapeutic advances in urology, 2013; 5(6), 338-353.
18. Ridge CA, Pua BB, Madoff DC. Epidemiology and staging of renal cell carcinoma. In Seminars in interventional radiology. 2014; 31(01): 003-008

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19. Barata PC, Rini BI. Treatment of renal cell carcinoma: current status and future directions. CA: a cancer journal for clinicians, 2017; 67(6), 507-524.
20. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. New England Journal of Medicine, 2013; 369(8), 722-731.
21. Lalani AKA, Li H, Heng DY, et al. First-line sunitinib or pazopanib in metastatic renal cell carcinoma: The Canadian experience. *Canadian Urological Association Journal*, 2017; 11(3-4), 112.
22. Rocchi L, Caraffi S, Perris R, Mangieri D. The angiogenic asset of soft tissue sarcomas: a new tool to discover new therapeutic targets. Biosci Rep. 2014; 34(6): e00147
23. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature, 2008; **454**: 436–444
24. Fox P, Hudson M, Brown C, et al. Markers of systemic inflammation predict survival in patients with advanced renal cell cancer. British journal of cancer, 2013; **109**: 147–153
25. Park YH, Ku JH, Kwak C, Kim HH. Post-treatment neutrophil-to-lymphocyte ratio in predicting prognosis in patients with metastatic clear cell renal cell carcinoma receiving sunitinib as first line therapy. Springerplus, 2014; **3**:243
26. Keizman D, Ish-Shalom M, Huang P, et al. The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. European Journal of Cancer, 2012; 48(2):202-208
27. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget, 2017; 8:75381-75388
28. Lolli C, Basso U, Derosa L, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. Oncotarget, 2016; 7:54564-54571
29. Hofbauer SL, Pantuck AJ, de Martino M, et al. The preoperative prognostic nutritional index is an independent predictor of survival in patients with renal cell carcinoma. In Urologic Oncology: Seminars and Original Investigations, 2015; 33(2):68.e1-7
30. Kwon WA, Kim S, Kim SH, et al. Pretreatment prognostic nutritional index is an independent predictor of survival in patients with metastatic renal cell carcinoma treated with targeted therapy. Clinical genitourinary cancer, 2017; 15(1):100-111

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