JBUON 2020; 25(5): 2490-2495
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Prognostic significance of basal 18F-FDG PET / CT maximum standardized uptake value in patients with metastatic renal cell carcinoma who were treated with sunitinib

Aydin Aytekin[1], Mehmet Naci Aldemir[2], Abdullah Sakin[2], Ufuk Telci[3], Ramazan Esen[2]

[1]Mardin State Hospital, Department of Medical Oncology, Mardin, Turkey. [2]Yuzuncu Yil University Faculty of Medicine, Department of Internal Medicine, Division of Medical Oncology, Van, Turkey. [3]Yuzuncu Yil University Faculty of Medicine, Department of Nuclear Medicine, Van, Turkey.

Summary

Purpose: *To determine whether there is a relationship between maximum standardized uptake (SUVmax) value of basal 18-Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG-PET/CT) that was performed before sunitinib treatment and treatment-related survival in patients with metastatic renal cell carcinoma (mRCC).*

Methods: *The data of 36 patients (female/male: 1/1, median age 57.36 years, range 31-74) were retrospectively analyzed in whom sunitinib treatment was started due to mRCC between 2008 and 2019 and who underwent basal 18F-FDG PET/CT examination before this treatment. The median SUVmax value was 6.8. Progression-free survival (PFS) and overall survival (OS) rates of patients, who had SUVmax value >6.8 (group I) (50%, n=18) and ≤ than 6.8 (group II) (50%, n=18), were compared.*

Results: *Both PFS and OS were significantly lower in the group with high SUVmax (SUVmax> 6.8, group I) before the sunitinib treatment than the group with low SUVmax (SUVmax ≤6.8, group II). When patients with SUVmax value> 6.8 (group I) (50%, n=18) and ≤6.8 (group II) (50%, n=18) were compared the median PFS of group I patients was 6.83 months (95%CI: 6.14-7.52), while the median PFS of group II patients was 11.24 months (95%CI: 8.4-14.06) (p=0.035). The median OS in group I and II was 12.91 months (95%CI: 10.17-15.65) and 54.54 months (95%CI: 8.51-100), respectively (p=0.042).*

Conclusion: *In this study it was found that PFS and OS were low in patients with high SUVmax value in 18F-FDG PET/CT performed before sunitinib treatment. As a result, 18F-FDG PET/CT SUVmax values measured before sunitinib treatment can be used to predict survival in mRCC patients.*

Key words: *maximum standardized uptake value, 18F-fluorodeoxyglucose positron emission tomography/computed tomography, prognosis, renal cell carcinoma, sunitinib, survival*

Introduction

Renal cell carcinoma (RCC) is a cancer that is naturally resistant to cytotoxic chemotherapy, radiotherapy and hormonal treatments, constituting approximately 2-3% of malignancies in adults [1] and approximately 80-85% of renal malignancies [2]. Before the discovery of angiogenesis inhibitors, cytokine-based treatments such as interleukin-2 and interferon were used as primary therapy in advanced RCC despite their limited clinical activity and marked toxicity. Successful results were observed by understanding the biology of RCC and developing treatments against vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) [2]. Sunitinib is a multitarget tyrosine kinase inhibitor used orally and targets VEGF receptors 1-3 and platelet derived growth

Corresponding author: Aydin Aytekin, MD. Mardin State Hospital, Department of Medical Oncology, Ozan Street, 47100, Artuklu Nur Mahallesi, Vali Mardin, Turkey.
Tel: +90 506 972 21 07, Email: aytekxx@gmail.com, draytekin@yahoo.com
Received: 05/03/2020; Accepted: 01/04/2020

factor receptors α and β. When compared with previous treatments it showed significant improvements in both progression-free survival (PFS) and overall survival (OS) in RCC [3]. Many prognostic and predictive factors have been developed in RCC patients receiving targeted therapy and cytokine therapy. Among the important ones are the following: Memorial Sloan Kettering Cancer Center (MSKCC) criteria, corrected calcium values, number of metastatic fields (one and more than one), thrombocytosis, LDH levels, presence of bone and liver metastasis [4-9].

Standard anatomical radiological imaging seems to be not sufficient to identify mRCC patients who will benefit from sunitinib treatment. 18-Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG-PET/CT) is an imaging method that mainly measures the tumor's metabolic activity and is used for diagnosis, staging and assessment of treatment response in many types of malignancies. Glucose is a molecule that is the primary source of carbons, amino acid and nucleic acid synthesis. 18F-FDG uptake, which reveals glucose metabolism, is closely related to the viability and proliferation capacity of cells [10]. Standardized uptake value (SUV) is a semi-quantitative measurement of the 18F-FDG uptake ratio in the tissue. Maximum standardized uptake value (SUVmax) is the highest FDG uptake in the displayed tumor tissue and is the most frequently used value in clinical practice. It has been discovered that this value has a prognostic significance in different types of cancers such as head and neck, lung cancer, cervical cancer and lymphoma [11-14].

Since 18F-FDG PET/CT radiotracer has urinary excretion and may not show the presence of primary lesion, it is not generally used in RCC evaluation [15]. Despite that, in a study [16] it was stated that the accumulation of FDG, which provides combined morphological and functional information, can be shown in 94.9% of all RCC lesions detected by CT, with the exception of <1 cm lesions in the lung and liver. In addition, Majhail et al [17] proved compatibility of metastases detected by FDG PET/CT with pathological diagnosis. They determined the pathological positive predictive value of 18F-FDG PET / CT as 100% as a result of biopsy or surgical resection applied to 36 distant metastatic lesions of 24 patients. In other studies, it was stated that 18F-FDG PET / CT is valuable in determining primary staging and characterization of renal masses visualized by CT or MRI [18] and determining distant metastases [15].

The aim of this study was to reveal the role of 18F-FDG-PET-CT which was performed before the sunitinib treatment in determining the prognosis related to the treatment in patients with metastatic RCC (mRCC).

Methods

In this study, the data of 36 patients, to whom sunitinib treatment was started due to mRCC between 2008 and 2019, were retrospectively analyzed. Approval for the study was obtained from the Local Ethics Committee. The study was conducted in accordance with the basic principles of the Helsinki Declaration and importance was given to the confidentiality of patient information. This study aimed to determine whether using 18F-FDG PET/CT before treatment has a prognostic importance in determining response to sunitinib treatment or not.

At the beginning of treatment age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS), tumor histology, grade, and MSKCC risk score were recorded. Patients over 18 years of age, who had ECOG-PS 0-2 and had normal blood glucose levels, were accepted to the study. Patients who received sunitinib treatment for less than 2 months, patients who had passed more than 3 months after the last PET-CT before treatment and patients who were removed from the follow-up were excluded from the study. Patients who underwent 18F-FDG PET/CT examination within 3 months before sunitinib treatment were included in the study (initial PET/CT before interferon treatment or sunitinib treatment). As a result, a total number of 36 patients, who had been followed up between 2008 and 2019 and PET/CT studies were performed before treatment, were detected.

The highest SUVmax values for the primary or metastatic tumor were recorded. The study population was divided into two groups according to median SUVmax value (6.8): SUVmax >6.8 (group I) and SUVmax ≤6.8 (group II). Then, the relationship of these values with progression-free survival (PFS) and overall survival (OS) was evaluated. PFS was defined as the time starting from the beginning of sunitinib treatment until the development of radiological progression or death from any cause. On the other hand, OS was defined as the time starting from treatment until the last follow-up or death.

Sunitinib was given as 50 mg/day orally for 4 weeks with 2-week stoppage or 50 mg/day orally for 2 weeks with 1-week stoppage. In case of grade 3 toxicity and above, the doses were reduced to 37.5 mg and, if necessary, to 25 mg. Since health insurance reimbursement in Turkey pays sunitinib therapy following primary care cytokine treatment, the majority of patients (32 patients) used IFN-α therapy for a certain period of time. However, since IFN intolerance is frequent, most patients discontinued the drug and switched to sunitinib treatment.

Statistics

SPSS 26 statistical software was used for statistical analyses. Survival rates were calculated using Kaplan-Meier method. The effect of OS and PFS differences according to cut-off SUVmax value was calculated using Log-rank test. The appropriateness of variables to nor-

mal distribution was examined by visual (histogram and probability graphics) and analytical methods (Kolmogorov-Smirnof/Shapiro-Wilk tests). Descriptive analysis was performed using the median and interquartile range for analyses that did not fit the normal distribution. P<0.05 was considered statistically significant.

Results

The median age of the patients was 57.36 years (range 31-74) and the female to male ratio was 1/1. According to ECOG PS status before sunitinib treatment 30.6% (n=11) of the patients had ECOG PS 0, 63.9% (n=23) had PS-1 and 5.6 % (n=2) had PS-2, respectively. The most common histological subtype was the clear cell type (75%, n=27). According to the MSKCC Risk Score, 7 patients (19.4%) were in the good risk group, 26 (72.2%) were in the medium risk group, and 3 (8.3%) were in the poor risk group. When the best responses to sunitinib treatment according to RECIST criteria were examined, none of the patients responded completely to the treatment but partial response (PR) was detected in 36.1% (n=13) of the patients, stable disease (SD) was detected in 38.9% (n=14) and progressive disease (PD) was detected in 25% (n=9). The demographic and clinicopathological features of the patients are shown in Table 1.

Of the 36 patients, 32 used first-line IFN-α (as required by the reimbursement law). Median IFN-α use duration was 1.8 months (range 0.33-24.61 months). The short duration of the median time was due to the discontinuation of the drug in most patients (n=21, 58.3%) because of intolerance and the treatment was switched to sunitinib therapy. When the IFN-α responses were analyzed PD was noted in 4 (11.1%) patients, SD in 3 (8.3%) and PR in 4 (11.1%) patients.

The median value of the SUVmax value was 6.82. When the number of regions with the highest involvement and SUVmax values (range) before treatment were examined we found 12 lung lesions with a median SUVmax 6.64 (1.7-19.1), 9 bone-vertebra lesions with a median SUVmax 6.85 (3.6-18.59), 6 lymph node lesions with a median SUVmax 9.6 (2.2-12.2), primary mass / local recurrence in 5 lesions with a median SUVmax 4.8 (3.1-9.3) and 4 liver lesions with a median SUVmax 6.85 (4.5-10.8).

During the follow-up period, 22 patients (61.1%) died. Progression developed in 27 patients (75%) during sunitinib treatment. When patients with SUVmax value higher than 6.8 (group I) (50%,

Table 1. Demographic and clinical features of patients

	n (%)
Median age, years (range)	57.36 (31-74)
Gender	
Male	50 (18)
Female	50 (18)
Tumour histology	
Clear Cell	75 (27)
Other	25 (9)
Furhman grade	
2	61 (22)
3	33.3 (12)
4	5.6 (2)
ECOG PS	
0	30.6 (11)
1	63.9 (23)
2	5.6 (2)

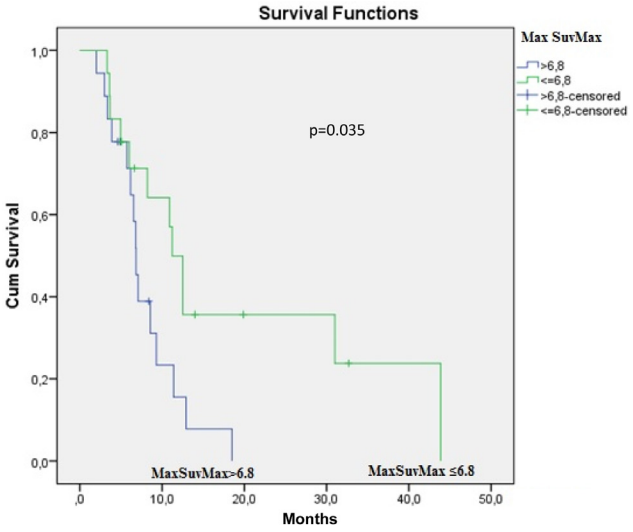

Figure 1. Kaplan-Meier estimates showing PFS differences between SUVmax values ≤ 6.8 and > 6.8.

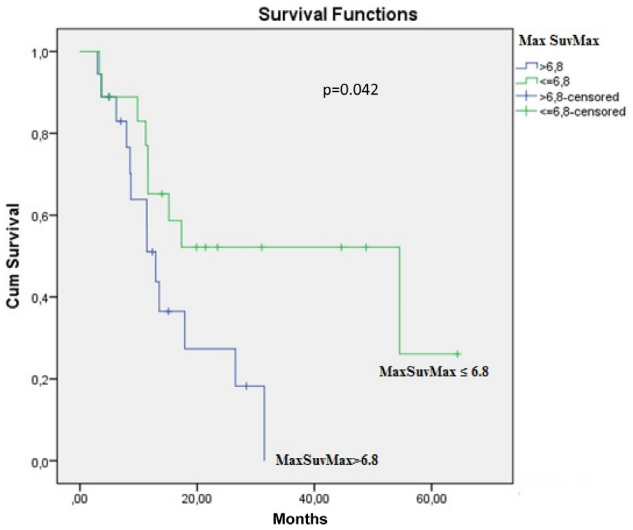

Figure 2. Kaplan-Meier estimates showing OS differences between SUVmax values ≤ 6.8 and > 6.8.

n=18) and equal to or lower than 6.8 (group II) (50%, n=18) were compared the median PFS of patients in group I was 6.83 months (95% CI: 6.14-7.52), while the median PFS of patients in group II was 11.24 months (95% CI: 8.4-14.06) (p=0.035) (Figure 1). When both groups were compared in terms of OS the median OS of group I was 12.91 months (95% CI: 10.17-15.65) and in group II it was 54.54 months (95% CI: 8.51-100) (p=0.042) (Figure 2).

Discussion

18F-FDG PET-CT could not enter the routine use of RCC with imaging purposes due to low or medium FDG uptake in the RCC lesions [19]. In addition, normal renal excretion of 18F-FDG may also hide the real pathology. However, these features do not mean that the value of SUVmax in lesions in RCC is not prognostic. Based on this point, our study was designed to investigate the prognostic value of 18F-FDG PET/CT in RCC.

Similar to some other types of cancer, basal FDG PET/CT applied before starting sunitinib and other TKIs in RCC has been shown to be effective in predicting treatment-related response and prognosis [16,20-25]. In most of these studies, the effects of all TKIs were examined. The number of studies with only sunitinib is very low. These evaluations are clinically useful because molecular targeted therapies do not always provide significant tumor shrinkage, unlike cytotoxic treatments. At this point, FDG PET/CT gains importance because it shows biological tumor activity.

In a study by Revheim et al with 14 patients [21] longer PFS has been reported in patients with low 18F-FDG uptake (SUVmax <5) before sunitinib treatment. Also in this study, it was stated that the statistical significance continued between the SUVmax values of 4.9-6.7.

In a study by Namura et al with 26 patients [16] high SUVmax values were reported to be associated with poor prognosis. In this study, the cut off SUVmax value was taken as the median value of 8.8 and the survivals were reported to be statistically significantly longer in patients below this value. Among 26 patients in this study 20 received TKI treatment (9 sorafenib, 9 sunitinib, 2 sorafenib + sunitinib treatment, 1 IFN-a+sorafenib treatment and 6 patients received cytokine treatment [16].

In a study of Kayani et al [20], which was conducted with 44 patients receiving sunitinib treatment, FDG-PET/CT median SUVmax value in the diagnosis was reported to be 6.8 (range <2.5-18.4) and patients with high SUVmax values and those with high PET positive lesions were found to have a higher risk of disease progression and poorer PFS and OS. In addition, it was also noted that the treatment response evaluated with PET-CT 4 weeks after sunitinib treatment was not related to PFS and as a result, it was emphasized that baseline (before treatment) PET/CT has prognostic significance.

In a study by Minamimoto et al [26] with 17 patients basal quantitive metabolic PET/CT measurements were predictive for 12-month PFS in mRCC patients receiving sunitinib therapy. Also in this study, it was stated that interim PET-CT, which was performed 12 weeks after sunitinib treatment, was not predictive for PFS alone. It is noted that basal PET/CT has the greatest prognostic capability in determining 12-month PFS. In this study, it was stated that interim PET/CT had minimal clinical value in monitoring sunitinib treatment and basal PET/CT can be accepted as a criterion for the treatment strategy.

In a study conducted by Horn et al [27] with 20 patients using sunitinib, basal 18F-FDG PET/CT SUVmax values were found to be significantly reverse-related with OS. In this study, the SUVmax cut-off value was taken as ≤6.9 and> 6.9.

In a study of Ueno et al [23] including 35 patients with RCC (19 were taking sunitinib and 16 sorafenib) short PFS and OS were detected in patients with baseline high SUVmax values (mean SUVmax 9).

In another study by Nakaigawa et al [25] a total number of 101 patients who received different treatments due to RCC were examined. After basal PET/CT evaluation, 40 patients were treated with sorafenib, 38 patients with sunitinib, 12 patients with interferon-α (IFN-α), 8 with temsirolimus, 1 with axitinib, 1 with pazopanib and 1 with chemotherapy. The median value of SUVmax values was 6.9 (ranging from undetectable to 23). When the cutoff value was taken as <8.8 and ≥8.8 with reference to a study [16] that was previously conducted by Namura et al, OS values of those with SUVmax ≥8.8 were statistically significantly shorter. Then, they divided 101 patients into 3 groups according to their SUVmax values as <7 vs 7 ≤- <12 vs 12≤. Median OS value in the <7 group was 41.9 months. On the other hand, median OS values in the group with SUV max value between 7 ≤-<12 and 12≤ were 20.6 months and 4.2 months, respectively. OS differences between all three groups were statistically significant. As a result, it was reported that patients with lower SUVmax values, regardless of tumor diameter and metastasis region, had a better OS than patients with higher SUVmax values.

In a study [25], it was suggested that the poor prognosis in RCC patients with high SUVmax values could be related with more glucose needs as an

energy source in RCCs that were rapidly progressing and as a result had higher FDG uptake.

In our study, it was emphasized that basal PET/CT has prognostic importance in determining PFS and OS in metastatic RCC patients receiving sunitinib therapy. Interim PET/CT measurements were also made in some of the mentioned studies, but basal PET/CT measurements were reported to be more valuable than interim analysis. In a study of Nakaigava et al with 81 patients receiving molecular therapies (43 sorafenib, 27 sunitinib, 8 temsirolimus and others) [28], it had been stated that the maximum SUVmax values measured after the first-line molecular treatment had an important role in determining survival in subsequent molecular treatments. The median SUVmax value was accepted as 7 in this study.

In our study, the value of 6.8 was taken as the SUVmax cut-off value. Interestingly, this cut-off value was used as 6.8 in the study of Kayani et al [20], 6.9 in the study of Horn et al [27] and 7 in the study of Nakaiawa et al [25]. SUVmax values, which were taken as the basis in many other studies, were close to these values (between 5 and 9). The SUV value is a semi-quantitive measurement of the 18F-FDG uptake ratio in the tissue, and SUV measurements may differ between PET centers [29]. Interestingly, the data we obtained while writing this study show that the cut-off (mean or median) values of SUVmax in all centers were very close to each other (range 5-9, generally between values of 6.8-8.8). The main conclusion is that high SUVmax values are associated with poor prognosis.

The present study has some limitations. The fact that PET/CT was not preferred too much due to the limitations mentioned in the RCC evaluation caused the number of patients to be low. We could not perform multivariate analyses due to the limited number of patients. In addition, our study was a retrospective one. In addition, treatments applied as a second step after sunitinib may have affected OS. However, high SUVmax values before sunitinib treatment indicate that patients will have poor prognosis regardless of treatment. In conclusion, this study shows that baseline FDG-PET/CT SUVmax values in RCC can be used to predict PFS and OS results in patients receiving sunitinib therapy. Considering that patients with high SUVmax values have poor prognosis, more aggressive and appropriate treatments can be planned for these patients.

Conclusion

In this study, basal PET-CT applied before sunitinib treatment was found to have low treatment efficacy in patients with high SUVmax value. As a result, PET/CT SUVmax value measured before sunitinib treatment can be used to predict survival in advanced RCC patients. FDG PET/CT can be used as an auxiliary parameter in the selection of treatment in patients with poor prognosis at the clinical decision stage. The benefit of FDG PET/CT appears to be important in predicting treatment responses rather than initial RCC diagnosis and staging, and it can be a new biomarker. Further research involving large patient populations is needed to demonstrate the utility of FDG-PET/CT in RCC.

Conflict of interests

The authors declare no conflict of interests.

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