ORIGINAL RESEARCH

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The Prognostic Significance of Metabolic Tumor Volume and Total Lesion Glycolysis Measured by 18F-FDG PET/CT in Patients with Non-Small Cell Lung Cancer

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ABSTRACT Objective: This study aims to determine the prognostic value of metabolic volumetric 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) parameters of the primary tumor, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) in patients with non-small cell lung cancer (NSCLC). **Material and Methods:** The study included a total of 102 patients who underwent PET/CT for staging. Histopathological diagnosis, stage of disease, survival time, maximum standard uptake value, MTV, and TLG values of the primary tumor were documented. The Kaplan-Meier test was used to examine the relationships between overall survival (OS) with PET/CT parameters and Tumor-Node-Metastasis stages. Univariate and multivariate Cox regression analyses were applied, and the association between OS with metabolic volumetric PET/CT parameters was estimated. **Results:** During the follow-up period, 93 (91.17%) patients died. All patients had a median OS of 10.15 months (range 0.5-74 months), whereas patients with M1 disease had a median OS of 7 months (range 0.5-56). The majority of (79.41%) patients had advanced-stage disease. The mean MTV ($p=0.012$) and TLG ($p=0.037$) values at the early stage (Stage I-II) were significantly lower than the locally advanced and advanced (Stage III-IV) stage. In univariate analysis, elder age ($p=0.004$), advanced stage ($p<0.001$), lack of the operable ($p<0.001$), high MTV ($p<0.001$), and TLG ($p<0.001$) values were significantly correlated with poor OS. In multivariate analysis, stage of the disease ($p<0.05$), age ($p=0.004$), operable ($p=0.022$), and TLG ($p=0.0019$) values were found to be the independent predictors for OS. **Conclusion:** In patients with NSCLC, MTV and TLG of the primary tumor are suitable parameters to predict prognosis at initial staging. Particularly high level of TLG was independently related to poor prognosis.

Keywords: Positron-emission tomography; survival rate; non-small cell lung carcinoma

Lung cancer is a common disease worldwide with a high disease-specific mortality rate and poor prognosis.[1] The majority of lung cancer patients (80-85%) present the non-small cell lung cancer (NSCLC) subtype having a 5-year survival rate at <50%.[2] Treatment modalities of patients are determined by the stage of disease.[3,4]

The imaging tool, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), is used to stage numerous malignancies.[5,6] Several studies have shown whether metabolic PET/CT parameters are prognostic determinants.[7] The literature has stated that metabolic PET/CT parameters are prognostic predictors to predict the clinical course.[8-10] PET/CT scanners execute whole-body imaging and can provide information about metabolic tumor volume (MTV).[11] Total lesion glycolysis (TLG) and MTV are three-dimensional (3D) measures, including both tumor volume and metabolic activity.[10] The maximum standard uptake value (SUVmax) represents the maximum metabolic activity of the tumor, reflecting the most active parts in

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the tumor.[12-14] Studies have shown that MTV and TLG are significant prognostic predictors in NSCLC.[9,11,15-18]

It is crucial to predict the prognosis independent of the stage at the initial staging of lung cancer. Although it has been highlighted in various studies that metabolic PET/CT parameters predict prognosis irrespective of stage in NSCLC, the only factor used in the decision of operation and treatment modality is the Tumor-Node-Metastasis (TNM)-8 staging system, which does not contain metabolic PET/CT parameters of primary tumor tissue. Stage-independent risk scoring of patients should be accomplished, and metabolic PET/CT parameters may play a significant role. This current study aims to show the role of metabolic PET/CT parameters in predicting prognosis in the initial staging of NSCLC patients.

MATERIAL AND METHODS

The current research was approved by the Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Approval date: 14.04.2016, Approval Number: 53043469-050.04.04), and written informed consent was obtained from all patients. This study was carried out following the Declaration of Helsinki Principles.

All patients with NSCLC who had PET/CT scanning for staging between April 2013 and March 2016 were assessed retrospectively. The followings were the exclusion criteria: history of other malignancies, previous chemotherapy/radiotherapy, and an operation. Patients with incomplete clinical-survival data, as well as the unknown clinical follow-up, were excluded. Overall survival (OS) was calculated from the initial PET/CT date to the time of death or last follow-up. There were 102 patients in this study, including 96 men and 6 women.

Demographic characteristics such as age and gender, clinical and pathological variables, and follow-up data were acquired from electronic medical records. Clinical staging was dependent on initial PET/CT results according to the 8th edition of the TNM classification system for lung cancer.[3] The presence of lymph nodes and distant metastases was determined through histopathological diagnosis or according to radiological imaging methods except PET/CT imaging.

PET/CT images were developed using the Siemens (Syngo.Via, Siemens, Erlangen, Germany) Biograph mCT PET/CT scanner. All the patients fasted for at least 6 hours before intravenous administration of 270-370 MBq of 18F-FDG. All the patients' pre-imaging fasting blood glucose levels were recorded to be <200 mg/dL. Consequently, the patients rested in a quiet room for about one hour and underwent PET/CT scanning from the head to the 1/3 proximal of the femur. CT scan data were taken with an average of 120 kV and 50 mAs, though the CT scan data varied slightly for some patients (particularly for overweight and cachectic patients) to improve image quality. PET data were collected at a rate of 2 min per-frame.

All images were visually and semi-quantitatively reviewed by two nuclear medicine physicians. The volume of interest (VOI) was drawn on the fusion slices of the PET/CT to measure SUVmax-mean, MTV, and TLG values of the tumor tissue. MTV was determined automatically in the software program, with a threshold value of >40% of SUVmax.[19] TLG was calculated automatically as follows: TLG= MTVxSUVmean.

STATISTICAL ANALYSIS

For statistical analysis, For statistical analysis, IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY) was used. The Kolmogorov-Smirnov test was used to evaluate whether the quantitative variables were normally distributed. Independent Samples t-test and Mann-Whitney U test were employed for variables displaying normal and non-normal distribution, respectively. Descriptive statistics for normally and non-normally distributed quantitative variables were calculated as mean±standard deviation and median (25-75 percentiles), respectively. The chi-square test was applied to decide the dependence between qualitative variables. The predictors of survival were analyzed by the Kaplan-Meier method. Cox regression analysis was applied to determine the effects of survival factors. The cut-off values for MTV and TLG variables were identified by receiver operating characteristics (ROC) analysis. The value of $p<0.05$ were considered statistically significant.

RESULTS

A total of 102 patients were included in the study, with a mean age of 67.44±9.9 years (range: 40-89). Table 1 represents the demographic-clinicopathologic characteristics, metabolic PET/CT parameters, survival time in all patients and patients with distant metastases.

The majority of the patients (99%) had a smoking history. The histopathological subtypes were classified into subgroups, with squamous cell carcinoma (SCC) being the most common (69.6%). About 49% of patients were in Stage IV disease. Though the - SUVmax of the primary tumor was higher in the SCC subtype (15.72±6.01) than in adenocarcinoma (13.35±7.94) (p=0.012), there was no association between histopathological subtypes and the MTV and TLG values. It is found that 44.4% of patients who survived were in Stage I disease, and 52.7% of patients with Stage IV disease died during follow-up.

The median survival time for all patients was 10.15 months [95% confidence interval (CI) range: 4.88-21.25], whereas 7.00 months (range: 3.50-14.00) for patients with distant metastases. A total of 93 (91.2%) patients died, and the survivors had a median follow-up time of 64 (range: 53.50-67.50) months. Thirteen (12.7%) patients had lung cancer surgery at the time of diagnosis, and 5 (38.5%) of them died during the follow-up period. It was determined that only one of the surviving patients did not undergo surgery. The values of MTV and TLG of the primary tumor tissue were lower in operable patients than in inoperable patients (all p=0.001). Survival times were longer in operable patients than that in inoperable patients (p<0.001). Figure 1

TABLE 1: Patient characteristics.

Variables	All patients (n=102, 100%)	Patients with M1 (n=50, 49%)
Age (mean±SD)	67.44±9.9	69.90±10.27
Gender		
Men	96 (94.1%)	44 (88.0%)
Women	6 (5.9%)	6 (12.0%)
SUVmax	13.56 (10.30-18.14)	13.56 (10.60-17.51)
SUVmean	8.24 (5.88-10.13)	7.98 (6.10-9.85)
MTV (cm^3)	37.25 (16.19-82.52)	37.27 (20.80-80.88)
TLG (g)	258.30 (148.01-681.75)	263.70 (154.06-707.70)
Histopathology		
SCC	71 (69.6%)	33 (66.0%)
Adenocarcinoma	31 (30.4%)	17 (34.0%)
Operation		
No (-)	89 (87.3%)	50 (100%)
Yes (+)	13 (12.7%)	0 (0%)
Stage (TNM-8)		
I-II	11 (10.8%)	0 (0%)
III	41 (40.2%)	0 (0%)
IV	50 (49.0%)	50 (100%)
Surviving status of patients		
Non-surviving	93 (91.2%)	49 (98%)
Surviving	9 (8.8%)	1 (2%)
OS (month)	10.15 (4.88-21.25)	7.00 (3.50-14.00)

SD: Standard deviation; SUV: Standard uptake value; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis; SCC: Squamous cell carcinoma; TNM-8: Tumor-Node-Metastasis-8; OS: Overall survival.

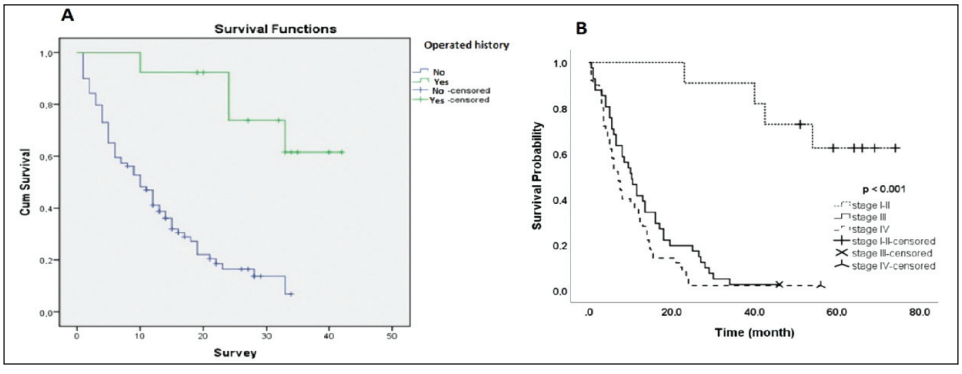

FIGURE 1: Kaplan-Meier curve of overall survival in patients with operated/non-operated patients (A) and Kaplan-Meier curve of overall survival according to the Tumor-Node-Metastasis-8 staging system (B).

shows the Kaplan-Meier OS curve of operated and non-operated patients and with history and the Kaplan-Meier OS curve according to the TNM-8 staging system.

As per the ROC analysis, the MTV and TLG of the primary tumor tissue cut-off values for evaluating prognosis were 22.05 cm^3 and 199.55 g, respectively. In the ROC curve, SUVmax-SUVmean was not significant. The sensitivity and specificity of MTV found to be were 73.1 and 88.9 cm^3 [area under curve (AUC)=0.739, 95% CI, 0.639-0.818], TLG values were 67.7 and 88.9 g (AUC=0.757, 95% CI, 0.663-0.837), respectively. The cut-off MTV ($p<0.001$) and TLG ($p=0.002$) values could forecast prognosis significantly (Figure 2).

The Kaplan-Meier survival analysis for MTV ($p<0.001$) and TLG ($p<0.001$) showed significant differences in OS. Shorter OS was detected when the MTV of the primary tumor tissue was >22.05 cm^3, and the TLG of the primary tumor tissue was >199.55 g. There was no significant relationship between-SUVmax and OS ($p=0.24$). The Kaplan-Meier curves of OS according to the cut-off MTV and TLG values of the primary tumor tissue are presented in Figure 3.

The median MTV ($p=0.02$) and TLG ($p=0.01$) were significantly lower in surviving patients as compared tothe non-surviving patients. Table 2 shows metabolic PET/CT parameters, stage distribution, and survival times in surviving and dead patients.

Univariate analysis revealed that early-stage disease, young age, operability, and low MTV/TLG values were all good prognostic predictors. Multi-

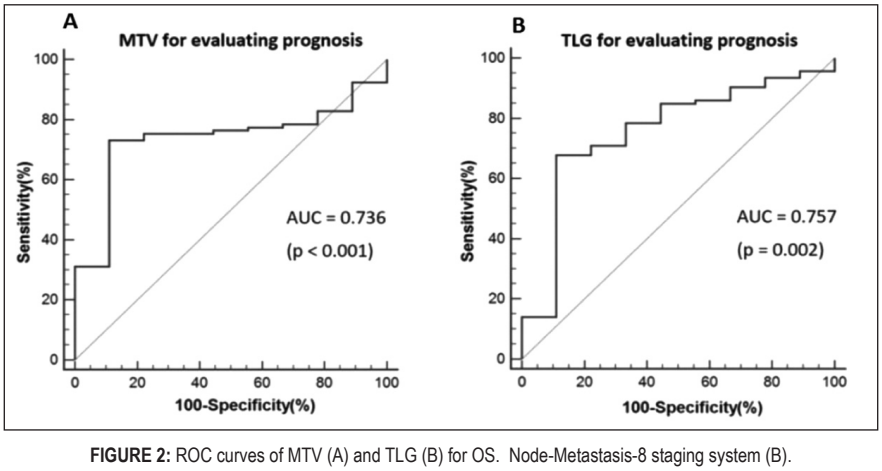

FIGURE 2: ROC curves of MTV (A) and TLG (B) for OS. Node-Metastasis-8 staging system (B).
ROC: Receiver operating characteristics; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis; OS: Overall survival; AUC: Area under curve.

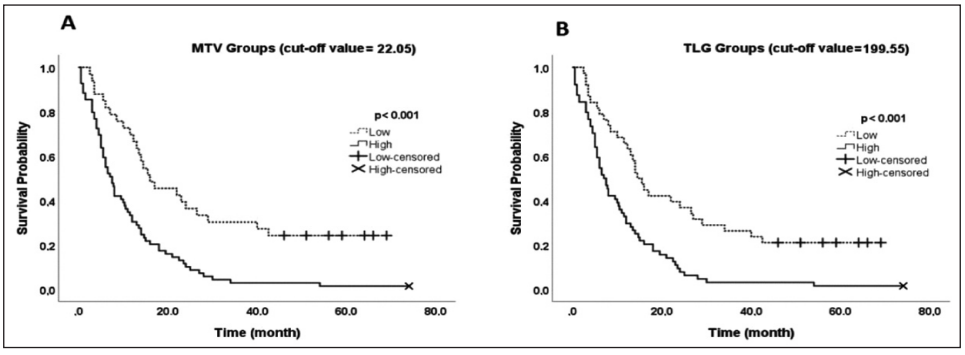

FIGURE 3: Kaplan-Meier curves of overall survival according to MTV (A) and TLG (B).
MTV: Metabolic tumor volume; TLG: Total lesion glycolysis.lesion glycolysis; OS: Overall survival; AUC: Area under curve.

TABLE 2: Metabolic PET/CT and clinical parameters in surviving and non-surviving patients.

	Surviving patients (n=9, 8.8%)	Non-surviving patients (n=93, 91.2%)	p value
Age (mean±SD)	64.22±12.32	69.96±10.03	0.112
Gender			
Men	8 (8.5%)	86 (91.5%)	0.536
Women	1 (12.5%)	7 (87.5%)	
SUVmax	13.62 (7.13-18.07)	13.51 (10.59-18.19)	0.392
MTV (cm^3)	17.47 (13.11-21.30)	39.21 (20.05-85.94)	**0.020**
TLG (g)	96.79 (47.61-184.90)	316.23 (155.57-720.86)	**0.011**
Stage			
I-II	7 (63.6%)	4 (36.4%)	**<0.001**
III-IV	2 (2.2%)	89 (97.8%)	
OS (months)	64.00 (53.50-67.50)	8.00 (4.25-15.75)	**<0.001**

PET/CT: Positron emission tomography/computed tomography; SD: Standard deviation; SUV: Standard uptake value; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis; OS: Overall survival.

TABLE 3: Univariate and multivariate analyses of clinical and metabolic PET/CT parameters.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Stage of disease				
Stage I-II (n=11) vs. Stage III (n=41)	9.821 (3.364-28.669)	**<0.001**	4.762 (1.269-7.872)	**0.021**
Stage I-II (n=11) vs. Stage IV (n=50)	14.154 (4.850-41.307)	**<0.001**	5.853 (1.514-2.632)	**0.010**
Gender				
Women vs. men	0.978 (0.452-2.117)	0.955		**0.981**
Age (1 year increase)	1.031 (1.010-1053)	**0.004**	1.031 (1.010-1052)	**0.004**
SUVmax				
≤8.91 vs. >8.91	1.414 (0.783-2.551)	0.250		0.213
SUVmean				
≤5.50 vs. >5.50	1.151 (0.686-1.929)	0.595		0.681
MTV (cm3)				
≤22.05 vs. >22.05	2.575 (1.605-4.129)	**<0.001**		0.089
TLG (g)				
≤199.55 vs. >199.55	2.408 (1.535-3.778)	**<0.001**	1.736 (1.095-2.752)	**0.019**
Operation				
Operation history (n=13) vs. no operation (n=89)	10.262 (4.025-26.165)	**<0.001**	3.867 (1.218-2.275)	**0.022**

PET/CT: Positron emission tomography/computed tomography; HR: Hazard ratio; CF: Confidence interval; SUV: Standard uptake value; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis.

variate analysis revealed that only disease stage, age, TLG value, and operability were independent factors for OS. Table 3 shows univariate and multivariate analyses of clinical and metabolic PET/CT parameters.

Investigation of the association between the disease stage and metabolic PET/CT parameters of tumor tissue showed that MTV (p=0.012) and TLG (p=0.037) were lower in early-stage disease (Stage I-II) compared to locally advanced (Stage III) and advanced (Stage IV) stage disease. The mean MTV and TLG values were 22.32 cm^3±18.56 and 232.27 g±294.45 in patients at Stage I-II, respectively, whereas the corresponding values in patients at Stage III-IV were 68.28 cm^3±73.90 and 569.69 g±61.21. On the other hand, no correlation was obtained between SUVmax and SUVmean with the stage of the disease.

DISCUSSION

Lung cancer has the highest risk of cancer-related death in both men and women. Numerous studies have been conducted to determine the efficacy of several laboratory-pathological markers to predict prognosis in lung cancer. The disease stage remains the most significant prognostic factor for predicting clinical outcomes in lung cancer patients.[3,4] Furthermore, other patient-specific characteristics, including age, gender, smoking history, performance status, pulmonary reserve, and comorbid diseases, are predictive factors for prognosis. Even though these factors are not included in the staging system, they have a significant impact on patient treatment procedures. Moreover, considering the extensive use of 18F-FDG PET/CT in lung cancer, changes in biological behaviors across tumors can be determined with studies assessing their role in survival prediction.[20]

The prognostic significance of metabolic PET/CT parameters of primary tumor tissue in NSCLC patients who had surgery history or received adjuvant chemotherapy/radiotherapy was evaluated. MTV and TLG values were found to be important prognostic predictors in the initial staging of patients with NSCLC. MTV and TLG values more effectively reflected the metabolic tumor burden than SUVmax or SUVmean.[9,16,21] The SUVmax is insufficient to assess the metabolic activity of the tumor tissue as a whole.[16] Furthermore, there are numerous factors associated with SUVmax having several variability sources, which are both biological (patient's weight, fasting blood glucose level, fasting time before imaging) and technological (PET/CT device features, amount of radioactive material given, time until extraction after injection, how VOI or region of interest is drawn in the tumor). Nevertheless, these factors do not affect MTV and TLG values significantly. Additionally, SUVmax only accounts for the most active parts in the VOI rather than the entire tumor metabolic volume, which can be confusing.[13,14]

Many studies have shown that metabolic PET/CT parameters can help predict survival in many different cancer types.[8-11,15,17,21] Numerous studies have demonstrated that metabolic parameters such as MTV and TLG can provide better prognostic data than SUVmax in patients with NSCLC, which is consistent with our findings.[16,19,22] However, Liu et al. reported that high SUVmax in addition to MTV and TLG predicted poor prognosis in operated patients with early-stage NSCLC.[23] Furthermore, subgroup analyses presented that the prognostic values of -SUVmax, MTV, and TLG were similar. Although previous studies show that a higher SUVmax is associated with poor clinical outcomes and tumor aggressiveness, we found no correlation between SUVmax and OS.[23] In contrast to this study, it is concluded that MTV and TLG values are better markers than SUVmax in predicting prognosis in patients with NSCLC. In this meta-analysis, which comprised 36 studies, 80.4% of patients had Stage I disease, 14.2% had Stage II, 4.5% had Stage III disease. Patients with Stage IV disease were not included in the study since only operated patients were included. However, most of our patients had the Stage IV disease (49%) and a few (12.7%) with surgery history. When the histopathological subgroup analysis was observed, studies that involved only patients who had adenocarcinoma or SCLC diagnosis together with NSCLC histopathological type were incorporated in the meta-

analysis.[23] The cause for this difference could be attributed to the differences in stage distribution, and the study included all histopathological subtypes of NSCLC, and the SCLC patients were excluded from the study.

Davison et al. reported that the metabolic PET/CT parameters were higher in patients who died by evaluating the survival status in NSCLC patients from baseline scanning data.[24] Similar to our study, this study also found no correlation between SUVmax and survey. Although the distribution of stages in this study differed from our study (26% Stage I, 15% Stage II, 41% Stage III, 18% Stage IV), all stages were included, and when the histopathological subgroup was examined, only NSCLC patients like ours were included in the study. When compared to other research with similar patient groups, our findings support the literature. SUVmax is a metabolic parameter that can be influenced by numerous factors.[14] MTV and TLG values, which comprise 3D volumetric values and the metabolic properties of the tumor, should be considered, especially in the clinical course and prognostic estimation.

It is found that the high MTV and TLG values were found in patients with the advanced stage disease than the early stage. However, there was no relationship between SUVmax and the stage of the disease. According to Cerfolio et al., the SUVmax increased as stages increased in early-stage NSCLC patients.[7] However, they didn' t estimate the relationship between metabolic parameters with the disease stage. These discrepancies could be explained by the fact that all their patients were at the early stage, and all patients were operated on; moreover, they did not include patients with stage 3B/C-4A/B disease. In our study, the majority of the patients were in advanced stages, and the number of patients who underwent surgery was limited (12.7%).

According to the literature, SUVmax is higher in SCC than adenocarcinoma, which is consistent with our results.[25] A significant correlation was found between SUVmax and the histopathological group. A prior study stated that the high MTV and TLG values were significantly higher in patients with SCC than others.[26] FDG affinity and SUVmax are lower in some adenocarcinoma subtypes, such as those with a lepidic/acinar pattern than in others. The FDG affinity of SCC is higher than that of adenocarcinoma; furthermore, differences in the proportion of each histopathological subgroup could have resulted from different outcomes.

Our study has some limitations, like it is a retrospective design and includes different histopathological subtypes such as adenocarcinoma and SCC. Different histopathological subtypes have different FDG affinities. We involved patients of all stages due to the limited number of patients. When we look at the distribution of the stages, the patients with the advanced-stage disease make up the largest group. Although it is more valuable to evaluate patients at the same stage in survival evaluation, our findings suggest that MTV and TLG can be prognostic markers at the time of diagnosis, regardless of the stage of NSCLC.

CONCLUSION

The study findings, like those of many other studies, reveal that MTV and TLG are significant prognostic indicators in NSCLC patients at the time of diagnosis. Particularly, TLG predicts prognosis regardless of disease stage and other clinicopathological factors. It is clear that early prediction of the prognosis will not only contribute to the course of the patients in this process but will also help us in the treatment decision. Since these parameters can determine the prognosis independent of the stage of the disease, they should not lose their currency as they can guide the clinician in choosing treatment, recognizing patients who need closer follow-up, and foretelling the clinical course. Well-designed studies investigating numerous patients in a single histopathological subgroup, including enough patients at each stage, are required to determine the optimal cut-off for metabolic PET/CT parameters on risk stratification for death or recurrence.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sibel Göksel, Arzu Cengiz, Hakan Öztürk, Yakup Yürekli;* ***Design:*** *Sibel Göksel, Arzu Cengiz, Hakan Öztürk, Yakup Yürekli;* ***Control/Supervision:*** *Sibel Göksel, Arzu Cengiz, Yakup Yürekli;* ***Data Collection and/or Processing:*** *Sibel Göksel, Arzu Cengiz;* ***Analysis and/or Interpretation:*** *Sibel Göksel, Hakan Öztürk;* ***Literature Review:*** *Sibel Göksel, Arzu Cengiz, Hakan Öztürk, Yakup Yürekli;* ***Writing the Article:*** *Sibel Göksel, Arzu Cengiz;* ***Critical Review:*** *Sibel Göksel, Arzu Cengiz, Yakup Yürekli;* ***References and Fundings:*** *Sibel Göksel, Arzu Cengiz, Yakup Yürekli;* ***Materials:*** *Sibel Göksel, Arzu Cengiz, Yakup Yürekli.*

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