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The prognostic value of tumor/lymph node standardized uptake value max ratio and correlation with hematologic parameters in stage III nonsmall cell lung cancer

Yusuf Açikgoz, MD[a,*], Fatih Gurler, MD[b], Bediz Kurt Inci, MD[b], Yakup Ergun, MD[a], Gokhan Ucar, MD[a], Merve Dirikoc, MD[a], Selin Akturk Esen, MD[a], Berna Okudan Tekin[d], Oznur Bal[a], Mutlu Dogan, MD[c], Dogan Uncu, MD[a]

Abstract

Stage III non-small cell lung cancer (NSCLC) is a highly heterogeneous subtype of lung cancer. There are still no widely accepted prognostic parameters for stage III NSCLC. In this study, we evaluated the prognostic value of the standardized uptake value (SUV) max ratio of primary tumor to lymph node (T/N SUV max) and its correlation with various hematological parameters.

Patient data were reviewed from the hospital database retrospectively. The T/N SUV max ratio was calculated by dividing the SUV max of the primary tumor by the maximal SUV max of the lymph node. The cut-off value for T/N SUV max ratio was determined by receiver operating characteristic analysis. Survival analysis was performed by Kaplan–Meier method with the Long-rank test. P value $< .05$ was considered statistically significant.

A total of 52 patients were included in this study. The optimal cut-off value for T/N SUV max was 1.96 (area under the curve: 0.74; 72.7% sensitivity and 73.7% specificity). Patients with T/N SUV max $\leq$1.96 were defined as high risk patients and those with $>$1.96 were defined as low risk patients. The median event (recurrence or progression) free survival was 24.3 months (95% confidence interval: 12.0–36.6) for low risk patients, and 9.2 months (95% confidence interval: 6.1–12.4) for high risk patients ($P = .0015$). There was an inverse correlation between T/N SUV max and hemoglobin concentration and mean corpuscular volume (rho: −0.349, $P = .011$; rho: −0.312, $P = .025$, respectively).

Low risk patients had a more favorable prognosis compared to high risk patients. We demonstrated that T/N SUV max can be of prognostic value in stage III NSCLC. T/N SUV max correlated only with hemoglobin and mean corpuscular volume.

Abbreviations: AUC = area under the curve, FDG = fluoro-2-deoxyglucose, HB = hemoglobin, MCV = mean corpuscular volume, NSCLC = nonsmall cell lung cancer, PET/CT = positron emission tomography/computed tomography, ROC = receiver operating characteristic, SUV = standardized uptake value.

Keywords: hemoglobin, lung cancer, positron emission tomography/computed tomography, prognosis, stage III, standardized uptake value max

1. Introduction

Lung cancer is the leading cause of cancer-related death for both genders all over the world.[1] For 2018, it was estimated to account for 18.4% of all cancer-related deaths.[1] Non-small cell lung cancer (NSCLC) constitutes the majority of lung cancer cases with a ratio of approximately 85% to 90%.[2] The 5-year survival rate for all stages is still only19%, while it is 31% for regional disease.[3] Stage III disease constitutes around 20% of all NSCLC cases.[4] Stage III NSCLC is a highly heterogeneous disease in terms of disease extent, treatment modalities, and disease course.[4,5] There are still no widely accepted prognostic factors that might predict the course of the disease.

18F-fluoro-2-deoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) gives valuable information on metabolic activity of tumors through accumulation of tracer 18F-FDG in tumor tissue. In NSCLC, FDG PET has been shown to be a useful tool not only for staging but also for determining prognosis.[6–8] In recent years, various FDG PET metrics, including tumor standardized uptake value (SUV) max to lymph node SUV max ratio (T/N SUV max) have been shown to provide important information regarding staging and

Editor: Jie Li.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] Department of Medical Oncology, Health Science University, Ankara City Hospital, [b] Department of Medical Oncology, Gazi University Medicine Faculty, [c] Department of Medical Oncology, Ankara Dr AY Oncology Training and Research Hospital, [d] Department of Nuclear Medicine, Health Science University, Ankara City Hospital, Ankara, Turkey.

[*] Correspondence: Yusuf Açikgoz, Department of Medical Oncology, Ankara City Hospital, 06100, Ankara, Turkey (e-mail: yacikgoz86@gmail.com).

How to cite this article: Açikgoz Y, Gurler F, Inci BK, Ergun Y, Ucar G, Dirikoc M, Esen SA, Tekin BO, Bal O, Dogan M, Uncu D. The prognostic value of tumor/lymph node standardized uptake value max ratio and correlation with hematologic parameters in stage III nonsmall cell lung cancer. Medicine 2020;99:48(e23168).

Received: 22 July 2020 / Received in final form: 26 September 2020 / Accepted: 8 October 2020

http://dx.doi.org/10.1097/MD.0000000000023168

prognosis of the disease.[9,10] However, some controversy still exists on the prognostic role of FDG PET metrics in NSCLC. While some authors have reported SUV max alone as a potential prognostic parameter, other studies demonstrated the prognostic value of different FDG PET metrics instead of SUV max alone, including metabolic tumor volume, total lesion glycolysis (TLG), and partial-volume-corrected total lesion glycolysis .[11–14] These conflicting results necessitate more accurate and easily accessible FDG PET related prognostic parameters.

Additionally, routine blood analysis is gaining more interest as a prognostic parameter due to features of easy accessibility and reproducibility. In the literature, different prognostic models have been postulated that consist of various combinations of hematological parameters. Of these, neutrophil-lymphocyte ratio, neutrophil-platelet score, and systemic inflammation index have been shown to serve as prognostic parameters for different types of solid tumors.[15–18] Similarly, pretreatment hemoglobin (HB), mean platelet volume, and mean corpuscular volume (MCV) have also been demonstrated to have prognostic and predictive value in lung cancer.[19–23] However, the relationship of FDG PET parameters to hematological parameters and their prognostic value has not been extensively studied up to the present.

In this study, we aimed to assess the prognostic value of T/N SUV max ratio and explore the relationship between T/N SUV max and various hematological parameters in patients with Stage III NSCLC, which is a highly heterogeneous subtype of NSCLC.

2. Materials and methods

2.1. Patients and data

We retrospectively reviewed the clinical records of 259 patients with advanced NSCLC followed up in our center between February 2012 and June 2019. Of these, 52 patients who met the inclusion criteria were included in the study. This retrospective study was approved by the institutional ethics committee of the Health Science University, Ankara City Hospital. The inclusion criteria were as follows:

(1) pathologically confirmed NSCLC,
(2) PET-CT scan results that must have been performed at the time of diagnosis,
(3) complete blood count analysis results that must have been performed before PET-CT scanning,
(4) stage III disease,
(5) available follow-up and survival data.

Patients with confirmed or suspected metastatic disease, known chronic liver or kidney disease, detectable infectious disease or second primary cancer were excluded from the study. Additionally, patients with a SUV max <2.5 were not included in the study.

Data collected from the patient registration database of the hospital included age at diagnosis, smoking history, comorbid disease, histological subtype, PET-CT results, treatment modalities (surgery, chemoradiotherapy, neoadjuvant, or adjuvant treatment), type of surgery, chemotherapy regimens administrated either in neoadjuvant or adjuvant settings or in chemoradiotherapy, results of complete blood count analysis, presence of recurrence, date of recurrence, site of recurrences and survival status. The ratio of SUV max of primary tumor to SUV max of lymph node (T/N SUV max) was calculated by dividing the SUV max of the primary tumor by the highest SUV max of lymph nodes.

Staging was performed according to the 8th edition of the American Joint Committee on Cancer. Chemotherapy regimens were administrated as follows:

(1) cisplatin 80 mg/m^2 on day 1, vinorelbine 30 mg/m^2 on day 1 and 8 every 3 weeks for cisplatin/vinorelbine,
(2) carboplatin area under curve (AUC) 5 on day 1, paclitaxel 75 mg/m^2 on day 1 every 3 weeks for carboplatin/paclitaxel,
(3) cisplatin 75 mg/m^2 on day 1, gemcitabine 1200 mg/m^2 on day 1 and 8 for cisplatin/gemcitabine.

[18F]-2-fluoro-2-deoxy-D-glucose PET-CT imaging was performed after at least 6 hours of fasting, through injection of 144 μ Ci/kg FDG. Blood glucose levels of all patients were <180 mg/dL before scanning. Following the injection, scanning was performed after an average of 60 minutes of resting time. Images were obtained from the orbitomeatal line to the upper thigh as a whole body scan. After attenuation correction with CT, images were analyzed in transaxial, coronal, and sagittal planes, and with additional maximum intensity projection images.

2.2. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Version 22.0 for Windows (SPSS Inc., Chicago, IL). The optimal cut-off value for T/N SUV max was determined by calculating the AUC of receiver operating characteristic (ROC) analysis. In the evaluation of AUC, the maximal joint point of sensitivity and specificity was determined by the Youden Index. Thereafter, patients were divided into 2 subgroups according to cut-off value as a high risk group and a low risk group. Comparison of 2 groups was performed by Mann–Whitney *U* test and Pearson Chi-square or Fisher test for continuous and categorical variables, respectively. Spearman rank correlation analysis was performed for analyzing the correlation between continuous variables and reported as Spearman rank correlation coefficient (rho). Event free survival was described as the time between date of diagnosis to date of recurrence for patients who underwent surgery or to date of progression for patients who were treated with chemoradiotherapy. Univariate and multivariate analyses for event (recurrence or progression) were performed by Cox proportional hazards regression model. We used Kaplan–Meier test for survival analysis, and outcomes were analyzed by Log-rank test. We reported 2-sided *P*-values, and a *P*-value $<.05$ was considered as statistically significant.

3. Results

3.1. Patients and tumor characteristics

A total of 52 patients with stage III NSCLC were included in this study. The median age of the entire cohort was 61 years (41–79), and the number of male patients was 49 (94%). The number of active smokers was 30 (58%) for all patients. There were 23 patients (45%) with adenocarcinoma, and 25 patients (48%) with squamous cell carcinoma. The median size of the primary tumor was 5.6 (1.4–13) for the entire cohort. The number of patients with stage IIIA, stage IIIB, and stage IIIC disease was 12 (23%), 23 (44%), and 17 (33%), respectively. The distribution of clinical T stage was as follows: 7 patients (14%) had cT1 disease, 11patients (21%) had cT2, 15 patients (29%) had cT3 and 19 patients (36%) had cT4 disease. Additionally, the number of patients who had cN1, cN2, and cN3 disease were 6 (12%), 23 (44%), and 23

(44%), respectively. The number of patients who underwent surgery was 24 (46%), and who were treated with chemo-radiotherapy was 28 (54%). Neoadjuvant treatment was given to 25 (48%) patients, and the most commonly used chemotherapy regimen was carboplatin + paclitaxel in neoadjuvant or adjuvant settings or as a part of chemoradiotherapy for the entire cohort.

The numbers of patients in the high risk group and the low risk group were 29 (56%) and 23 (44%), respectively. The baseline clinical and tumor characteristics were not statistically different between the groups except for neoadjuvant treatment status. The ratio of patients who received neoadjuvant treatment was statistically higher in the high risk group than the low risk group ($P=.005$). The number of patients who received neoadjuvant treatment was 19 (66%) in the high risk group, while it was 6 (26%) in the low risk group. The baseline features and comparison of all patients and both groups are illustrated in Table 1.

3.2. ROC analysis for T/N SUV max ratio

ROC analysis was performed to determine prognostic value and a cut-off for T/N SUV max ratio by defining recurrence or progression (event) as the endpoint. The AUC was 0.74 (95% confidence interval [CI]: 0.60–0.88, $P=.004$). The maximal joint point of sensitivity and specificity was determined using the Youden Index. The optimal cut-off value for T/N SUV max was 1.96 with 72.7% sensitivity and 73.7% specificity. Patients with T/N SUV max $\leq$1.96 were defined as high risk patients (n: 29, 56%) and those with >1.96 were defined as low risk patients (n: 23, 44%). The ROC curve is shown in Figure 1.

Table 1

Baseline features of all patients and both groups.

Characteristics	Total, n (%)	High risk group n (%)	Low risk group n (%)	P-value
Number of patients	52	29 (56%)	23 (44%)	
Median age (min-max)	61 (41–79)	61 (41–75)	61 (50–79)	.883
Gender				
Male	49 (94%)	27 (93%)	22 (96%)	1.000
Female	3 (6%)	2 (7%)	1 (4%)	
Smoking status				
Smoker	30 (58%)	15 (52%)	15 (65%)	.403
Non-smoker	22 (42%)	14 (48%)	8 (35%)	
Histology				
Adenocarcinoma	23 (45%)	14 (48%)	9 (39%)	
Squamous cell carcinoma	25 (48%)	12 (42%)	13 (57%)	.483
Others	4 (7%)	3 (10%)	1 (4%)	
Primary tumor size				
Median (min-max)	5.6 (1.4–13)	4.1 (1.4–9.2)	6.9 (2.5–13)	.138
Stage				
IIIA	12 (23%)	5 (17%)	7 (30%)	.467
IIIB	23 (44%)	13 (45%)	10 (44%)	
IIIC	17 (33%)	11 (38%)	6 (26%)	
Clinical T stage				
cT1	7 (14%)	4 (14%)	3 (13%)	.253
cT2	11 (21%)	9 (31%)	2 (9%)	
cT3	15 (29%)	7 (24%)	8 (35%)	
cT4	19 (36%)	9 (31%)	10 (43%)	
Clinical N stage				
cN1	6 (12%)	1 (4%)	5 (22%)	.122
cN2	23 (44%)	14 (48%)	9 (39%)	
cN3	23 (44%)	14 (48%)	9 (39%)	
Local treatment				
Surgery	24 (46%)	10 (35%)	14 (61%)	.058
Chemoradiotherapy	28 (54%)	19 (65%)	9 (39%)	
Neoadjuvant treatment				
Yes	25 (48%)	19 (66%)	6 (26%)	.005*
No	27 (52%)	10 (34%)	17 (74%)	
Chemotherapy regimen				
Cisplatin + vinorelbine	9 (17%)	4 (14%)	5 (22%)	.428
Carboplatin +paclitaxel	16 (31%)	7 (24%)	9 (39%)	
Gemciatbine + cisplatin	13 (25%)	9 (31%)	4 (17%)	
Others	14 (27%)	9 (31%)	5 (22%)	

3.3. Survival analysis

The median follow-up time was 25.3 months (4.1–103.2) for all patients. There were 33 patients (64%) who experienced an event (recurrence or progression) at the time of final analysis. The median event free survival was statistically longer in low risk patients compared to high risk patients ($P=.015$). The median event free survival was 24.3 months (95% CI: 12.0–36.6) for low risk patients, and 9.2 months (95% CI: 6.1–12.4) for high risk patients. Kaplan–Meier survival analysis is illustrated in Figure 2.

3.4. Univariate and multivariate analysis

Univariate and multivariate analyses were performed by defining event occurrence as the endpoint. Age, smoking status, gender, histology, stage, risk group, local treatment modalities, and neoadjuvant treatment status were analyzed in univariate analysis and all were included in the multivariate analysis model. According to univariate analysis, of those variables, only risk group (high risk group vs low risk group) was statistically significantly associated with increased event (recurrence or progression) risk with a hazard ratio of: 2.59 (95% CI: 1.15–5.81) ($P=.021$). Similarly,

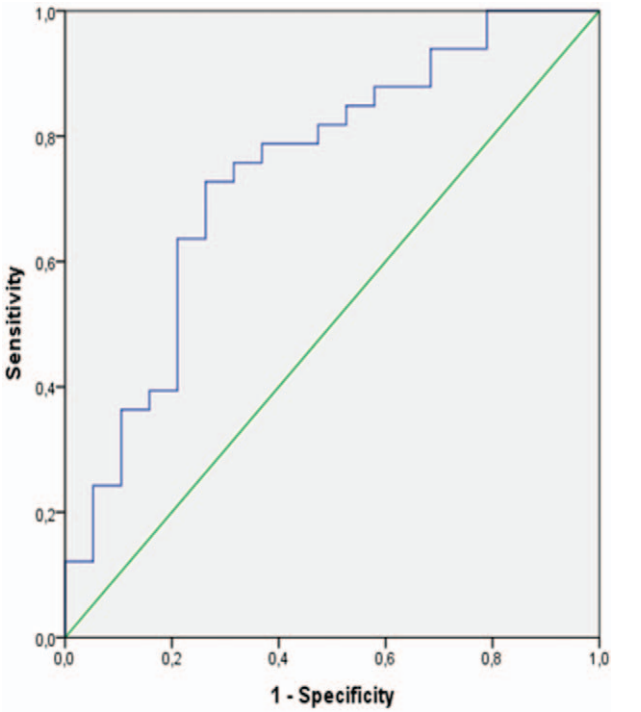

Figure 1. ROC curve for T/N SUV max ratio. ROC = receiver operating characteristic, T/N SUV = standardized uptake value max ratio of primary tumor to lymph node.

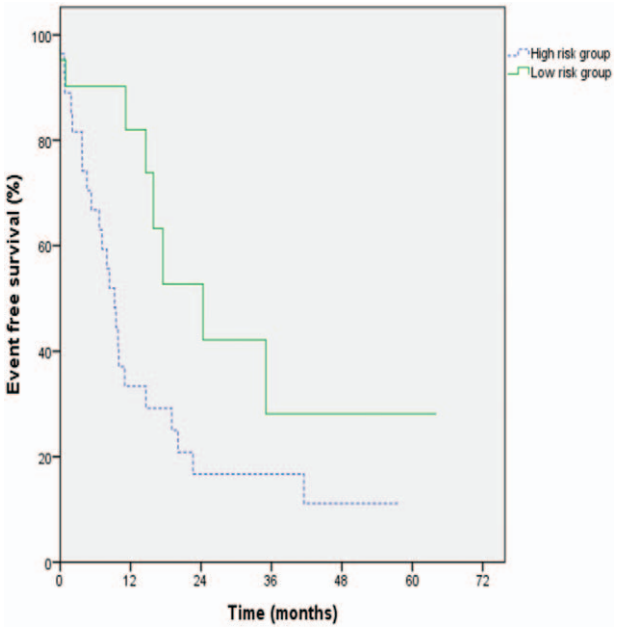

Figure 2. Kaplan–Meier survival curves.

multivariate analysis showed that only risk group (high risk group vs low risk group) was an independent prognostic factor for event (recurrence or progression) occurrence (HR: 4.09, 95% CI: 1.29–12.95, $P = .016$). Univariate and multivariate analyses are demonstrated in Table 2.

Table 3

Spearman rank correlation analysis.

	T/N SUV max ratio	
	Rho*	*P*-value
White blood cell count (WBC)	−0.094	.507
Neutrophil count (Neu)	0.035	.805
Lymphocyte count (Lym)	−0.258	.064
Hemoglobin concentration (Hb)	−0.349	.011*
Mean corpuscular volume (MCV)	−0.312	.025*
Platelet count (PLT)	0.014	.921
Mean platelet volume (MPV)	0.196	.173

T/N SUV = standardized uptake value max ratio of primary tumor to lymph node.
* Spearman rank correlation coefficient.

3.5. Correlation analysis of hematological parameters and T/N SUV max ratio

In addition to the prognostic analysis of T/N SUV max ratio, we further performed Spearman correlation analysis in order to investigate the correlation between T/N SUV max ratio and various hematological parameters. We performed a correlation analysis between T/N SUV max ratio and white blood cell count (WBC), neutrophil count, lymphocyte count, HB concentration, MCV, platelet count, and mean platelet volume. Correlation analysis revealed that only HB and MCV had statistically significant correlations with T/N SUV max. Both HB concentration and MCV were inversely correlated with T/N SUV max ratio (rho: −0.349, $P = .011$; rho: −0.312, $P = .025$, respectively). The results of correlation analysis are shown in Table 3 and illustrated in Figure 3 and Figure 4.

Table 2

Univariate and multivariate analysis.

Variables (n)	Univariable HR (95% CI)	*P*-value	Multivariable HR (95% CI)	*P*-value
Age (52)	0.97 (0.93–1.01)	.255	0.97 (0.91–1.02)	.316
Gender				
Male (49)	1	.770	1	
Female (3)	1.19 (0.35–3.99)		1.00 (0.27–3.71)	.992
Smoking status				
Smoker (30)	1	.593	1	.738
Non-smoker (22)	1.22 (0.58–2.54)		1.17 (0.46–2.92)	
Histology				
Adenocarcinoma (23)	1	.064	1	.350
Squamous cell carcinoma (25)	0.49 (0.23–1.05)		0.50 (0.19–1.30)	
Others (4)	1.82 (0.51–6.41)		0.94 (0.19–4.56)	
Stage				
IIIA (12)	1	.455	1	.096
IIIB (23)	0.56 (0.22–1.38)		0.32 (0.10–1.06)	
I IIC (17)	0.70 (0.27–1.80)		0.24 (0.06–0.91)	
Risk groups				
Low risk group (23)	1	.021*	1	.016*
High risk group (29)	2.59 (1.15–5.81)		4.09 (1.29–12.95)	
Local treatment				
Surgery (24)	1	.313	1	.938
Chemoradiotherapy (28)	1.45 (0.70–3.01)		0.96 (0.35–2.57)	
Neoadjuvant treatment				
Yes (25)	1	.208	1	.307
No (27)	0.63 (0.30–1.29)		0.61 (0.23–1.57)	

CI = confidence interval, HR = hazard ratio.

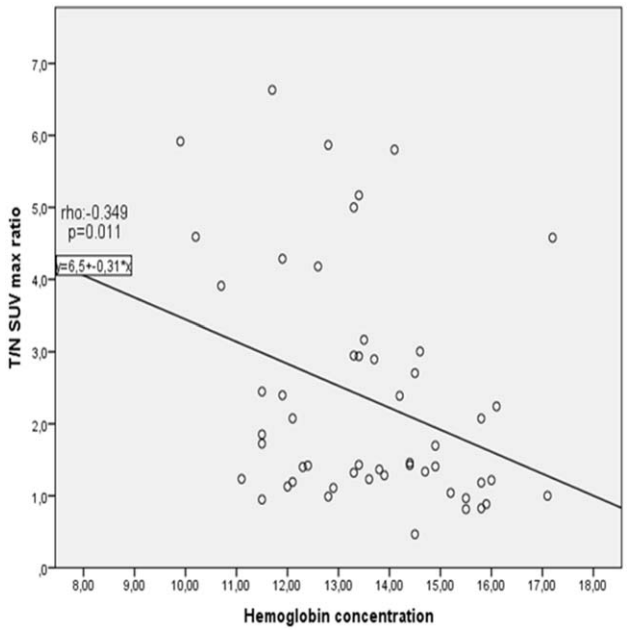

Figure 3. Correlation between T/N SUV max ratio and hemoglobin concentration. T/N SUV = standardized uptake value max ratio of primary tumor to lymph node.

4. Discussion

The present study indicates that T/N SUV max ratio with a cut-off of 1.96 can discriminate high risk and low risk patients in a highly heterogeneous subset of NSCLC. In this study, we specifically focused on clinical assessment of patients, such as cT and cN staging, in order to facilitate the likelihood of translation of those findings into clinical practice. On the other hand, we did not include patients with any SUV max <2.5 or with suspicious metastatic disease in order to avoid false negativity or potential biases. Patients in the high risk group statistically significantly had shorter median event free survival compared to patients in the low risk group. Baseline features were not statistically different between the groups except for neoadjuvant treatment status. The ratio of patients who had received neoadjuvant treatment was statistically higher for patients with high risk than for those with low risk. This observation might be interpreted as data supporting the assumption that disease in high risk patients had an aggressive behavior at presentation as well as during the disease course. Noteworthy, neoadjuvant treatment status had no influence on event free survival according to both univariate and multivariate analysis. Moreover, due to the fact that all PET-CT parameters were obtained at the time of first diagnosis before treatment, there was no effect of neoadjuvant treatment on PET-CT parameters. In addition, patients in the high risk group had a nearly 4-fold increased risk of recurrence irrespective of treatment modalities and neoadjuvant treatment status according to multivariate regression analysis. Risk grouping was statistically significantly related to event in both univariate and multivariate regression analysis. Our multivariate analysis model consisted of widely accepted prognostic factors. However, we could not determine stage as an independent prognostic factor for recurrence, which may be a result of the low number of patients. In addition, our correlation analysis revealed a statistically significant negative correlation of T/N SUV max only with HB and MCV.

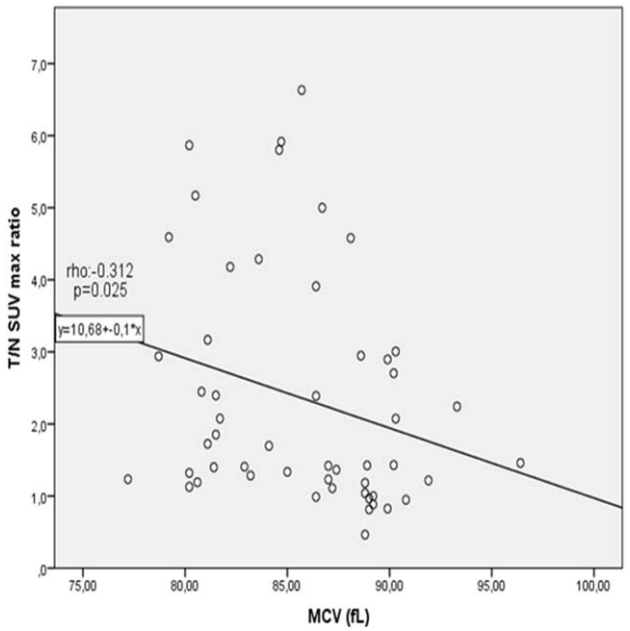

Figure 4. Correlation between T/N SUV max ratio and MCV. MCV = mean corpuscular volume, T/N SUV = standardized uptake value max ratio of primary tumor to lymph node.

In the literature, various PET-CT parameters have been studied to increase the discriminatory capacity of PET-CT in evaluation of disease extent or prediction of treatment response. SUV max is one of the most frequently reported metrics of PET-CT. However, there are conflicting reports on the prognostic or predictive value of SUV based metrics. While some studies reported pre-treatment SUV max as a potential prognostic parameter, others could not demonstrate a prognostic role of pre-treatment SUV max.[11,13,24–26] In addition to this observation, these studies support the role of PET-CT as a prognostic and predictive method beyond a staging tool. Of these, only the ACCRIN study, which included a total of 189 stage III patients had a prospective design and evaluated the prognostic value of various pre-treatment PET-CT metrics in patients treated with chemo-radiotherapy. According to the first report of this study, SUV max alone has not been shown to be an independent prognostic factor for either locoregional failure nor mortality in both univariate and multivariate analysis.[26] Univariate and multivariate analysis, which was performed by defining locoregional failure as an end-point, did not reveal a statistically significant prognostic value of SUV max alone with a HR = 1.02 (95% CI = 0.99–1.04, $P = .26$) and HR = 1.00 (95% CI = 0.97–1.02, $P = .64$), respectively.[26] Similarly, in a subsequent analysis of the ACCRIN study, SUV max alone was not shown to have a statistically significant prognostic value for locoregional failure either in univariate analysis or in multivariate analysis (HR = 1.01 99% CI = 0.97–1.05, $P = .41$; HR = 1.02 99% CI = 0.98–1.05, $P = .33$, respectively).[13] In addition to failure of SUV max alone as a prognostic parameter, SUV max has been reported to show variability up to 3%between different centers.[27] In order to overcome this drawback of SUV max alone, Cerfolio RJ et al have proposed the ratio of lymph node SUV max to primary tumor SUV max as a possible universal parameter according to results of the study conducted in cN2 positive patients.[28] This study had

similar results to our study and showed that a ratio of 0.56 has statistically significant predictive capacity with 94% sensitivity and 72% specificity. Noteworthy, after dividing the cut-off point in our study by 1 to convert it to lymph node/primary tumor SUV max, we found that the converted cut-off point (0.51) was very close to the cut-off point found in that study. However, all patients in that study had received chemoradiotherapy, and data about stage except for clinical N status was not stated in the study. The authors concluded that this ratio might be a standardized measurement with promising results.[28] Another study conducted in patients with NSCLC demonstrated that a T/N SUV max ratio of 5 or lower is a statistically significant predictor of malignant lymph node with 92.8% sensitivity and 47% specificity.[9] Although only 22% of patients had stage IIIA disease, the result of that study showed a similar trend of T/N SUV max ratio as found in our study.[9] Taken together, the predictive and prognostic value of SUV based metrics are still under question, but the ratio of primary tumor SUV max and lymph node SUV max is providing a promising and easily applicable solution to overcome disadvantages of SUV based metrics alone.

Our efforts to explore the correlation of T/N SUV max ratio with various hematologic parameters revealed a statistically negative correlation of T/N SUV max ratio only with HB and MCV (rho = −0.349, $P = .011$; rho = −0.312, $P = .025$), respectively. In the literature, to the best of our knowledge, there is only 1 study, which was conducted in patients with stage I NSCLC, investigating the relationship between SUV max and hematologic parameters.[29] In this study, they found a weak but statistically significant positive correlation of primary tumor SUV max and WBC, neutrophil count, and lymphocyte count.[29] In contrast to this result, we could not find any correlation between T/N SUV max and WBC, neutrophil count or lymphocyte count. We rather found a negative correlation between T/N SUV max and HB concentration and MCV. We interpreted this apparent inconsistency to be a result of differences in patient disease stages. On the other hand, in the literature there are a few studies demonstrating a negative correlation between PET-CT parameters and HB.[30,31] However, those studies were conducted in patients with multiple myeloma. The negative correlations observed in these studies may be related to multiple myeloma itself. We believe the negative correlation between T/N SUV max ratio and HB and MCV might be a reflection of tumor vascularisation. Similar to lower HB levels, higher HB levels can also cause tumor hypoxia, which in turn results in more resistant disease.[32] Additionally, we interpreted the negative correlation between T/N SUV max and MCV as simply a reflection of a negative correlation of HB.

In conclusion, stage III NSCLC is a highly heterogeneous group of NSCLC with respect to disease course, treatment modalities, and response. Efforts to find simple, easily accessible, and reproducible prognostic parameters are increasing in recent years. In this regard, T/N SUV max ratio is a promising simple, easily accessible and reproducible parameter that can increase the power of PET-CT as a prognostic tool beyond a staging tool. The negative correlation between T/N SUV max and HB concentration and MCV may be a reflection of the tumor microenvironment, such as tumor hypoxia. However, we think this issue is an area still worthy of more mechanistic studies. Finally, the major limitation of this study was its retrospective nature and relatively low number of patients. Therefore, further studies with a larger patient population are required to confirm these findings.

Author contributions

Conceptualization: Yusuf Acikgoz, Gokhan Ucar, Oznur Bal, Mutlu Dogan.
Data curation: Yusuf Acikgoz, Fatih Gurler, Bediz Kurt Inci, Berna Okudan.
Formal analysis: Yusuf Acikgoz, Yakup Ergun.
Supervision: Mutlu Dogan, Dogan Uncu.
Writing – original draft: Yusuf Acikgoz.
Writing – review & editing: Yusuf Acikgoz, Merve Dirikoc, Selin Akturk Esen, Mutlu Dogan.

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