Original Article

The Effect on Survival and Mortality of the Highest SUVmax Value on Metastatic Foci in Postoperative Kidney Tumors

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Abstract

Objective: One-third of patients newly diagnosed with a kidney tumor have metachoronous disease, 25-50% have synchronous metastasis, and approximately 30-40% of patients have metastasis at the time of diagnosis. Metastasis mostly occurs in the lungs, regional lymph nodes, bones, and liver. The present study was aimed to determine the effect on mortality the values of standard uptake value (SUV)max measured with positron emission tomography (PET) in metastases of kidney tumors. **Material and Methods:** A retrospective review was conducted of the files of 77 patients newly diagnosed with kidney tumor and disease staging determined with PET in the Nuclear medicine Department of Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital between August 2007 and April 2012. The gender, age, histological types, metastases, SUVmax values, and dates of death of the patients were recorded in the SPSS software. **Results:** It was observed that higher SUVmax values indicated a shorter survival time (r = .303) (P = 0.022). Patients with metastasis lived for a shorter period (P < 0.001), particularly those with liver metastasis (r = .515) (P = 0.049). Metastases were most frequently seen in lymph nodes (42.1%); the SUVmax values of lung metastases were higher (P = 0.025) and papillary carcinomas showed higher SUVmax uptake (P = 0.015). **Conclusions:** In the present study, it was concluded that the higher the SUVmax value the shorter the survival time. The survival time of patients with metastasis was shorter, and this could be estimated through the measured SUVmax values.

Keywords: *Positron Emission Tomography (PET/CT), SUVmax, Kidney Tumors, Survival, Metastasis*

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Introduction

The kidney tumors were grouped under seven categories in the 2004 categorization of the World Health Organization (WHO).[1,2] Among the malign kidney tumors in the adult period, 85–90% are clear cell, papillary, and chromophobe type tumors, whereas 85–90% of benign tumors are adenoma and oncocytoma type tumors.[3,4] The incidence rate in the entire world is 5.8/100000 and the mortality rate is 1.4/100000. The incidence rate in 60–70-year-old males is 1.5 times more than females.[5] Radical nephrectomy implemented in the early stages of kidney cancer and nephron sparing surgery have been used as the gold standard treatment approaches for many years.[6,7] Nevertheless, metastasis is seen in approximately 20–30% of patients and the most common locations of metastasis are the lungs, lymph nodes, liver, and bones.[8,9] The prognostic factors of tumor in renal cell carcinoma are tumor stage and size, Fuhrman grade, histological subtype, presence of lymphovascular invasion, and the presence of a sarcomatoid component. Therefore, similar to all tumors, the staging is critical in kidney tumor.[10,11] The imaging method most commonly

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used in the diagnosis, staging, and follow-up of various cancer types is 18F-fluorodeoxyglucose positron emission tomography (PET/CT), which is also now being frequently used in patients with kidney tumor. Since the introduction of PET/CT use, staging of kidney tumors has been more accurate.[12] PET/CT is a noninvasive method that enables visualization of the glucose metabolism in the body, which can be quantified as the standard uptake value (SUVmax).[13] While the elimination of F-18FDG from the body through the kidneys limits the use of PET/CT for the evaluation of urinary system malignancies, the accompanying use of CT images ensures increased anatomical details, thereby resulting in lower rates of false positivity.[14]

Very few studies have been performed to evaluate the contribution of SUVmax values determined via PET/CT in kidney tumors on the estimation of mortality and survival. Therefore, this study can be considered to contribute to literature by providing an evaluation of the effect on survival and mortality estimations of SUVmax values measured by PET/CT in patients diagnosed with kidney tumor.

Material and Methods

A retrospective analysis was made from the files of 77 patients diagnosed with kidney tumor and disease staging determined with PET/CT in the Nuclear Medicine Department of Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital between August 2007 and April 2012. The Local Ethics Committee granted approval for the study. The inclusion criteria for cases in the study were diagnosis of kidney tumor and pretreatment staging applied with PET/CT. Analysis was made primarily of the PET/CT SUVmax values and other clinical, histopathological, laboratory, and treatment parameters affecting the prognosis.

The gender, age, histological type, metastases, SUVmax values, and date of death of the patients were recorded in the SPSS programme. The survival time was defined as the period from the date of PET/CT imaging, according to which the survival was calculated, and the date of death received from MERNIS (The Central Civil Registration System) or the final application date if the patient was alive.

All patients underwent routine FDG PET/CT scans with Biograph 6 PET/CT (Siemens Medical Systems, CTI, Knoxville, TN, USA). All patients fasted for at least 6 h and glucose levels in peripheral blood were confirmed to be ≤140 mg/dl before FDG injection. Approximately 5.5 MBq/kg of FDG was administered intravenously 1 h before image acquisition. After the initial low-dose CT (Biograph 6: 40 mA, 120 kVp), standard PET imaging was performed from the skull base to the proximal thighs with an acquisition time of 3 min/bed in three-dimensional mode. Images were then reconstructed using the ordered subset expectation maximization algorithm (2 iterations, 20 subsets).

All patients underwent PET/CT scan before the treatment and the SUVmax values were recorded. The nodules in the organs except for kidneys with measured SUVmax value between 2 and 22 were accepted as metastatic.

Statistical methods

All data were analyzed using SPSS 23.0 (IBM Corporation, Armonk, New York, United States) software. The conformity of the data to normal distribution was analyzed through the Liliefors corrected Kolmogorov–Smirnov test, and variance homogeneity was analyzed with the Levene test. The independent-samples *t*-test was used with the Bootstrap results and the Mann–Whitney U test was used with the simulation method in the comparison of two independent groups. Of the nonparametric tests, the Kruskal–Wallis H was used with the Monte Carlo simulation method for the comparison of independent multiple groups, whereas the nonparametric post hoc test (Miller (1966) was used for the Post Hoc analysis.

The Pearson Correlation and Spearman rho tests were used to analyze the correlations between quantitative variables. The Fisher Exact test (Exact) was used in the comparison of categorical data. The Kaplan-Meier (product limit method)-Log Rank (Mantel-Cox) analysis was used to analyze the effects of the factors on mortality and survival time. The quantitative data were stated as mean ± standard deviation (SD) and median range (minimum–maximum) values in the tables. The categorical data were expressed as numbers (*n*) and percentages (%). The data were analyzed at 95% confidence interval and a value of $P < 0.05$ was accepted as statistically significant.

Results

The study included a total of 77 patients, comprising 53 (68.8%) males and 24 (32.1%) females, with a mean age of 57.6 ± 12.4 years (range, 27-80 years) [Table 1]. The mean survival time of the patients was 1075.3 ± 921.1 days (range, 8-3043 days). Metastasis was determined in 57 (74%) patients and no metastasis in 20 (26.0%) patients [Table 1]. Primary tumors were mostly located in the left kidney (57.1%). Of these patients, 64 (83.1%) underwent surgery. Metastases were mostly seen in the lymph node (42.1%), followed by the lungs (21.1%) and bones (14.0%). The most frequent type of cancer was clear cell (71.9%) [Table 1].

Table 1: Demographic features of the patients included in the study

		n	%
Metastasis	Absent	20	26.0
	Present	57	74.0
Gender	Female	24	31.2
	Male	53	68.8
Mortality	Alive	63	81.8
	Dead	14	18.2
Operation status	Non-operated	13	16.9
	Operated	64	83.1
Primary tumor localization	right kidney	33	42.9
	left kidney	44	57.1
Operated	no	13	16.9
	right kidney	29	37.7
	left kidney	35	45.5
Metastasis location where SUVmax was obtained	lungs	12	21.1
	kidney	1	1.8
	liver	3	5.3
	bone	8	14.0
	lymph node	24	42.1
	recurrence	4	7.0
	pleura	3	5.3
	adrenal	1	1.8
	soft tissue	1	1.8
Pathological diagnosis	clear cell	41	71.9
	chromophobe	1	1.8
	papillary	7	12.3
	renal cell	7	12.3
	sarcomatoid renal cell	1	1.8

	N	Mean±SD	Median (Max-Min)
Age	77	57.6 ± 12.4	57.0 (80–27)
Survival (days)	77	1,075.3 ± 921.1	814.0 (3043–8)
The highest SUVmax in metastasis	57	9.4 ± 5.1	8.1 (21–2)
Lung metastasis	27	8.3 ± 5.7	5.5 (20–1.4)
Bone metastasis	15	6.7 ± 3.3	5.5 (16–3.6)
Lymph node metastasis	33	9.2 ± 5.2	9.0 (21–1.1)
Soft tissue metastasis	3	8.7 ± 4.5	9.0 (13–4)
Pleura metastasis	6	8.5 ± 7.4	5.0 (19–2.6)
Adrenal metastasis	9	5.6 ± 2.3	4.6 (10–3.5)
Liver metastasis	7	6.0 ± 1.0	6.0 (7–5)
Kidney	1	2.00	2.00

SD: Standard Deviation; Max.: Maximum; Min.: Minimum

The mean age of the patients with metastasis was 58.9 ± 13.1 years and of those without metastasis 53.9 ± 9.8 years. The higher mean age of the patients with metastasis was not found to be statistically significant (P = 0.073). The survival time of the patients with metastasis was 449 days (range, 8-–043 days) and of those without metastasis, 1916.5 days (range, 333–3042 days). The shorter survival time of the patients with metastasis was found to be statistically significant (P < 0.001). Of the operated patients, 44 (77.2%) were

Table 2: Evaluations of the patients included in the study according to the presence of metastasis

		Metastasis		*P* value
		Absent	Present	
		n = 20	*n* = 57	
Age *		53.9 ± 9.8	58.9 ± 13.0	0.073
Survival (days) **		1916.5 (3042–333)	449.0 (3043–8)	<0.001
Gender	Female	9 (45.0)	15 (26.3)	0.162
	Male	11 (55.0)	42 (73.7)	
Mortality	Alive	19 (95.0)	44 (77.2)	0.098
	Dead	1 (5.0)	13 (22.8)	
Operation Status	Non-operated	0 (0.0)	13 (22.8)	0.017
	Operated	20 (100.0)	44 (77.2)	
Primary tumor localization	right kidney	10 (50.0)	23 (40.4)	0.600
	left kidney	10 (50.0)	34 (59.6)	
Operated	no	0 (0.0)	13 (22.8)	0.035
	right kidney	10 (50.0)	19 (33.3)	
	left kidney	10 (50.0)	25 (43.9)	

Fisher Exact Test(Exact); Independent t-test(Bootstrap); Mann–Whitney U Test(Monte Carlo). *Mean ± Standard deviation; **Median (Maximum–Minimum)

Table 3: The relationship between estimated survival time, metastasis and gender

	Estimated Survival Time (days)	Dead	Alive	*P* Value
	Mean ± SD	*n* (%)	*n* (%)	
Metastasis				
Absent	2906.6 ± 132.0	1 (5.0)	19 (95.0)	<0.001
Present	1912.0 ± 173.7	13 (22.8)	44 (77.2)	
Gender				
Female	2608.6 ± 171.7	6 (25.0)	18 (75.0)	0.346
Male	2299.1 ± 206.8	8 (15.1)	45 (84.9)	
Total	2414.7 ± 142.8	14 (18.2)	63 (81.8)	

Kaplan–Meier Test Log Rank (Mantel-Cox); SD: Standard Deviation

Table 4: The correlation between age and survival time and SUVmax and metastases

	Age		Survival time	
	r	*P*	*r*	*P*
The highest SUVmax in metastasis	0.046	0.734	–0.303*	0.022
Lung metastasis	–0.063	0.754	–0.226	0.257
Bone metastasis	0.321	0.243	–0.515*	0.049
Lymph node metastasis	0.239	0.180	–0.124	0.491

Pearson Correlation Test; Spearman's rho Test; r, Correlation coefficient

determined to have metastasis. The higher number of operated patients and those with metastasis was found to be statistically significant ($P = 0.017$). Compared to the other groups, the higher number of 25 (43.9%) patients, who were operated on the left kidney and determined to have metastasis, was found to be statistically significant ($P = 0.035$) [Table 2 and Figure 1] = [The estimated survival time of patients with metastasis was 2906.6 ± 132.0 days and 1912.0 ± 173.7 days in those without metastasis.] The shorter survival time of the patients with metastasis was found to be statistically significant ($P < 0.001$). The estimated survival time of female patients was 2608.6 ± 171.7 days, and 2299.1 ± 206.8 days in male patients. The longer survival time of the female patients was not found to be statistically significant ($P = 0.346$) [Table 3].

The patient age was determined to have a positive correlation with the SUVmax value ($r = 0.046$), bone metastasis ($r = 0.321$), lymph node metastasis ($r = 0.239$), and a negative correlation with lung metastasis ($r = -0.063$) [Figure 2]. None of these correlations were found to be statistically significant ($P > 0.05$). A negative

Table 5: Evaluation between the SUVmax values and the histopathological diagnosis, metastasis location and operated kidney

		The highest SUVmax in metastasis				*P* Value
		n	Median	Maximum	Minimum	
Pathological diagnosis	Clear cell = I	41	7.2	21	2	I–II = 0.015
	Papillary = II	7	12.0	20	7.5	I–III = 0.823
	Renal cell = III	7	7.0	19	3	II–III = 0.099
Metastasis location where SUVmax was obtained	Lungs = I	12	13.0	20	3	I-II = 0.025
	Bone = II	8	5.1	10	3.6	I–III = 0.398
	Lymph node = III	24	9.0	21	3.3	II–III = 0.003
Operated	No	13	10.0	20	6	0.056
	Right kidney	19	9.0	21	2.6	
	Left kidney	25	7.0	19	2	

The Kruskal–Wallis Test Post Hoc Test: nonparametric post hoc test (Miller(1966)

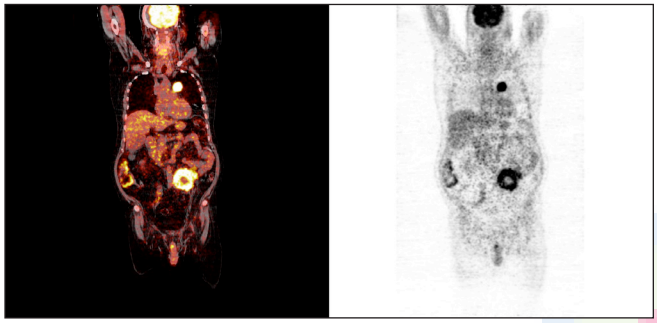

Figure 1: Local recurrence (SUVMax: 18) and mediastinal lymphadenopathy (SUVMax:18) in PET/CT imaging was determined 68-years-old male patient's survival was calculated as 350 days.

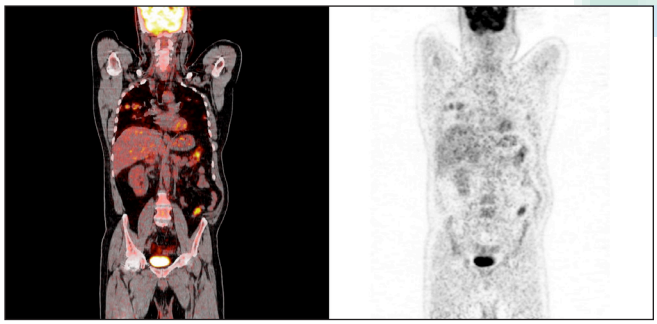

Figure 2: Pleura (SUVMax: 17) and lung metastasis (SUVMax:14) in PET/CT imaging was determined 52-years-old male patient's survival was calculated as 750 days.

correlation was determined between the SUVmax values measured in metastases and survival times. The longer survival time with the increase of SUVmax value was found to be statistically significant ($r = -.303$) ($P = 0.022$). A negative correlation was determined between bone metastases and survival times. The shorter survival time with the increase of bone metastasis was found to be statistically significant ($r = -.515$) ($P = 0.049$) [Table 4].

The mean SUVmax was 7.2 (2–21) in patients with clear cell histopathology, 12 (7.5–20) in patients with papillary carcinoma histopathology, and 7 (3–19) in patients with renal cell carcinoma histopathology. The higher level of SUVmax value measured in papillary carcinoma compared to the SUVmax value measured in clear cell carcinoma was found to be statistically significant ($P = 0.015$). The SUVmax value was measured as 13 (3–20) in lung metastasis, 5.1 (3.6–10) in bone metastasis, and 9 (3.3–21) in lymph node metastasis. The higher level of SUVmax value in lungs metastasis compared to the SUVmax value in bone metastasis was found to be statistically significant ($P = 0.025$). The higher level of SUVmax value measured in lymph node metastases compared to the SUVmax value in bone metastases was found to be statistically significant ($P = 0.003$) [Table 5].

Discussion

In this retrospective study analyzing the effect on patient mortality of PET/CT measurements of SUVmax values of metastases in patients with kidney tumor, the following results were determined: (1) the higher the SUVmax values the shorter the survival time; (2) patients with metastasis live shorter lives; (3) liver metastasis in particular indicated shorter survival; (4) left kidney tumors caused more metastases; (5) metastases mostly occur in the lymph nodes, (6) the SUVmax values of lung metastases are higher; (7) papillary carcinomas have a higher SUVmax uptake.

Various molecular-targeting therapies have become available for the treatment of advanced kidney tumors. Accurate prognostication is desirable for choosing the appropriate treatment for individual patients. PET/CT is a noninvasive tool for evaluating glucose accumulation,

which can be an index of biological characteristics of cancer. We prospectively evaluated PET/CT as a prognostic indicator in patients with advanced kidney tumors.

PET/CT measurements have been reported to have 90% sensitivity, 91% specificity, and 90% precision in the diagnosis and staging of kidney tumors. The positive predictive value has been shown to be 95% and negative predictive value 81%.[15,16] As the entire body can be scanned with a single examination, it is possible to determine systemic metastases, particularly in the bones. PET/CT sensitivity has been reported as 60–70% and specificity as 90–100% in the determination of lymph node metastases. With all these features, PET/CT can be considered to be an effective method for the diagnosis and staging of kidney tumors.[17,18] In a study by Shandal *et al*. conducted to evaluate the importance of PET/CT in advanced stage kidney tumors, sensitivity, and specificity were determined as 90–95%; it was emphasized that PET/CT is reliable in the examination of kidney tumors.[19] In a study by Kumar *et al*., PET/CT was determined to be a beneficial examination method in the postoperative recurrence evaluation of patients diagnosed with kidney tumor who had undergone radical surgery.[20] In the present study, it was attempted to benefit from the efficient features of PET/CT in determining cancer and metastasis. Using PET/CT, SUVmax values were measured over the tumors and metastases of the patients included in the study and the effects of these values on mortality and survival were analyzed. The study revealed that survival decreased with increasing SUVmax values and patients with metastasis lived shorter lives.

Of all kidney tumors, 90% are renal cell carcinoma and most of these are metastatic. A third of patients newly-diagnosed with kidney tumour have metachoronous disease and 25–50% have synchronous metastasis.[21] Approximately 30–40% of patients have metastasis at the time of diagnosis. Metastases occur mostly in the lungs, regional lymph nodes, bones, and liver.[22] In the present study, 74% of the patients were determined with metastasis and 83.1% of these underwent surgery. Metastases were mostly seen in the lymph node (42.1%), followed by the lungs (21.1%), and bones (14.0%). The most frequent type of cancer was clear cell (71.9%). The cut-off SUVmax value could not be determined in terms of the evaluation of metastatic lesions because of the insufficient number of patients included in the study.

In the study by Noda *et al*., 31 patients with RCC were evaluated by two independent observers with the use of PET/CT. The tumor SUVmax, tumor-liver SUV, rate, and tumor-spleen SUV rate were correlated. As a result of the study, they showed that only the tumor-liver SUV rate was a significant parameter.[23]

In the study by Sharma *et al*., the bone metastases of 36 patients with RCC were analyzed as visual and semi-quantitative [maximum standardized intake value (SUVmax)] by two nuclear medicine specialists with the use of PET/CT and bone scintigraphy. As a result of the study, they showed that the PET/CT had higher diagnostic accuracy compared to the bone scintigraphy in the determination of bone metastasis in patients with renal cell carcinoma (RCC).[24]

In the study by Noboru *et al*., 101 patients with RCC underwent PET/CT scan before treatment and the maximum SUVmax values were recorded. As a result of the study, they determined that the participants with SUVmax values between 7.0 and 12.0 lived 20.6 months, and the participants with SUVmax $\geq$ 12.0 lived 4.2 months on the average. They emphasized that the PET/CT was a useful prognostic indicator in patients with metastatic RCC and could be used in the clinical decision making.[25] In the study performed by us, the survival times of the patients with and without metastasis were found to be 449 (3043-8) and 1916.5 (3042-333) days, respectively. The survival times of the patients with metastasis were found to be significant shorter. Negative correlation was determined between the SUVmax values measured in patients with metastasis and their survival times. The reducing survival time with increasing SUVmax value was found to be statistically significant ($r = -.303$) ($P = 0.022$). Negative correlation was determined between the bone metastases and the survival time. The reducing survival time with increasing SUVmax values measured in bone metastasis was found to be statistically significant ($r = -.515$) ($P = 0.049$). However, no difference was determined between the survival times and genders.

In the study by Lacob *et al*. performed among 39 patients with metastatic RCC treated with tyrosine kinase inhibitors, it was emphasized that PET/CT was a safe method that could be used in prognosis and survival estimations.[26]

In the study by Kakizoe *et al*. performed among 48 patients with metastatic RCC who were treated with tyrosine kinase inhibitors, the pre and postoperative PET/CT values were compared. As a result of the study, they did not determine any difference between the primer tumor SUVmax change and the SUVmax changes measured in metastases. They determined that the kinase inhibitor treatment was effective equally on primer tumors and metastases.[27] In the present study, the SUVmax value measured in papillary cancer to be higher than the SUVmax value measured in clear cell cancer was found to be statistically significant. Considering these results, it is estimated that the survival times of the

patients with papillary cancer diagnosis could be lesser because of the negative correlation between the SUVmax values measured in patients with metastasis and the survival time. Not to correlate the SUVmax values and survival times according to the pathological diagnosis is one of the weaknesses in this study.

This study is one of the rare studies where the relationship between SUVmax values and the survival was determined. Hence, it is considered to contribute to the literature.

In conclusion, it was determined that the higher the SUVmax value, the shorter the survival time, patients with metastasis live shorter lives and the survival time of patients could be estimated via measured SUVmax values.

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Conflicts of Interest

There are no conflicts of interest.

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