

Relationship between FDG-PET/CT and hematological parameters in squamous cell lung cancer without distant metastasis

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Abstract

Objective: This study aimed to investigate the relationship between 18Fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) parameters and hematological parameters in squamous cell lung cancer without distant metastasis and to investigate the prognostic value of these parameters.

Patients and Methods: This study included 155 patients who underwent 18F-FDG PET/CT imaging for squamous cell lung cancer. Metabolic and hematological parameters were analyzed. Metabolic parameters included maximum and mean standardized uptake values (SUVmax and SUVmean), metabolic tumor volume (MTV), total lesional glycolysis (TLG), and maximum tumor-to-blood SUV ratio (SURmax). Hematological parameters included neutrophil, lymphocyte, platelet, neutrophil/lymphocyte count ratio (NLR), and platelet/lymphocyte count ratio (PLR)

Results: Overall survival was significantly shorter in patients with TLG > 194, NLR > 3.3, and PLR > 157.2 ($p < 0.001$, $p = 0.001$, and $p = 0.001$, respectively). There was a poor correlation between TLG and NLR ($p < 0.001$, $r = 0.302$), TLG and PLR ($p < 0.001$, $r = 0.304$). TLG (> 194; hazard ratio 1.704, 95% CI 1.056–2.751, $p = 0.027$) and Tumor-Node-Metastasis (TNM)-based staging (stage II; hazard ratio 1.965, 95% CI 0.739–5.227, $p = 0.019$) were independent prognostic factors for overall survival.

Conclusion: While PET/CT metabolic parameters had both predictive and independent prognostic values in squamous cell lung cancers, PLR and NLR had only predictive values. It shows that PET/CT metabolic parameters related to the course of the disease are more valuable than hematological parameters in squamous cell lung cancer.

Keywords: 18F-FDG PET/CT, Neutrophil/Lymphocyte Ratio, Squamous Cell Lung Cancer, Prognosis

Introduction

Cancer is the leading cause of death for people under 70 years old in many countries worldwide. Lung cancer is also the most common type of cancer. Also, it is the most common cause of cancer-related death in males and second in women after breast cancer (1). Good knowledge of the prognostic factors associated with the type of cancer can guide the clinician in planning treatment and contribute to predicting recurrence and survival during follow-up. Well-known prognostic factors in lung cancer include TNM classification, age, sex, histological subtype, and some genetic factors that can be related to lung cancer (2).

18F-FDG PET/CT is an imaging modality that is frequently applied for oncologic purposes and allows for monitoring the metabolic activity of the tumor. 18F-FDG PET/CT imaging is recommended for the diagnosis of suspected lung masses (3) and is frequently used in lung cancer staging and treatment response evaluation. Studies have shown that PET metabolic parameters of primary tumors

are prognostic factors in patients with non-small cell lung cancer (NSCLC) (4-6). In these studies, SUVmax, volume-based MTV and TLG have been considered as important prognostic factors.

While the search for prognostic biomarkers continues in lung cancer, some published studies have revealed some inflammatory parameters in the blood that may be related to prognosis. Neutrophil count in tumor stroma has been shown to predict undesirable outcomes and tumor-associated lymphocytes are associated with a better prognosis (7). According to another studies, the NLR value has been dedicated as a prognostic factor (8-10).

This study aimed to investigate the prognostic value of 18F-FDG PET/CT metabolic parameters and hematological parameters in patients with squamous cell lung cancer without distant metastasis. Another aim was to investigate the relationship between them



Material and Methods

Patients

Included in this retrospective study were 155 patients who underwent 18F-FDG PET/CT imaging in our clinic between May 2016 and December 2017 who had squamous cell lung cancer without distant metastasis. Patients whose pre-treatment PET CT imaging results and hematological parameter counts were measured simultaneously were enrolled in the study. Patients who had distant metastasis or whose clinicopathological information could not be reached were excluded. The staging of the patients was performed with the 8th edition of the TNM staging system of the International Lung Cancer Study Association (IASLC). The median follow-up period of patients was 23 months (1-33). Neutrophil, lymphocyte, and platelet counts of patients were recorded. NLR was calculated by the neutrophil/lymphocyte count ratio. PLR value was calculated by the platelet/lymphocyte count.

FDG PET / CT Imaging and Analysis

After a 6-hour fasting period, patients with blood glucose < 200 mg / dL received intravenous administration of 8–11 mCi 18F-FDG. 18F-FDG PET/CT images were performed using the PHILIPS GEMINI TF 16 Slices PET/CT device. The vertex-upper femoral area was scanned one hour after injection. CT imaging (140 kV, 100mAs, 5 mm slice) was performed firstly and thereafter PET imaging was conducted. PET and CT images were uploaded to a workstation and then interpreted. In axial images, the area of interest (VOI) was drawn to include tumor tissue in the lung semi-automatically. 41% SUV was accepted as the threshold to calculate SUVmean and MTV of each lesion automatically at the workstation. TLG was calculated by multiplying SUVmean with MTV. For SURmax, a SUVmean measurement of blood was measured from the descending aorta.

Statistical Analysis

All statistical analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL). Overall survival time was calculated as the time between death or last follow-up from the initial FDG-PET/CT imaging. The area under the curve (AUC) and cut-off values were calculated using the Receiver Operator Characteristic (ROC) analysis to evaluate the overall life prediction of PET/CT metabolic parameters and hematological parameters. A Spearman correlation test was used for correlation evaluation. To evaluate the effect of age, sex, histopathological and hematological parameters, and PET parameters on survival, a multivariate Cox regression analysis was used. Survival analyses were performed using Kaplan–Meier with log-rank test. $P < 0.05$ was considered statistically significant.

Results

Of the 155 patients included in the study, 11 (7%) were female and 144 (93%) were male. The mean age of the patients was 67.6 ± 7.2 years. Median survival was 21 (1–33) months. Patients were followed up for 33 months. At the end of the follow-up period, 100 (64.5%) patients died and 55 (35.5%) patients were alive. During the follow-up,

110 (71%) patients had progression and 45 (29%) patients had stable disease or complete response. While 40 (26%) patients underwent the surgical operation for treatment, 115 (74%) patients had received only chemotherapy and radiotherapy. The demographic and clinicopathological characteristics of the patients are summarized in Table 1.

Table 1. Demographic and clinicopathological characteristics of the patients

All patients (n = 155)	
n (%)	
Gender	
Female	11 (7.1)
Male	144 (92.9)
Status	
Alive	55 (35.5)
Dead	100 (64.5)
Stage TNM (8th edition)	
1a1	1 (0.6)
1a2	6 (3.9)
1a3	10 (6.5)
1b	7 (4.5)
2a	8 (5.2)
2b	21 (13.5)
3a	50 (32.3)
3b	33 (21.3)
3c	19 (12.3)
Mean \pm SD/ median (min–max)	
Age	67.6 \pm 7.2
SUVmax	16 (4-48)
SUVmean	8,51 \pm 2.9
MTV	34 (1-591)
TLG	314 (3.3-5674.6)
SURmax	10.02 \pm 4.2
Neutrophil	6.9 (2.8-17.3)
Lymphocyte	2.0 \pm 0.87
Platelets	334 (73-771)
NLR	3.6 (1.7-17.3)
PLR	174.62 (53.4-830)

SUVmax: maximum standardized uptake value; SUVmean: mean standardized uptake value; TLG: total lesion glycolysis; MTV: metabolic tumor volume; SUR max: maximum standard tumor-to-blood, NLR: neutrophil/lymphocyte ratio, PLR: Platelets/lymphocyte ratio.

For predicting overall survival, the AUC for the 18F-FDG PET/CT metabolic parameters belonged to TLG (0.719, $p < 0.001$) (Figure 1). When the cut-off value of TLG is taken as 194, sensitivity was 73% and specificity was 62%. AUC values were 0.689 for SUVmax, 0.697 for SUVmean, 0.707 for MTV, and 0.595 for SURmax.

For predicting overall survival, the AUC for the hematological parameters belonged to NLR (0.647, $p = 0.002$) and PLR (0.652, $p = 0.002$) (Figure 2). When the cut-off value for NLR was taken as 3.3, sensitivity was 66% and specificity was 58%. When the cut-off value for PLR was taken as 157.2, sensitivity was 69% and specificity was 56%. AUC value was 0.62 for platelets ($p = 0.01$).

Figure 1. ROC curves for 18F-FDG PET/CT parameters

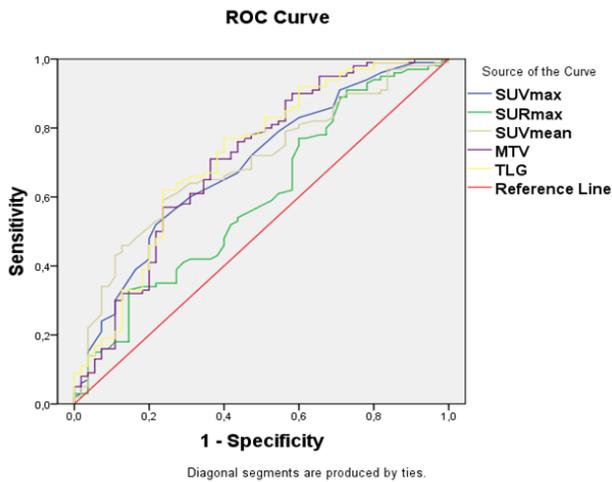
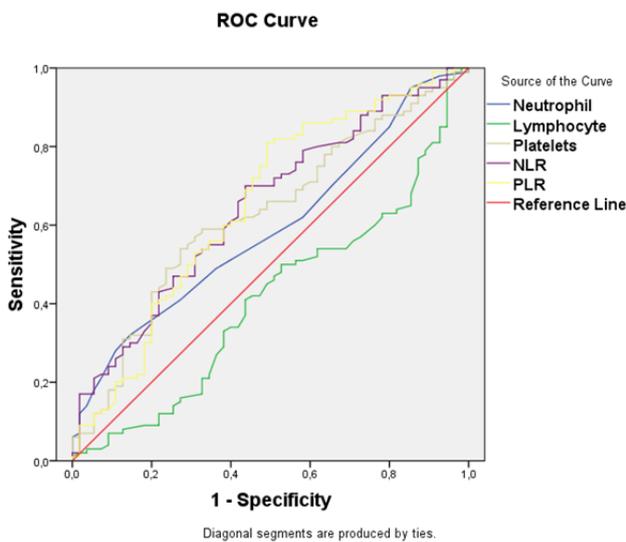
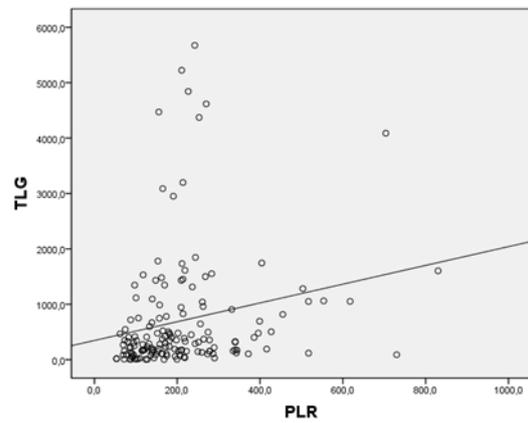
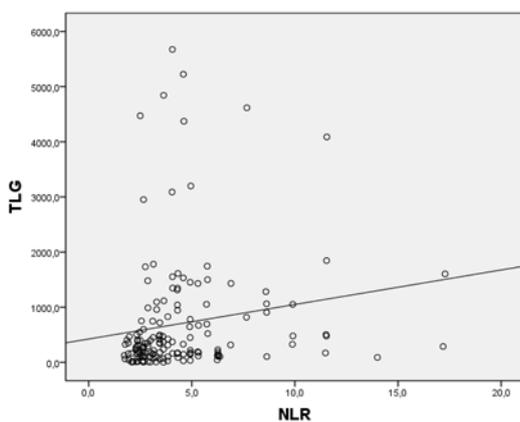


Figure 2. ROC curves for hematologic parameters



There was a poor correlation between TLG and NLR ($p < 0.001$, $r = 0.302$) and TLG and PLR ($p < 0.001$, $r = 0.304$) (Figure 3).

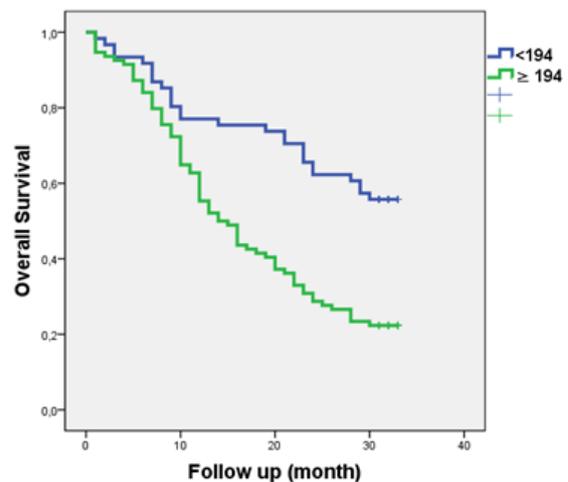
Figure 3. Correlations between TLG and both PRL and NRL



The Kaplan–Meier analysis for the overall survival, taking into account the cut-off values for TLG, is shown in Figure 4. When 194 cut-off values were used for TLG, there was a significant difference in overall survival ($p < 0.001$).

The mean survival was 25 months in patients with $TLG < 194$ and 17 months in patients with $TLG \geq 194$.

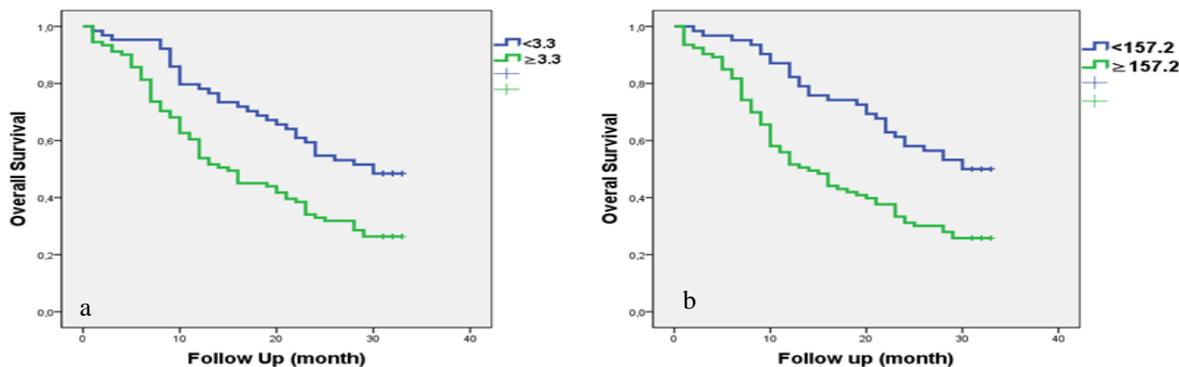
Figure 4. Kaplan–Meier curve depicting the overall survival according to TLG ($p < 0.001$)



The Kaplan–Meier analysis for the overall survival, taking into account the cut-off values for NLR and PLR are shown in Figure 5. There was a significant difference in overall survival when the cut-off value of 3.3 was used for NLR ($p = 0.001$) and when the cut-off value of 157.2 was used for PLR ($p = 0.001$).

Mean survival was 24 months in patients with $NLR < 3.3$ and 18 months in patients with $NLR \geq 3.3$. Mean survival was 24.9 months in patients with $PLR < 157.2$ and 17.3 months in patients with $PLR \geq 157.2$.

In the multivariate Cox regression analysis for overall survival, TNM stage (stage III; hazard ratio 3.362, 95% CI 1.360–8.310, $p = 0.009$) and TLG (> 194 ; hazard ratio 1.704, 95% CI 1.056–2.751, $p = 0.029$) were independent prognostic factors (Table 2). However, gender, age, NLR, and PLR were not.

Figure 5. Kaplan–Meier curve depicting the overall survival according to NLR ($p = 0.001$) (a) and PLR ($p = 0.001$) (b)**Table 2.** Results of multivariate Cox regression analysis for overall survival

Variables	Wald	HR	95 % CI	P
Sex (M)	0.095	0.876	0.378-2.033	0.830
Age (>65)	0.560	1.181	0.763-1.828	0.559
TNM stage	8.538	NA	NA	0.033*
II	1.832	1.965	0.739-5.227	0.019*
III	6.895	3.362	1.360-8.310	0.106
TLG (>194)	4.763	1.704	1.056-2.751	0.027*
NLR (<3.3)	3.016	1.478	0.951-2.297	0.294
PLR (<157.2)	1.710	0.721	0.441-1.177	0.191

TNM: The TNM Classification of Malignant Tumors; TLG: total lesion glycolysis; NLR: neutrophil/lymphocyte ratio, PLR: Platelets/lymphocyte ratio.

Discussion

In our study, TLG was the most valuable metabolic parameter in estimating general life expectancy in squamous cell lung cancer without distant metastasis, while the most valuable hematological parameters were NLR and PLR. There was a poor correlation between TLG and the hematological parameters. In multivariate analysis, in terms of overall survival, the TNM stage and TLG were independent prognostic factors, whereas NLR and PLR were not.

18F-FDG PET/CT is widely used for staging, detecting of the recurrence, determining target volume for RT, and evaluating responses to chemotherapy and chemoradiotherapy in lung cancer patients (11). Studies have shown that SUVmax and volumetric parameters of primary tumors at 18F-FDG PET/CT are important prognostic factors in NSCLC patients (4,12,13). In a study by Dong et al., the patients with high SUVmax in their primary tumors had shorter overall survival and a higher risk of distant metastasis (12). In the meta-analysis conducted by Liu et al. found a higher risk of recurrence and death in NSCLC patients with high SUVmax, MTV, and TLG values of primary tumors (13). In the study by Im et al., the risk of death was higher in NSCLC patients with high MTV or TLG, and MTV and TLG were significant prognostic factors in both stage I/II and stage III/IV patients (4). There are a few studies in the literature investigating the prognostic value of PET/CT in patients with squamous cell lung cancer, a subtype of NSCLC. One of them was the work of Zhang and his colleagues (14).

In this study, overall survival was significantly lower in patients with SUVmax greater than 11.2. Also, SUVmax was an independent risk factor. In the study of Ito et al. (15), the SUVmax of the tumor was associated with recurrence in both adenocarcinoma and squamous cancer subtypes in patients with lung cancer. In our study, the most valuable 18F-FDG PET/CT parameter in estimating the risk of death was found to be TLG. According to these results, a significantly shorter overall survival is expected in patients with TLG > 194. In addition to this, they had a predictive value for survival in SUVmax, SUVmean, and MTV, and had similar AUC values.

Recent studies have shown that inflammatory markers have prognostic value in patients with NSCLC. One of these studies is the work of Wang et al (16). According to this study, the NLR rate is a useful clinical index for predicting overall survival and treatment response in patients with NSCLC. In a similar study by Peng et al. patients with high NLR (> 5) had a worse prognosis and worse response to treatment (7). Mizuguchi et al. (17) reported that NSCLC patients with a low NLR rate had a better prognosis. In meta-analyses which other similar studies in the literature are analyzed; they indicated that NLR is a prognostic factor in lung cancer (18-20). A study by Minami et al (21). showed that patients with NLR < 5.28 had longer overall survival and progression-free survival in patients with squamous cell lung cancer. In that study, they showed that the lymphocyte monocyte ratio (LMR) also had predictive value.

They also reported that LMR is an independent risk factor, unlike NLR. Significantly shorter overall survival is expected in patients with > 3.1 NLR in our study. But NLR and PRL were not an independent risk factor in patients with squamous cell lung cancer. Our results were similar to Minami et al.'s research.

Neutrophils and type T and B lymphocytes play important roles in tumor inflammation, and the imbalance between neutrophils and lymphocytes is thought to be secondary to tumor hypoxia or necrosis. Therefore, the NLR may reflect the imbalance between neutrophils and lymphocytes in cancer patients and is thought to be indicative of systemic inflammation (18). 18F-FDG PET/CT provides quantitative information about the metabolic activity of the tumor. FDG is a glucose analog. Generally, malignant cells tend to use glucose instead of free fatty acids. Besides, if malignant cells are hypoxic, they use anaerobic metabolism. Anaerobic metabolism requires much more glucose than aerobic metabolism. Even if malignant cells are not hypoxic, malignant cells tend to use anaerobic metabolism. Due to these mechanisms, cancer tissue is detected because of their higher rate of glucose metabolism than surrounding tissues (22). At the site of inflammation/infection, inflammatory cells (neutrophils, activated macrophages, and lymphocytes) increase the accumulation of 18F-FDG via a common mechanism with the tumor tissue. FDG due to such behavior in the inflammatory/infectious tissue; guidelines recommend 18F-FDG for localization of infection in cases such as peripheral osteomyelitis (non-diabetic and non-diabetic foot), spinal infection, fever of unknown origin, metastatic infection and bacteremia (23). Both NLR and 18F-FDG PET/CT metabolic parameters have been identified as independent risk factors in NSCLC. There are several studies in the literature that reveal the possible relationship with each other. Jeong et al (24). examined the relationship between SUVmax and hematological prognostic parameters (total white blood cell, neutrophil, lymphocyte, and platelet count, NLR and PLR) in patients with stage I NSCLC. In this study, SUVmax and hematological parameters showed poor correlation. They also indicated that the prognostic value of SUVmax, an indicator of FDG uptake of the tumor, was superior to hematological parameters. Another study was performed by Mirili et al.25 in patients with small-cell lung cancer. A moderate correlation was found between NLR and MTV. In a Cox regression analysis, NLR, and whole-body (WB) TLG were found to be independent risk factors associated with prognosis. There was a poor correlation between NLR/PLR and TLG in our study. TLG was an independent prognostic factor, while NLR and PLR were not.

Conclusion

As a result, PET CT metabolic parameters had both predictive and prognostic value in squamous cell lung cancers. Among the hematological parameters, PLR and NLR had predictive value, but not independent prognostic value. There was a weak correlation between TLG and PLR and NLR. This result indicates that PET/CT metabolic parameters related to the course of the disease are more

valuable than hematological parameters in squamous cell lung cancer.

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Author's contributions: **FD, AY;** Project design, Patient examination, Treatment, Statistical Analyses **FD;** Article preparation and revisions

Conflict of interest: The authors declare that they have no conflict of interest. The study was authorized by the Tokat GOP University local ethics committee.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018 Nov;68(6):394-424
2. Thakur MK, Gadgeel SM. Predictive and prognostic biomarkers in non-small cell lung cancer. *Semin Respir Crit Care Med.* 2016 Oct; 37: 760–70.
3. Vansteenkiste J, Crinò L, Doooms C, Douillard J, Faivre-Finn C, Lim E et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol.* 2014 Aug;25(8):1462–1474.
4. Im HJ, Pak K, Cheon GJ, Kang KW, Kim SJ, Kim IJ et al. Prognostic value of volumetric parameters of 18F-FDG PET in non-small-cell lung cancer: a meta-analysis *Eur J Nucl Med Mol Imaging.* 2015 Feb;42(2):241-51.
5. Khiewvan B, Ziai P, Houshmand S, Salavati A, Ziai P, Alavi A. The role of PET/CT as a prognosticator and outcome predictor in lung cancer. *Expert Rev Respir Med.* 2016;10(3):317-30.
6. Lee JW, Lee SM, Yun M, Cho A. Prognostic value of volumetric parameters on staging and posttreatment FDG PET/CT in patients with stage IV non-small cell lung cancer. *Clin Nucl Med.* 2016 May;41(5):347-53.
7. Peng B, Wang YH, Liu YM, Ma LX. Prognostic significance of the neutrophil to lymphocyte ratio in patients with non - small cell lung cancer: a systemic review and meta - analysis. *Int J Clin Exp Med.* 2015 Mar 15;8(3):3098-106.
8. Deng M, Ma X, Liang X, Zhu C, Wang M. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with smallcell lung cancer? *Oncotarget.* 2017 Jun 6;8(23):37200-37207.
9. Yuan C, Li N, Mao X, Liu Z, Ou W, Wang SY. Elevated pretreatment neutrophil/white blood cell ratio and monocyte/lymphocyte ratio predict poor survival in patients with curatively resected non - small cell lung cancer: Results from a large cohort. *Thorac Cancer.* 2017 Jul;8(4):350-358.
10. Bar-Ad V., Palmer J., Li L. Neutrophil to lymphocyte ratio associated with prognosis of lung cancer. *Clin Transl Oncol.* 2017 Jun;19(6):711-717.
11. Cremonesi M, Gilardi L, Ferrari ME, Piperno G, Travaini LL, Timmerman R et al. Role of interim (18)F-FDG-PET/CT for the early prediction of clinical outcomes of Non-Small Cell Lung Cancer (NSCLC) during radiotherapy or chemo-radiotherapy. A systematic review. *Eur J Nucl Med Mol Imaging.* 2017 Oct;44(11):1915-1927.
12. Dong M, Liu J, Sun X and Xing L. Prognostic significance of SUVmax on pretreatment 18 F-FDG PET/CT in early-stage non-small cell lung cancer treated with stereotactic body radiotherapy: A meta-analysis. *J Med Imaging Radiat Oncol.* 2017 Oct;61(5):652-659.

13. Liu, J., M. Dong, X. Sun, W. Li, L. Xing and J. Yu. Prognostic Value of 18F-FDG PET/CT in Surgical Non-Small Cell Lung Cancer: A Meta-Analysis. *PLoS One* [Internet]. 2016 Jan; 11: e0146195. Available from : <https://doi.org/10.1371/journal.pone.0146195>.
14. Zhang M, Wang D, Sun Q, Pu H, Wang Y, Zhao S et al. Prognostic significance of PD-L1 expression and 18F-FDG PET/CT in surgical pulmonary squamous cell carcinoma. *Oncotarget*. 2017 May 29;8(31):51630-51640.
15. Ito R, Iwano S, Kishimoto M, Ito S, Kato K, Naganawa S. Correlation between FDG-PET/CT findings and solid type non-small cell cancer prognostic factors: are there differences between adenocarcinoma and squamous cell carcinoma?. *Ann Nucl Med*. 2015 Dec;29(10):897-905.
16. Wang Z, Zhan P, Lv Y. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio in non-small cell lung cancer patients treated with systemic therapy: a meta-analysis. *Transl Lung Cancer Res*. 2019 Jun;8(3):214-226.
17. Mizuguchi S, Izumi N, Tsukioka T, Komatsu H, Nishiyama N. Neutrophil-lymphocyte ratio predicts recurrence in patients with resected stage I non-small cell lung cancer. *J J Cardiothorac Surg*. 2018 Jun 27;13(1):78.
18. Yin Y, Wang J, Wang X, Gu L, Pei H, Kuai S, et al. Prognostic value of the neutrophil to lymphocyte ratio in lung cancer: a meta-analysis. *Clinics (Sao Paulo)*. 2015 Jul;70(7):524-30.
19. Yu Y, Qian L, Cui J. Value of neutrophil-to-lymphocyte ratio for predicting lung cancer prognosis: a meta-analysis of 7,219 patients. *Mol Clin Oncol*. 2017 Sep;7(3):498-506.
20. Gu XB, Tian T, Tian XJ, Zhang XJ. Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis. *Sci Rep*. 2015 Jul 24;5:12493.
21. Minami S, Ihara S, Komuta K. Pretreatment Lymphocyte to Monocyte Ratio as a Prognostic Marker for Advanced Pulmonary Squamous Cell Carcinoma Treated With Chemotherapy. *J Clin Med Res*. 2018 Aug;10(8):657-664.
22. Jadvar H and Parker JA. *Clinical PET and PET/CT*. Springer: Verlag; 2005. 45-69 p.
23. Rahman WT, Wale DJ, Viglianti BL, Townsend DM, Manganaro MS, Gross MD et al. The impact of infection and inflammation in oncologic 18F-FDG PET/CT imaging. *Biomed Pharmacother*. 2019 Sep;117:109168.
24. Jeong E, Hyun SH, Moon SH, Cho YS, Kim BT, Lee KH. Relation between tumor FDG uptake and hematologic prognostic indicators in stage I lung cancer patients following curative resection. *Medicine (Baltimore)*. 2017 Feb;96(5):e5935.
25. Mirili C, Guney IB, Paydas S, Seydaoglu G, Kapukaya TK, Ogul A et al. Prognostic significance of neutrophil/lymphocyte ratio (NLR) and correlation with PET-CT metabolic parameters in small cell lung cancer (SCLC). *Int J Clin Oncol*. 2019 Feb;24(2):168-178.