The prognostic value of preoperative PET/CT evaluation of maximum standardized uptake value in renal cell carcinomas

Ann. Ital. Chir., 2017 88: 48-54
pii: S0003469X17026197

Halil Komek*, Serdar Altindag*, Canan Can*, Nursin Aguloglu*, Hasan Morcali*, Abidin Tuzun**, Seyhmus Kavak***

**Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital Department of Nuclear Medicine. Diyarbakir, Turkey*
***Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital Department of General Surgery. Diyarbakir, Turkey*
****Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital Department of Radiology. Diyarbakir, Turkey*

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AIM: *The use of positron emission tomography (PET/CT) in kidney tumors has increased greatly in recent years. There have been few studies on the effect of SUVmax values detected by PET/CT on the mortality and survival estimation in patients with kidney tumors. In this study, it is hoped to contribute to the literature of research on survival and mortality estimations of kidney tumour patients through an evaluation of SUVmax values measured with PET/CT scan.*
MATERIAL AND METHODS: *A retrospective review was made of the files of 21 patients newly-diagnosed with kidney tumor and with 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 largest tumor seen on CT was considered as the tumour size and was stated in cm. The survival time was defined as the time from the date of PET/CT Imaging, which was taken into consideration while calculating the survival, and the date of death received from MERNIS (The Central Civil Registration System) or the final application date if the patient was alive.*
RESULTS: *The lower the SUVmax value in the kidney tumour, the longer the survival time. The mortality risk of male patients was 12-fold higher than females and mortality increased 4-fold when SUVmax values were ≥ 4.5.Patients with a tumour on the right kidney had a longer survival time. With increasedage,survival time decreased. The SUVmax values and tumor size measured in left kidney tumors were higher than those measured in right kidney tumors.*
CONCLUSIONS: *In the present study, it was concluded that the lower the SUVmax values and the smaller the tumour size, the longer the survival time. Mortality rates increased when SUVmax values were ≥ 4.5 (p=0.001).The use of PET/CT scan can be considered to contribute to mortality and survival estimations in patients with kidney tumor.*

KEY WORD: FDG, Renal cell Carcinoma, SUVmax

Introduction

Kidney cancer comprises approximately 2%-3% of all adult cancers [1]. The prevalence in males is twice that of females [2,3]. Smoking, obesity and hypertension are known to be critical risk factors [4,5]. Radical nephrectomy and nephron-sparing surgery have been used as the gold standard treatment approaches in the treatment of kidney tumors for many years [6,7]. Many prognostic factors have been defined for patients and tumors in renal cell carcinomas, of which the most important are tumor stage and size, Fuhrman grade, histological subtype, lymphovascular invasion, and the presence of a sarcomatoid component. Therefore, as in all tumours, staging is critical in kidney tumors [8-10]. With the extensive use of ultrasonography (USG), computerized tomography (CT)

Pervenuto in Redazione Luglio 2016. Accettato per la pubblicazione Settembre 2016.
Correspondence to: Halil Komek, MD, Department of Nuclear Medicine, Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital. Diyarbakir, Turkey (e-mail: halilkomek@gmail.com)

and magnetic resonance imaging (MRI), the incidental determination of kidney tumors has increased and therefore many patients are now diagnosed at an early stage. Moreover, tumor stages can be determined more accurately and easily [11-14]. In addition to tumor staging methods, the imaging method used nowadays in staging and follow-up of various cancer types is18F-fluorodeoxyglucose positron emission tomography (PET/CT). PET/CT differs from other methods as it allows entire body imaging in a single session and also reveals biochemical functions [15]. PET/CT is a non-invasive method in which the glucose metabolism is imaged. While glucose metabolism in any part of the body can be imaged, it can also be quantified as the standard uptake value (SUV) [16,17]. Although F-18 is limited by the elimination of FDG from the body through the kidneys and for PET/CT in evaluating the urinary system malignancies, the accompanying use of CT images ensures increased anatomical detail and decreases false positivity. Despite having a limited role in the diagnosis of kidney tumors, PET/CT is a very practical method in staging, restaging, demonstrating distant organ and bone metastases, masses in the kidney fold, distinguishing recurrences, determining prognoses and evaluating the response to treatment [18]. There have been very few studies performed to evaluate the contribution of SUVmax values determined via PET/CT in patients with kidney tumor on the estimations 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 method

A retrospective review was made of the files of 21 patients newly-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. Approval for the study was granted by the Local Ethics Committee. The inclusion criteria for cases in the study were diagnosis of kidney tumor and pre-treatment 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 program. The diseases of 7 patients were diagnosed with nephrectomy and of 14 patients with biopsy. The tumor size was determined as the largest tumor on the CT section, stated in cm. The survival time was defined as the period from the date of diagnosis 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 PET/CT scans with Biograph 6 PET/CT (Siemens Medical Systems, CTI, Knoxville, TN, USA). All patients fasted for at least 6 hrs and glucose levels in peripheral blood in all patients were confirmed to be ≤140 mg/dl before FDG injection. Approximately 5.5 MBq/kg of FDG was administered intravenously 1 hr 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).

Statistical methods

All data were analysed using SPSS23.0 (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. 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. 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 odds ratio was used to define the most important risk factor among the categorical significant risk factors. The Kaplan-Meier (product limit method)-Log Rank (Mantel-Cox) analysis was used to analyze the effects of the factors on the mortality and survival time. The relationship between the classification by the cut off values calculated according to variables of the groups and the real classification, their sensitivity and specificity values were analyzed and stated through ROC (Receiver Operating Curve). 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 21 patients, comprising 7 (33.3%) males and 14 (66.7%) females, with a mean age of 61.9±15.1 years (range, 22-80 years). Tumors were determined in the left kidneys of 16 (76.2%) patients and in the right kidneys of 5 (23.8%) patients. Of these patients, 18 (85.7%) were diagnosed with clear cell carcinoma, 2 (9.5%) were diagnosed with papillary carcinoma, and 1 (4.8%) was diagnosed with renal cell car-

TABLE I - *Demographic, tumor and pathological features of the patients included in the study*

		N.	%
Gender	**Female**	7	**33.3%**
	Male	14	66.7%
Mortality	Alive	7	33.0%
	Dead	14	66.7%
Primary Localization	right kidney	5	23.8%
	left kidney	16	76.2%
Pathological diagnosis	clear cell	18	85.7%
	papillary	2	9.5%
	renal cell	1	4.8%
TNM Stage	Stage I	7	33.3%
	Stage II	8	38.1%
	Stage III	3	14.3%
	Stage IV	3	14.3%
		Mean ± SD.	**Median (Max-Min)**
Age		61.9±15.1	66 (80-22)
Survival (Day)		941.9±851.01	995 (3023-8)
The highest SUVmax in the primary lesion		6,01±5,2	4.7 (26-1.5)
Tm Size (cm)		6.1±3.2	5 (12-2)

SD.: Standard Deviation

cinoma (Table I). The mean survival time of the patients was 941.9±851.01 days (range, 8-3023 days). The mean SUVmax value of the patients, which was measured via PET/CT, was 6.01±5.2(range, 1.5-26). The mean tumor size was 6.1±3.2 cm (range, 2-12 cm) (Table I).When the patients were evaluated according to the TNM classification, most patients were determined to be at stage 2 (38. 1%) followed by stage 1 (33.3%) (Table I).

The mean age of the male patients was 63.7±10.99 years and of the female patients, 58.3±21.78 years. The mean age of males was not found to be statistically significantly higher than that of females (p=0.500) (Table II). The mean survival time of females was 1,417.3±941.78 days and of males was 704.2±722.71 days. No statistically significant difference was determined (p=0.078) (Table II). Of the patients who died, 12 (85.7%) were male and 2 (14.3%) were female. According to the Odds ratio (confidence interval) calculation, the mortality of males was 12-fold (1.2-115.36) higher than that of females.

According to the highest SUVmax values in the primary lesion, the mean SUVmax value in living patients was 2.85 (4.4-1.5), while it was determined as 6.35 (26-2.3) in patients who died. The higher mean SUVmax values of the patients who died was found to be statistically significant (p=0.001) (Table III).

The mean age of the patients with right kidney tumor was 68.8±12.38 years, and of the patients with left kid-

TABLE II - *Tumor and Localization Features of the Patients by Gender*

		Gender		
		Female	**Male**	**P Value**
Age*		58.3±21.78	63.7±10.99	0.500
Survival (days)*		1,417.3±941.78	704.2±722.71	0.078
Mortality	Alive	4 (66.7)	2 (14.3)	**0.037**
	Dead	2 (33.3)	12 (85.7)º	12 (1.2-115.36) [a]
The highest SUVmax in the primary lesion**		3.8 (9-1.5)	5.65 (26-1.8)	0.085
Tm Size (cm)*		4.6±2.88	6.9±3.15	0.132
Primary Localization	right kidney	1 (14.3)	4 (28.6)	0.624
	left kidney	6 (85.7)	10 (71.4)	

Fisher Exact Test(Exact) - Independent T Test(Bootstrap) - Mann Whitney U Test(Monte Carlo)
º Reference for Odds Ratio [a] Odds ratio(Confidence Interval); *Mean ± Standard deviation; **Median (Maximum-Minimum)

TABLE III: *Classification of Mortality According to Tumor Characteristics*

	Mortality		
	Alive	**Dead**	**P Value**
Age	53.0±21.12	64.4±10.49	0.227
Survival (days)	1,720.8±337.51	459.4±454.44	**0.001**
The highest SUVmax in the primary lesion	2.85 (4.4-1.5)	6.35 (26-2.3)	**0.001**
Tm Size (cm)	5.8±4.01	6.5±2.80	0.708
Primary Localization	right kidney	1 (16.7)	3 (21.4) 1
	left kidney	5 (83.3)	11 (78.6)

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

TABLE IV - *Evaluation of Tumor Localisation According to Tumor Characteristics*

	Primary Localization		
	Right kidney	**Left kidney**	**P Value**
Age	68.8±12.38	59.8±15.55	0.252
Survival (days)	1,202.6±1,267.71	860.4±712.28	0.582
The highest SUVmax in the primary lesion	4.7 (26-1.6)	4.9 (10-1.5)	0.700
Tm Size (cm)	7.8±4.15	5.6±2.76	0.182

*Independent T Test(Bootstrap) - Mann Whitney U Test(Monte Carlo) - *Mean ± Standard deviation; **Median (Maximum-Minimum)*

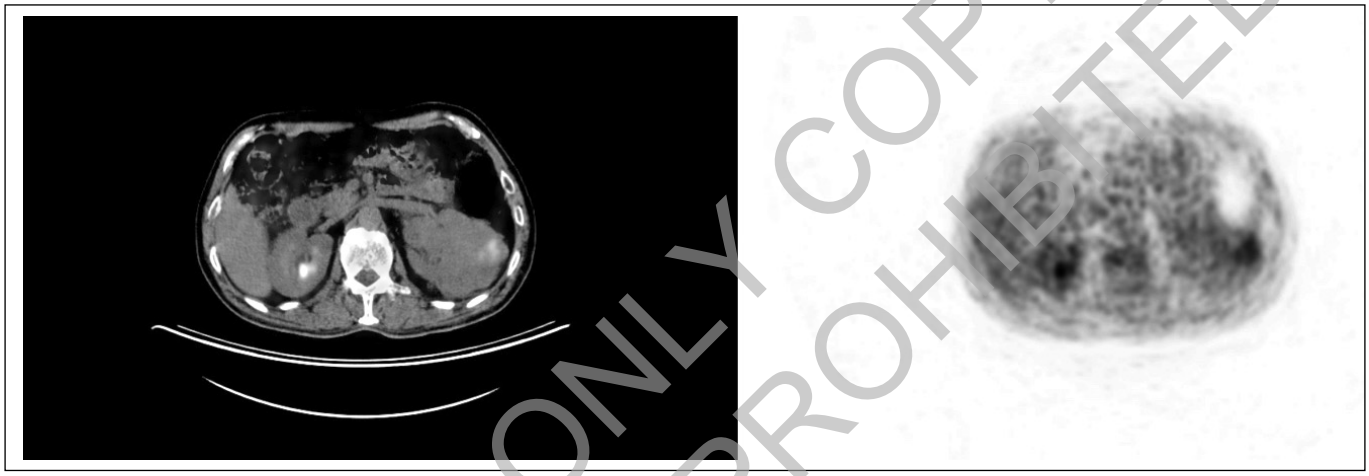

Fig. 1: 7*6,5 cm mass (SUVMax: 6.6) in the left kidney in PET/CT imaging was determined 66-years-old male patient's survival was calculated as 700 days.

ney tumor, 59.8±15.55 years. The older age of patients with right kidney tumor was not found to be statistically significant (p=0.252) (Table IV) (Fig. 1).

The mean life expectancy of the patients with right kidney tumor was 1,202.6±1,267.71 days and of the patients with left kidney tumor, 860.4±712.28 days. The longer life expectancy of patients with right kidney tumor was not found to be statistically significant (p=0.582) (Table I, V).

The mean SUVmax value of the patients with right kidney tumor, measured with PET/CT, was 4.7 (range, 1.6-26) and of the patients with left kidney tumor, 4.9 (range, 1.5-10). The lower SUVmax value of the patients with right kidney tumor was not found to be statistically significant (p=0.700) (Table II).

The mean tumor size of the right kidney tumors was 7.8±4.15 cm and of the left kidney tumors was 5.6±2.76 cm. The larger tumor size of the right kidney tumors was not found to be statistically significant (p=0.182) (Table IV). A negative correlation was determined between age and survival (r=-0.153). No statistically significant relationship was found between these two values (p=0.507)(Table V). A negative correlation was determined between age and SUVmax value (r=-0.081). No statistically significant relationship was found between these two values (p=0.726) (Table V). A negative correlation was determined between age and tumor size (r=-0.071). No statistically significant relationship was found between these two values (p=0.761) (Table V). A negative correlation was determined between survival and SUVmax value (r=-0.694). The decrease of SUVmax value with increasing survival was found to be statistically significant (p<0.001)(Table V). A negative correlation was determined between survival and tumor size (r=-0.305). No statistically significant relationship was found between these two values (p=0.180). A positive correlation was determined between SUVmax value and tumor size (r=0.221). No statistically significant relationship was found between these two values (p=0.336) (Table V).

The estimated life expectancy of female patients was 1,380.7±309.16 days and of male patients, 735.7±201.29 days. The longer life expectancy of female patients compared to males was found to be statistically significant (p=0.048) (Table VI). The estimated life expectancy of patients with right kidney tumor was 747.5±377.99 days and of patients with left kidney tumor, 1,029.8±222.13

TABLE V - *The Correlation Comparison of Tumor Characteristics*

Correlation	r	P	
Age	Survival (days)	-.153	0.507
Age	The highest SUVmax in the primary lesion	-.081	0.726
Age	Tm Size (cm)	-.071	0.761
Survival (days)	The highest SUVmax in the primary lesion	-.694**	<0.001
Survival (days)	Tm Size (cm)	-.305	0.180
The highest SUVmax in the primary lesion	Tm Size (cm)	.221	0.336

Pearson Correlation Test - Spearman's rho Test r: Correlation Coefficient

TABLE VI - *Evaluation of Estimated Life Expectancy According to Gender and Localization*

		Estimated Life Expectancy Mean ± SD	P Value
Gender			
	Female	1.380.7±309.16	**0.048**
	Male	735.7±201.29	
Primary Localization			
	right kidney	747.5±377.99	0.677
	left kidney	1,029.8±222.13	

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

TABLE VII. *The effect of SUVmax value of the tumor on mortality*

The highest SUVmax in the primary lesion	Mortality				
	Alive	Dead	AUC±Se	Odds Ratio (95% CI)	P Value[b]
4.5>	6(100)**	2(14.3)	0.952±0.045	4 (1.2-13.3)	0.002
4.5<	0(0)	12(85.7)	5		

Roc(Receiver Operating Curve) Analysis; AUC: Area under the ROC curve; Se: Standard Error; CI: Confidence Interval
*Sensitivity; **Specificity; °Significant Odds Ratio; [b]P Value for Cut Off

days. The longer life expectancy of patients with left kidney tumor was not found to be statistically significant (p=0.677)(Table VI).

The cut-off value was calculated as 4.5 in the SUVmax calculation according to mortality. This sensitivity of this value was 85.7%, specificity was 100% and AUC±Se value was 0.952±0.045 and this cut-off value was found to be statistically significant in mortality differentiation (p=0.002). The mortality rate of patients with SUVmax value of >4.5 was found to be 4 (1.2-13.3) times higher.

Discussion

In the present study, which analysed the relationship between the SUVmax values measured with PET/CT and the survival and mortality, it was determined that (a) the lower the SUVmax value, the longer the survival (b) female patients had a longer life expectancy(c) the risk of mortality in male patients was 12 times greater than in female patients(d) mortality increased 4 -fold when the SUVmax value was ≥4.5(e) the right kidney tumors were larger than the left kidney tumors (f) the survival time of patients with right kidney tumor was longer, but this finding was not statistically significant (g)with increased age, the survival time was shorter, SUVmax value was lower and tumor size was smaller, but these findings were not statistically significant (h) the smaller the tumor size, the longer the survival, but this finding was not statistically significant (i) the SUVmax value measured in left kidney tumors was higher than that of right kidney

tumors, but this finding was not statistically significant.

PET/CT is commonly used in the evaluation of tumor metabolism in cancer patients. F-18 may restrict the elimination of FDG from the body through the kidneys and thereby limit the use of PET/CT for the evaluation of urinary system malignancies. However, the tomographic imaging feature of PET/CT enables detailed evaluation of anatomic detail and decreases findings of false positivity [19,20]. The present study focused on the effect on survival and mortality of SUVmax values measured with the advantages of these features of PET/CT. It was determined that survival time was prolonged and patients lived longer with decreasing SUVmax values. With this in mind, it can be considered that survival can be estimated via SUVmax values determined before treatment. The cut-off value was calculated as 4.5 in the SUVmax value calculation according to mortality. This sensitivity of this value was 85.7%, specificity was 100% and AUC±Se value was 0.952±0.045 and this cut-off value was found to be statistically significant in mortality differentiation (p=0.002). The mortality rates of patients with SUVmax value of >4.5 were found to be 4 (1.2-13.3) times higher. When the patients were evaluated according to the TNM classification, most patients were determined to be at stage 2 (38.1%) followed by stage 1 (33.3%).

PET/CT has been reported to have sensitivity of 90%, specificity of 91%, accuracy of 90%, positive predictive value of 95% and negative predictive value of 81% in the diagnosis and staging of kidney tumors [21,22]. As the entire body can be scanned with a single examination, it is possible to determine systemic metastases particularly in the bones [23]. PET/CT sensitivity has been reported to be between 60%-70% and specificity to be between 90%-100% in the determination of lymph node metastases [24]. With all these features, PET/CT can be considered to be an effective method in the diagnosis and staging of kidney tumors.

In a study by Onishi et al., cell reproduction was analyzed via PET/CT in renal cell carcinoma and PET/CT was determined to be very successful in the follow-up of cell reproduction in kidney tumors [25].

In a study by Ramdave et al., the treatment decisions were reported to be changed following the PET/CT examination of 6 patients for whom radical nephrectomy had been planned with the pre-diagnosis of kidney tumor with conventional methods. Partial nephrectomy was applied to 3 patients and conservative follow-up as a result of benign tumor diagnosis was decided for the other 3 patients [26].

In a study by Mizuno et al., PET/CT was used in the estimation of the biological properties of kidney tumors. As a result of the study, higher stage tumors were determined with increasing SUVmax values [27]. In the present study, it was determined that the higher the SUVmax values, the shorter the survival, female patients lived longer, right kidney tumors were larger than left kidney tumors and patients with right kidney tumor lived longer. In addition, it was seen that the mortality risk for males was 12 times greater than that of females. Another remarkable finding of the study was a 4-fold higher mortality rate of patients with SUVmax value of >4.5 with 87.5% sensitivity, 100% specificity and AUC±Se value of 0.952±0.045.

Conclusions

The results of this study showed that survival increased with decreasing SUVmax values, mortality increased with SUVmax values of ≥4.5 and with a smaller tumor size, survival increased. The use of PET/CT in patients with kidney tumor can be considered to contribute to the estimations of mortality and survival. However, further studies are needed to define SUVmax as an independent prognostic factor.

Riassunto

Scopo del lavoro: L'uso della tomografia PET/CT nei tumori renali è stato grandemente utilizzato negli anni recenti. Ci sono stati pochi studi sugli effetti dei valori massimi della Standard Uptake (SUVmax) rilevati con la PET/CT sulla stima della mortalità e della sopravvivenza dei pazienti con tumori renali.

Con questo studio si spera di contribuire alle conoscenze in letteratura sulla prognosi della mortalità e della sopravvivenza di pazienti con tumori renali mediante la ricerca basata sulla SUVmax misurata con PET/CT.

Materiali e metodo: Si tratta di una ricerca retrospettiva sulle cartelle cliniche di pazienti con tumore renale di recente diagnosi, e con stadiazione determinata con PET/CT nel Dipartimento di Medicina Nucleare della Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital tra Agosto 2007 e Aprile 2012.

La grandezza del tumore è stata considerata quella massima rilevata con CT e definita in cm. La durata della sopravvivenza è stato definito come l'intervallo tra la data di esecuzione della PET/CT, considerata al momento del calcolo della sopravvivenza, e la data del decesso comunicata dal MERNIS (The Central Civil Registration System) o dalla data dell'ultimo contatto con il paziente ancora vivo.

Risultati: Il minor valore di SUVmax del tumore renale corrisponde al maggiore periodo di sopravvivenza. Il rischio di mortalità dei pazienti maschi è stato 12 volte maggiore di quello della donne, con mortalità accresciuta di 4 volte quando i valori di SUVmax erano ≥4.5. I pazienti con tumore del rene destro hanno avuto una sopravvivenza più lunga, mentre l'aumento dell'età corri-

sponde ad una sopravvivenza più breve. I valori di SUVmax e le dimensioni dei tumori del rene sinistro erano maggiori di quelli misurati nei tumori del rene destro. CONCLUSIONI: Con questo studio si conclude che i valori inferiori di SUVmax e le minori dimensioni del tumore corrispondono alla maggiore durata della sopravvivenza. L'incidenza della mortalità risulta accresciuta quando i valori di SUVmax erano ≥ 4.5 (p=0.001).
L'uso della PETR/CT può essere considerato un contributo alla prognosi di mortalità e sopravvivenza in pazienti con tumori del rene.

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