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Prognostic Significance of ^{18}F-FDG PET/CT Imaging in Survival Outcomes in Patients with Renal Cell Carcinoma

Renal Hücreli Karsinom Hastalarının Sağkalım Sonuçlarında ^{18}F-FDG PET/BT Görüntülemenin Prognostik Önemi

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Abstract

Objectives: Renal cell carcinoma (RCC) comprises 85%-90% of primary renal malignant tumors originating from the renal tubular epithelium and has different genetic characteristics. This study aimed to investigate the potential predictive role of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and metabolic parameters in overall survival (OS) analysis in patients with RCC.

Methods: ^{18}F-FDG PET/CT images of 100 patients performed for initial staging before surgical or oncological treatments were analyzed retrospectively. Maximum standard uptake value (SUV_{max}-T) of the primary tumor was calculated and its relationship to patient survival was analyzed. The median follow-up time was 5.61 years (0.01-8.7 years).

Results: SUV_{max}-T levels in the patients ranged from 2.1 to 48.9 (median 5.9, mean 9.0±7.9). SUV_{max}-T was significantly higher in RCC-related death more positive than in the negative cases (p<0.001). However, there was not any statistical significance for gender and pathological subtypes on the survival outcomes of patients (p=0.264 and p=0.784). The patients' 1-year, 3-year, and 5-year OS rates were 71%, 61%, and 57%, respectively. The highest action of SUV_{max}-T for estimating OS was a cut-off level of 5.4, which maintained sensitivity and specificity of 81% and 75%, respectively. However, cancer staging remained independent significance for OS (p<0.001).

Conclusion: SUV_{max} of primary tumor and cancer stage were demonstrated as significant prognostic factors for OS in patients with RCC. Evaluation of ^{18}F-FDG accumulation with PET/CT may help plan treatment strategies and predict survival outcomes of these patients at diagnosis.

Keywords: Fluorine-18-fluorodeoxyglucose, positron emission tomography, prognosis, renal cell carcinoma, survival

Öz

Amaç: Renal hücreli karsinom (RHK), renal tübüler epitelden kaynaklanan primer renal malign tümörlerin %85-90'ını oluşturur ve farklı genetik özellikler içerir. Bu çalışmanın amacı RHK tanılı hastalarda genel sağkalım analizinde ^{18}F-florodeoksiglukoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) ve metabolik verilerin potansiyel öngörücü rolünü araştırmaktır.

Yöntem: Hastalar (n=100) geriye dönük olarak cerrahi veya onkolojik tedaviler uygulanmadan önce, evreleme ^{18}F-FDG PET/BT görüntüleme ile incelendi. Primer tümörün maksimum standartlaştırılmış alım değeri (SUV_{maks}-T) hesaplandı ve hasta sağkalımı ile ilişkisi analiz edildi. Medyan takip süresi 5,61 yıl idi (0,01-8,7 yıl).

Bulgular: Tüm hastalarda SUV_{maks}-T ölçümleri 2,1 ile 48,9 arasında idi (medyan 5,9, ortalama 9,0±7,9). SUV_{maks}-T, RHK ile ilişkili eksitus pozitif olgularda negatif olgulardan anlamlı olarak daha yüksek idi (p<0,001), ancak hastaların sağkalım sonuçlarında cinsiyet ve patolojik alt tipler için

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istatistiksel bir anlamlılık yoktu (p=0,264 ve p=0,784). Tüm hastalar için 1-yıllık, 3-yıllık ve 5-yıllık genel sağkalım oranları sırasıyla %71, %61 ve %57 idi. Genel sağkalımı öngörmede SUV_{maks}-T'nin en yüksek performansı sırasıyla %81 ve %75 duyarlılık ve özgüllük sağlayan 5,4'lük bir cut-off seviyesi ile elde edildi. Öte yandan, kanser evrelemesi genel sağkalım için bağımsız bir öneme sahipti (p<0,001).

Sonuç: Primer tümör SUV_{maks} ve kanser evresi, RHK'li hastalarda genel sağkalım için önemli prognostik faktörler olarak gösterildi. ^{18}F-FDG tutulumunun PET/BT ile değerlendirilmesi, tedavi stratejilerinin planlanmasına ve bu hastaların tanı anında sağkalım sonuçlarının tahmin edilmesine yardımcı olabilir.

Anahtar kelimeler: Flor-18-florodeoksiglukoz, pozitron emisyon tomografisi, prognoz, renal hücreli karsinom, sağkalım

Introduction

Kidney cancers have histological subtypes with different characteristics, account for approximately 3% of adult cancers, and are in the third rank among urogenital cancers (1). Renal cell carcinoma (RCC) comprises 85%-90% of primary renal malignant tumors originating from the renal tubular epithelium and has different genetic characteristics (2). RCCs, highly angio-invasive tumors, tend to metastasize to the lungs, bones, liver, and brain by hematogenous and lymphatic spread. Survival in RCC is poor, especially in the clear cell subtype, which is prone to diagnosis at an advanced stage, and 20%-30% of patients are also in the metastatic stage during this period (3,4). Therefore, the management of these patients is very challenging. The 5-year survival rate is less than 20%, even if the metastatic tumor is removed, the survival is between 25 and 50% (5). However, the incidence of renal tumors, which are often incidentally diagnosed as smaller and low-grade tumors, is increasing because of the widespread use of non-invasive imaging tools. The histological subtype, grade, size, extracapsular spread, and lymphovascular invasion status can be considered among the main factors affecting the prognosis of renal tumors (6).

Positron emission tomography integrated with computed tomography (PET/CT) imaging has become a key modality for imaging patients with cancer and is frequently used in renal cancers, particularly to detect recurrence and evaluate treatment response. Cancer staging with ^{18}F-fluorodeoxyglucose (FDG) PET imaging is since malignant tumoral cells have higher glucose metabolism than normal cells (7). However, renal cancers are prone to exhibit low tracer uptake (8,9).

Whilst there is a wealth of literature addressing the use of ^{18}F-FDG PET/CT in renal tumors, the relationship between PET metabolic measurements obtained from the pre-treatment initial staging examination and patients' survival after long-term follow-up has not been well investigated. Therefore, we investigated the potential predictive role of ^{18}F-FDG PET/CT and metabolic data in the analysis of survival in patients with RCC.

Materials and Methods

Patients

A total of 100 patients [66 men and 34 women; mean age 58.1±11.7 (range: 34-82 years)] with RCC were examined between August 2013 and March 2022 on ^{18}F-FDG PET/CT scans were retrospectively enrolled in the analyses at the initial staging before surgical or oncological treatments.

The University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (number: 88, date: 02.03.2022) and the Declaration of Helsinki rules were followed to conduct this study.

^{18}F-FDG PET/CT Scan and Interpretation of Images

^{18}F-FDG doses according to patient weight (3.7 mBq/kg) were injected into the patients when their blood glucose values were <140 mg/dL. Initially, CT (n=68 with contrast-enhanced, n=32 without contrast-enhanced) data followed by PET scan were received 60 min after ^{18}F-FDG injection between the vertex-proximal thigh in an mCT 20 PET/CT scanner (Siemens Molecular Imaging, Hoffman Estates, IL) and all images were examined first visually and then semi-quantitatively. Regions with increased ^{18}F-FDG uptake than background and nearby structures in primary tumors, nodal and distant metastases were recorded. Maximum standardized uptake value (SUV_{max}) was measured automatically by drawing an elliptical volume of interest to include the pathological tumoral lesions in the three planes in ^{18}F-FDG PET/CT. The review process was carried out by combining the metabolic findings from the PET component with anatomical information obtained from the CT component. Initial staging images were evaluated to determine whether primary tumor SUV_{max} (SUV_{max}-T) predicted patient survival. According to the 8th edition of the American Joint Committee on Cancer 2018 tumor, node, and metastasis (TNM) staging system, the disease stage was determined, and the patients were followed up for at least 5 years or until death to evaluate their survival outcomes (10).

Statistical Analysis

Study data were evaluated by SPSS 25.0 software (IBM, Armonk, NY, USA) and p<0.05 was considered

statistically significant. Numbers and percentages were used to indicate the categorical data. Median and mean with standard deviation values were used to express the quantitative calculations. The relationship between survival and categorical variables was assessed by Pearson chi-squared. Time from PET/CT to death or final analysis of the study was calculated to determine overall survival (OS) and survival curves were performed and compared using the Kaplan-Meier method and Mantel-Cox Log-rank test. Receiver operating characteristic curve (ROC) analysis was used to express the cut-off values for OS. Univariate analyses of SUV_{max} on survival outcomes were measured using the Cox regression analysis. Independent variables related to OS were determined by significant factors by using multivariate logistic regression analysis. The data were expressed at a 95% confidence interval (CI).

Results

Overall, 65 patients had clear cell RCC, 21 had chromophobe RCC, nine had papillary RCC, and five had unclassified RCC. The clinicopathological TNM staging was stage 1 in 40 patients, stage 2 in 14 patients, stage 3 in 9 patients, and stage 4 in 37 patients. Distant metastases were visualized in 34 patients on ^{18}F-FDG PET/CT, and the lungs and bones were the most common sites of distant metastasis (Figure 1). Information on the characteristics of the patients is presented in Table 1. The median follow-up time was 5.61 years (range, 0.01-8.7 years; 0.78 years for deceased patients, 7.78 years for living patients). Fifty-two RCC-related deaths occurred; the remaining 48 patients were alive at the last check.

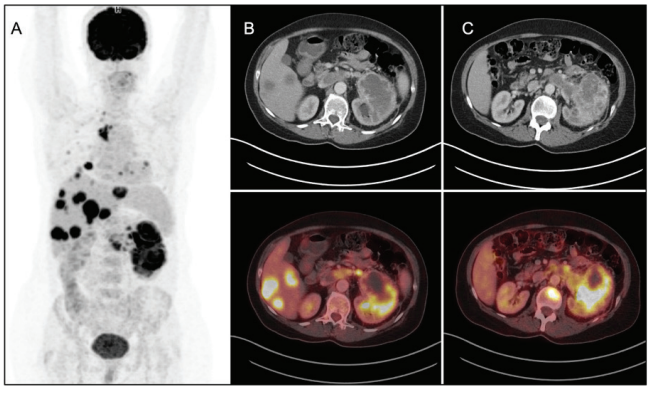


Figure 1. Maximal intensity projection (A), axial CT, and fusion PET/CT (B, C) images of a 57-year-old woman with clear cell RCC. The patient had T4 and stage 4 cancer with lung, liver, bone, and lymph node metastases. Primary tumor SUV_{max} was 25.1. She died 6 months after the initial evaluation ^{18}F-FDG PET/CT

PET/CT: Positron emission tomography/computed tomography, RCC: Renal cell carcinoma, SUV_{max}: Maximum standard uptake value, FDG: Fluorodeoxyglucose

SUV_{max}-T levels in the patients ranged from 2.1 to 48.9 (median 5.9, mean 9.0±7.9). In our study, there were significant differences according to the PET metabolic parameters of the primary tumor. SUV_{max}-T was significantly higher in patients with distant metastases than in the negative ones ($p<0.001$). Also, SUV_{max}-T was significantly higher in the RCC-related death group than in the other group ($p<0.001$). There was statistical significance in OS between groups for tumor and cancer staging ($p<0.001$). However, there was no statistical significance for gender and histological subtypes on patients' survival outcomes ($p=0.264$ and $p=0.784$) (Figure 2).

The time-dependent ROC curves were generated to analyze the efficacy of SUV_{max}-T to predict OS (Figure 3). High SUV_{max}-T was associated with a shorter OS and the highest SUV_{max}-T value to predict OS was a cut-off level of 5.4, which retained 81% and 75% sensitivity and specificity, respectively. Considering 1-year, 3-year, and 5-year survival, the best clinical performance of SUV_{max}-T was achieved at a cut-off level of 7.4, 5.5, and 5.5, which indicated the

Table 1. Characteristics of the patients

Variables	n
Age, median (range)	58 (34-82)
Sex	
Male	66
Female	34
Histopathological type	
Clear cell	65
Chromophobe	21
Papillary	9
Unclassified	5
Tumor stage	
T1	46
T2	22
T3	20
T4	12
TNM cancer staging	
I	40
II	14
III	9
IV	37
Nephrectomy	
Yes	66
No	34
RCC-related death	52

TNM: Tumor, node, and metastasis, RCC: Renal cell carcinoma

highest sensitivity and specificity, respectively (Table 2). These results suggest that SUV_{max}-T is a reliable parameter for predicting OS. The patients' 1-year, 3-year, and 5-year OS rates were 71%, 61%, and 57%, respectively. Furthermore, OS rates were 52% vs. 48% in patients with SUV_{max} ≤5.4 vs. >5.4 on ^{18}F-FDG PET/CT. Also, univariate Cox regression analysis identified the values of SUV_{max}-T as a significant prognostic marker for OS (p<0.001, Odds ratio: 1.135, 95% CI: 1.098-1.173).

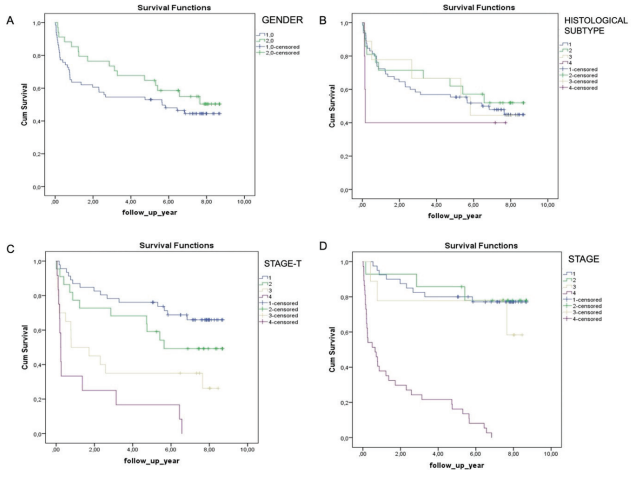


Figure 2. Kaplan-Meier curves of overall survival by patient's gender (A; blue: male, green: female), histological subtype (B), tumor staging (C), and cancer staging (D)

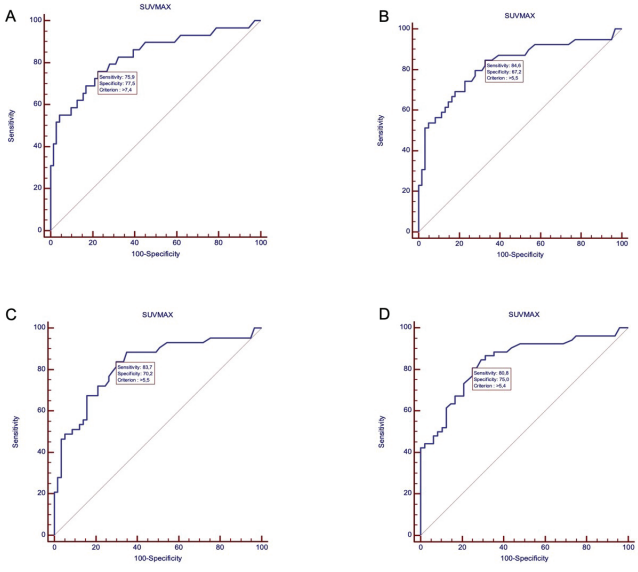


Figure 3. Receiver operating characteristic curve analysis of the patients comparing the prognostic accuracy for 1-year survival (A), 3-year survival (B), 5-year survival (C), and overall survival (D) and determining the cut-off values (p<0.0001, each)

The effect of SUV_{max} on OS was compared with that of possible prognostic markers and the SUV_{max} levels exhibiting statistical significance in univariate analysis were included in the multivariate analysis. The findings of the multivariate analysis are indicated in Table 3. Analysis of SUV_{max} in association with patients' gender, histological tumor subtypes, and tumor staging at the initial pretreatment period revealed that SUV_{max}-T was a significant independent prognostic factor of OS in patients with RCC (p<0.001). However, cancer staging remained independent significance for OS (p<0.001). Regardless of the tumor stage and the histopathological subgroups, patients with a higher SUV_{max} had a shorter OS than patients with a lower SUV_{max} (Figure 4). In this study, the mean OS for 48 patients with SUV_{max} ≤5.4 was 7.4 years (95% CI: 6.623-8.181), while in 52 patients with SUV_{max} >5.4, the mean OS was 3.3 years (95% CI: 2.349-4.170). Differences in OS among these patients were statistically significant (SUV_{max} ≤5.4 vs. >5.4, p<0.001).

Discussion

Oncological PET/CT imaging has proven its importance in diagnosis, staging, evaluation of treatment response, and recurrence detection in most cancer types and is an indispensable modality in this field. Since RCC exhibits low glucose metabolism and tumoral ^{18}F-FDG uptake, PET/CT is more limitedly preferred as an imaging tool in the initial staging (11,12). However, several researchers have examined the efficacy of ^{18}F-FDG PET in determining the metabolic and molecular characterization of renal tumors (13,14). In a retrospective study investigating the impact of SUV_{max} levels on patient mortality in renal tumors, it was determined that patients with metastasis lived shorter, liver metastases showed shorter survival, and the lung metastases had higher SUV_{max} levels (15).

Diagnostic values of PET/CT at different SUV_{max} cut-off values in survival analysis are available for RCC in the literature (16,17). Komek et al. (18) investigated the relationship between the mortality results of 21 patients with RCC and showed that SUV_{max} values of ≥4.5, obtained from pre-treatment ^{18}F-FDG PET/CT imaging, resulted in increased mortality. Furthermore, a cut-off value of 8.8 and SUV_{max} values higher than this have been reported as predictors of survival for advanced RCC (19). In this study, we evaluated the patient outcomes and mortality rates according to different SUV_{max} values, which refer to 1-year, 3-year, and 5-year results and we determined the patients' mortality rates as 29%, 39%, and 43%, respectively (Figure 5). Nakaigawa et al. (20) evaluated 101 patients with RCC during the pretreatment or follow-up period and classified study patients into three subgroups based on their highest

Table 2. Receiver operating characteristic analysis for the efficacy of SUV_{max} in predicting mortality relative to patient survival time

SUV_{max}	Cut-off level	Death	AUC	p value	Sensitivity (%)	Specificity (%)	95% CI
1-year survival	> 7.4	29	0.831	<0.0001	75.9	77.5	0.742-0.898
3-year survival	>5.5	39	0.821	<0.0001	84.6	67.2	0.732-0.891
5-year survival	>5.5	43	0.821	<0.0001	83.7	70.2	0.732-0.891
Overall survival	>5.4	52	0.837	<0.0001	80.8	75.0	0.750-0.903

SUV_{max}: Maximum standardized uptake value, AUC: Area under curve, CI: Confidence interval

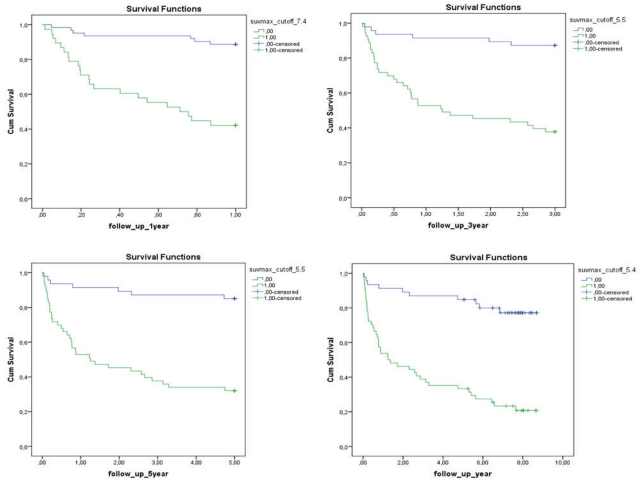


Figure 4. Kaplan-Meier survival graphs with log-rank (Mantel-Cox) present significant differences in survival outcomes of study patients classified by SUV_{max} values. SUV_{max} >7.5 for 1-year survival (A), SUV_{max} >5.5 for 3-year survival (B), SUV_{max} >5.5 for 5-year survival (C), and SUV_{max} >5.4 for overall survival (D) were associated with mortality and shorter OS (p<0.001 for all)

SUV_{max}: Maximum standard uptake value, OS: Overall survival

SUV_{max} levels and reported significant differences in OS for RCC. Subjects were followed for a median of 18 months and the median OS of patients with SUV_{max} <7.0, ≥7.0, and <12.0, and ≥12.0 was found as 41.9, 20.6, and 4.2 months, respectively. In this study, the median follow-up time of our patients was 5.61 years, and we observed the mean OS as 7.4 and 3.3 years, respectively, for SUV_{max} ≤5.4 vs. >5.4 levels, with sensitivity and specificity results of 81% and 75%. Additionally, the SUV_{max} threshold of 7.4 was significant in distinguishing patient mortality and survival within 1 year after PET/CT evaluation (Figure 6).

The use of volumetric measures such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) provided a correlation with prognosis in published studies (21). Nakajima et al. (22) showed that MTV and TLG calculated from PET data are also important prognostic markers in the survival analysis of RCC patients. Further pre-treatment TLG was found to be an independent indicator of the prognosis of OS in another study (23). Besides PET measurements,

Table 3. Multivariate logistic regression analysis for patient survival outcomes

Variable	OR	95% CI	p value
SUV_{max}	1.076	1.036-1.118	**<0.001**
Age	1.028	0.997-1.060	0.081
Gender	0.660	0.358-1.218	0.184
T-stage	0.928	0.688-1.252	0.625
TNM stage	1.985	1.444-2.729	**<0.001**

SUV_{max}: Maximum standardized uptake value, OR: Odds ratio, CI: Confidence interval, TNM: Tumor, node, and metastasis

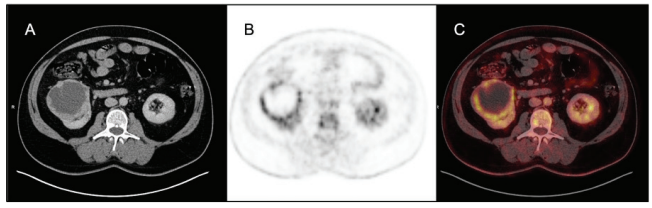


Figure 5. Axial CT (A), PET (B), and fusion PET/CT (C) images of a 54-year-old man patient with clear cell type RCC. The patient had stage 3 cancer with a T3 tumor on PET/CT performed at the initial staging. Primary tumor SUV_{max} was 6.5. He died of recurrent metastatic disease 2.7 years after initial evaluation ^{18}F-FDG PET/CT

PET/CT: Positron emission tomography/computed tomography, RCC: Renal cell carcinoma, SUV_{max}: Maximum standard uptake value, FDG: Fluorodeoxyglucose

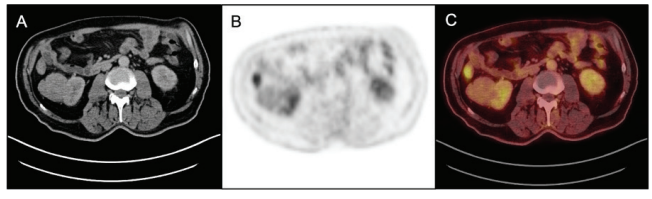


Figure 6. Axial CT (A), PET (B), and fusion PET/CT (C) images of a 67-year-old living patient with stage 1 cancer were received 7.4 years ago. He had chromophobe type RCC in the right kidney with a SUV_{max} value of 3.9

PET/CT: Positron emission tomography/computed tomography, RCC: Renal cell carcinoma, SUV_{max}: Maximum standard uptake value, FDG: Fluorodeoxyglucose

the prognostic value of pathological subtypes was investigated, and the clear cell variant was more prone to metastasis than the other two variants and exhibited a poor prognosis, but we did not observe any significant difference between the survival times of the histological

subgroups (24). Tumor size, grading system, various other markers, and different radiopharmaceuticals used in hybrid molecular imaging have been reported in several articles as potential predictors of the prognosis of patients with RCC (25,26,27).

Study Limitations

This study had some limitations. First, our retrospective study showed a heterogeneous distribution among pathological subgroups and tumor stages. Also, the differences in the patients' treatment protocols and follow-up strategies may have affected the survival analyses. Therefore, well-designed prospective studies are required to validate our findings.

Conclusion

Patients with high primary tumor SUV_{max} had increased mortality rates and shorter survival. SUV_{max} and the high-cancer stage were demonstrated as the significant prognostic predictors in patients with RCC. We think that SUV_{max} can act as a potential biomarker and reflect the disease prognosis. Evaluation of ^{18}F-FDG accumulation using PET/CT may help plan treatment strategies and predict survival outcomes of these patients at diagnosis.

Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (number: 88, date: 02.03.2022) and the Declaration of Helsinki rules were followed to conduct this study

Informed Consent: Externally peer-reviewed.

Peer-review: Externally peer-reviewed.

Authorship ÛContributions

Surgical and Medical Practices: G.T., C.G., Ö.F.Ş., E.A., N.E., T.F.Ç., Concept: G.T., C.G., Ö.F.Ş., E.A., N.E., T.F.Ç., Design: G.T., C.G., Ö.F.Ş., E.A., N.E., T.F.Ç., Data Collection or Processing: G.T., C.G., Ö.F.Ş., E.A., N.E., T.F.Ç., Analysis or Interpretation: G.T., C.G., Ö.F.Ş., E.A., N.E., T.F.Ç., Literature Search: G.T., C.G., Ö.F.Ş., E.A., Writing: G.T., T.F.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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