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Does 18F FDG PET/CT paramaters predict histopathologic response to the neoadjuvant therapy in patients with non-small cell lung cancer?

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Abstract

Objective: Progression-free and overall survival are better correlated with metabolically active tumor volume (MTV) and total lesion glycolysis (TLG), as compared to the maximum standardized uptake value (SUVmax) in NSCLC patients. In this study, we aimed to evaluate the correlation between the PET-CT parameters and histopathologic tumor regression score in non-small cell lung cancer(NSCLC) patients after treatment with neoadjuvant chemotherapy.(1)

Methods: This retrospective study evaluated stage III lung cancer patients who were treated with neoadjuvant chemotherapy followed by surgical resection at a single institution between 2014 and 2018. The 3-dimensional volumes of interest were drawn in primary tumor and largest lymph node on the pretreatment examination and corresponding location on the post-treatment examination to obtain a pre- and post-treatment SUVmax, SUVmean, MTV and TLG. All hematoxylin- and eosin-stained surgery specimens were assessed based on a 4-tiered scale.

Results: Patients who had lower than 10% histologic response established higher values of SUVmax, in tumor as compared to good responders in basal PET CT assessment (p:0.014). Patients who established higher than 10% pathologic response showed higher reduction rates in terms of SUVmax (p:0.002), mean tumor volume (p:0.024), and total lesion glycolysis (p:0.009). The overall survival for patients with <10% histologic response was 15.26 months while the patients with good histologic response had 35.36 months and the difference was statistical significance (p<0.001). Due to univariate analysis, the higher SUVmax, TLG and MTV reduction have been found in association with better overall survival.

Conclusion: PET CT parameters may be useful to predict histopathologic response for NSCLC patients who received neoadjuvant chemotherapy.

Key words: PET, CT, Metabolic tumor volume, Total Lesion Glicolysis, 18F-FDG

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide (1). Definitive chemoradiation or induction therapy followed by surgical resection is a fundamental treatment option for locally advanced disease (2). Assessment of response to induction chemotherapy is critical to evaluate surgical eligibility and prognosis. Additionally, as the pathologic ypN2 nodes may be a predictor of decreased overall survival, 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) utility in N2 nodes and its association with histopathologic response is also important.

The relationship between SUVmax and histopathologic tumor regression after induction chemotherapy has been shown in non–small cell lung cancer (NSCLC) patients (3). However, there are some limiting factors. Elevated macrophage infiltration may result in a falsely elevated SUVmax and a bulky lesion which still contains residual vital tumor may show a false negative complete metabolic response according to SUVmax (4). According to literature, 18F-FDG PET with a complete metabolic response has advantages as compared with computed tomography (CT) volume assessment for evaluating histopathologic response (5).

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It has been shown that, a decrease in SUVmean was correlated with a favorable progression-free and overall survival after induction chemotherapy (6).

Metabolically active tumor volume (MTV) and total lesion glycolysis (TLG) are PET parameters which assess total tumor burden, showed better correlation with progression-free and overall survival in NSCLC patients as compared to SUVmax (7-8).

In this study, we aimed to assess the predictive value of 18F-FDG PET parameters, for histopathologic tumor response and to evaluate the prognostic value of metabolic response for overall survival (OS) in NSCLC patients after treatment with induction chemotherapy.

Materials and Methods

Patients

This retrospective study evaluated stage III lung cancer patients who were treated with neoadjuvant chemotherapy followed by surgical resection at a single institution between 2014 and 2018.

All patients who had pre- and post-induction chemotherapy FDG-PET were included in the study. Patients who developed metastatic disease after chemotherapy or those who did not undergo surgery for any other reason were excluded from the study. All patients were evaluated by a multidisciplinary team consisting of radiation oncology, medically oncology, thoracic surgery, and pulmonary medicine. Pulmonary function tests were done for all patients. The study was approved by the Adnan Menderes University Institutional Review Board.

Treatment

All patients were treated with preoperative chemotherapy and after surgical resection. Patients received 3 cycles of one of the induction chemotherapy schedules. Following completion of induction therapy, all patients underwent resection of the primary tumor, in terms of pneumonectomy (2.3%) lobectomy (88.6%) or bilobectomy (9.1%) and mediastinal lymph node dissection.

PET Analysis

All patients underwent 18F- FDG PET/CT imaging after 6-8 hours of fasting period. Before injection of 18F-FDG, the medical history, weight and blood sugar level of the patients were recorded. A blood sugar level of <180 mg/dl was required prior to imaging. Oral contrast was given to all patients. After intravenous administration of 270-370 MBq of 18F-FDG, patients rested in a quiet room for 60 minutes. Imaging was performed with (Siemens Biograph mCT 20 Excel) PET/CT scanner. Images were acquired from the head to the feet. The CT transmission scan was acquired with 140 kVp and 110 mA and 3 mm slice thickness. PET scan was acquired at 2-4 min per bed position. The 3-dimensional volumes of interest were drawn in primary tumor and largest lymph node on the pretreatment examination and corresponding location on the post-treatment examination to obtain a pre- and post-treatment SUVmax, SUVmean, MTV and TLG, as previously described (9).

TLG reflects metabolic volume and is expressed as the product of the average uptake intensity and the uptake volume at the area where the uptake intensity is at least 42% of the maximal uptake. Per cent reduction in SUVmax was calculated using the following formula: [(post-treatment index value−pretreatment index value)/pretreatment index value]×100.

Histopathologic Assessment of Tumor Regression

All hematoxylin- and eosin-stained surgery specimens were assessed based on a 4-tiered scale as proposed by Junker et al. (10). The system interprets the proportion of viable tumor cells in comparison to the degree of tumor necrosis and fibrosis. In summary, score 1 is no or only minor tumor regression; Score 2 is the presence of more than 10% vital tumor tissue; score 3 is less than 10% vital tumor epithelia in all tumors; and score 4 is the presence of complete tumor regression and original tumor volume is replaced with only fibrotic and necrotic areas and macrophage-rich xanthomatous inflammation.

Statistical analysis

Continuous data were expressed as median and range. The difference in SUVmax parameters was compared by the Mann–Whitney U-test. Overall survival was defined as time from the diagnosis of disease until death or until the last follow-up. Survival time was estimated by Kaplan–Meier survival analysis. Receiver operating characteristic (ROC) analysis was used for PET parameters in order to determine a binomial cutoff value that would optimally predict pathologic response. However, if ROC curves were not significant; median values were obtained for all PET parameters. The effects of SUVmax, SUVmean, MTV and TLG reduction during neoadjuvant chemotherapy (NACT) on overall survival (OS) were calculated by Cox proportional hazard regression. p values <0.05 were considered as statistically significant

Results

Patients

Patient characteristics are shown in Table 1. Twenty-one patients with non small cell lung cancer who were operated after neoadjuvant chemotherapy included in this study. Median age was 66 years (52-84 years). All patients had PET-CT before and after neoadjuvant chemotherapy. The most common histology was squamous cell carcinoma (52.4%) and the most preferred operation type was lobectomy (81%).

Patients who had >10% viable tumor in surgical pathology specimen were considered to have a good histologic response, whereas those with a value 10% or less were considered worse histological response. Ten patients (47.6%) demonstrated a good histological response (<10% vital tumor tissue) and 11 patients (52.4%) showed a worse histological response (>10% vital tumor tissue). PET BT parameters before and after neoadjuvant chemotherapy. The mean PET-CT paramaters (SUVmax, SUVmean, MTV and TLG) before and after chemotherapy in both involved lymph nodes and primary tumor and the percentage of reduction in parameters by histologic response are shown in

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Table 2. The median reduction rate of SUVmax, SUVmean, MTV and TLG were 19.5 %, 35.72 %, 37.2%, 56.6% respectively in patients with low histologic tumor regression whereas of those were 61.4%, 50%, 73.1%, 89.4% in patients with >10% histologic tumor regression.

Association of PET BT parameters and pathologic response

Patients who had lower than 10% histologic response established higher values of Suvmax, in tumor as compared to good responders in preoperative PET CT assessment (p:0.014). Patients who established higher than 10% pathologic response showed higher reduction rates in terms of SUVmax (p:0.002), mean tumor volume (p:0.024), and total lesion glycolysis (p:0.009). (Figure 1)

Prognostic value on Overall survival

Overall survival was 28.9 months for the entire study population. The overall survival for patients with <10% histologic response was 15.26 months while the patients with good histologic response had 35.36 months and the difference was statistical significance (p<0.001). All FDG-PET parameters for both primary tumor and nodal disease were evaluated for potential association with OS. Of these, in univariate analysis; higher SUVmax reduction (HR 0.168, CI:0.033-0.855 , p:0.03), higher MTV reduction (HR 1.143, CI:1.011-1.293, p:0.033), and higher TLG reduction values (HR 0.154, CI:0.032-0.754, p:0.02) were associated with better overall survival.

The other FDG-PET parameters showed no significant association with OS. Among clinical features, gender and >10% histopathologic response (HR 0.243, CI: 0.063-0.939, p:0.04) were significantly associated with increased OS. In multivariate analysis, frontal we did not find any significant predictor of survival (Table 3)

Table 1: Patient demographic characteristics

Parameter		N (%)
Age		66 (52-84)
Gender	Female	1 (4.8%)
	Male	21 (95.2%)
Histology	Squamous	11 (52.4%)
	Adeno	9 (42.9%)
	Adenosquamous	1 (4.8%)
Side	Right	12 (57.1%)
	Left	9 (42.9%)
N2 involvement	Yes	8 (38.1%)
	No	13 (61.9%)
Postchemo N2	Yes	4 (19%)
	No	17 (81%)
Operation type	Lobectomy	17 (81%)
	Pneumonectomy	3 (14.3%)
	Bilobectomy	1 (4.8%)
Histological response	<10% response	10 (47.6%)
	>10% response	11 (52.4%)
Ypstage	Complete	2 (6.7%)
	Stage I	4 (19%)
	Stage II	12 (57.2%)
	Stage III	5 (23.8%)

Table 2. PET paramaters before and after chemotherapy according to histologic response. *p<0.05

		Tumor regression<10%			Tumor regression>10%		
		Before chemotherapy	After chemotherapy	Reduction	Before chemotherapy	After chemotherapy	Reduction
Tumor	**SUVmax**	14.10 (8.90-50.90)	11.35 (4.90-38.70)	19.52%	18.40 (10.20-24)	7.10 (1.90-14.90)	61.42%
	SUVmean	10.70 (5.10-32)	5.75 (2.10-26.90)	35.72%	8.30 (5.80-13.60)	4.40 (0.90-9.90)	50%
	MTV	7.85 (1.90-44.70)	8.15 (2.10-14.30)	37.27%	28.30 (7.20-68.50)	7.60 (0.90-17.30)	73.17%
	TLG	152.30 (9.70-654.0)	37.55 (6.70-285.10)	56.66%	354.00 (30.90-911.10)	38.00 (3.70-77.00)	89.47%
Lymph nodes	**SUVmax**	4.20 (2.70-16.80)	3.35 (2.10-13.10)	11.01%	5.00 (2.10-13.60)	2.90 (1.30-7.20)	32.50%
	SUVmean	2.40 (1.80-11.10)	2.15 (1.60-8.40)	14.4%	3.00 (1.5-8.20)	1.80 (0.90-3.70)	30.61%
	MTV	1.95 (0.40-14.60)	1.20 (0.50-10.80)	24.77%	2.40 (0.90-6.10)	1.40 (0.50-4.40)	27.86%
	TLG	4.25 (0.90-106.10)	2.90 (0.90-79.90)	29.40%	5.60 (1.5-36.90)	2.50 (0.80-16.30)	63.81%

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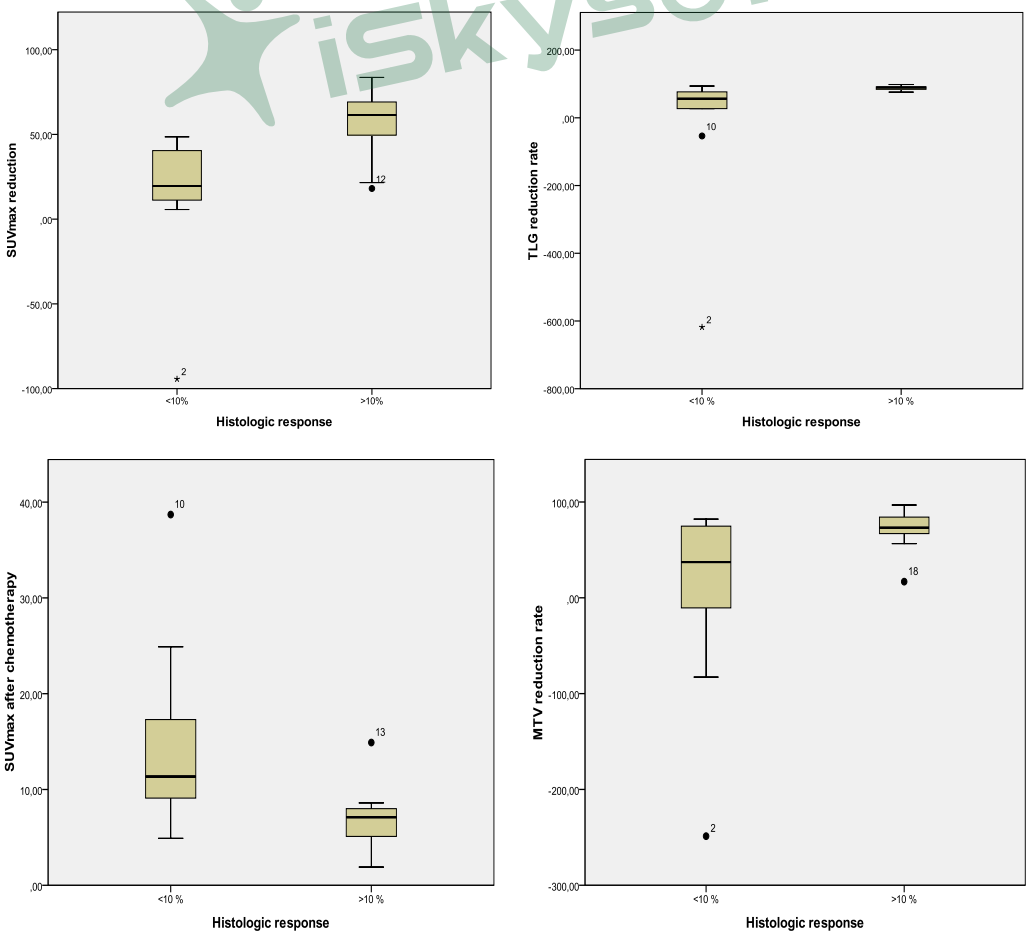
Table 3: Univariate and multivariate analysis for clinical characteristics and PET/CT indices

Characteristic		Univariate			Multivariate		
		HR	CI	p-value	HR	CI	p-value
Gender		0.058	0.004-0.930	0.04*	0.143	0.008-2.406	0.177
Postchemo N2		1.251	0.257-6.089	0.781			
Histologic response		0.079	0.014-0.443	0.004*	0.094	0.007-1.223	0.071
Operation type		1.296	0.738-2.278	0.367			
Pre SUV max	<14.45	0.37	0.92-1.486	0.16			
	≥14.45						
Post SUVmax	<13.35	2.554	0.603-10.816	0.20*	0.606	0.105-3.500	0.575
	≥13.35						
SUVmax reduction	<48.68	0.168	0.033-0.855	0.03*	0.189	0.022-1.592	0.126
	≥48.68						
Pre SUVmean	<8.05	0.708	0.188-2.657	0.6			
	≥8.05						
Post SUV mean	<4.35	1.532	0.377-6.215	0.55			
SUVmean reduction	45.19	0.45	0.112-1.809	0.26			
Pre MTV	23.05	0.463	0.115-1.870	0.28			
Post MTV	7.3	0.533	0.142-1.992	0.34			
MTV reduction	52.23	0.243	0.063-0.939	0.04*	0.378	0.044-3.265	0.376
Pre TLG	192.8	0.865	0.228-3.281	0.83			
Post TLG	33.35	1.042	0.277-3.925	0.95			
TLG reduction	77.66	0.154	0.032-0.754	0.02*	0.775	0.047-12.778	0.858

Figure 1: A-SUVmax reduction according to histologic response B-TLG reduction according to histologic response C-SUVmax after chemotherapy according to histologic response D-MTV reduction according to histologic response



Discussion

Stage III non-small cell lung cancer (NSCLC) consist of a very heterogeneous group of patients with variable localization and extent of disease. Treatment is controversial in many aspects. In the era of personalized therapy, it is important to select patients who most likely to benefit from a specific treatment. PET-BT is an accurate diagnostic tool for NSCLC patients and became the standard of care for in both staging and evaluating response to therapy. In this study we evaluated stage III lung cancer patients who operated after neoadjuvant therapy to detect variables to predict histological response and showed that lower SUV max, SUV mean and TLG in tumor after chemotherapy were associated with better histological response. Additionally, higher reduction ratio of MTV and TLG were associated with better histological response. In our knowledge, this is the first study demonstrating predictive value of MTV and TLG reduction rate on histologic response in NSCLC.

SUV is the most frequently used semi-quantitative measurement for tumor glucose metabolism however; SUV accuracy may be affected by many factors, such as a patient's body composition, blood glucose level, body habitus, length of uptake period, and resolution (11-13).

It is important to identify which patients could benefit from surgery after neoadjuvant therapy to avoid unnecessary surgery. Surrogate markers are required to predict chemotherapy outcome and pathologic response. Studies have shown that, the change in SUVmax value was correlated with pathologic response degree in NSCLC after neoadjuvant therapy. Cerfolio et al., evaluated the correlation between percentage of change in SUVmax and nonviable tumor in 56 NSCLC patients who were operated after neoadjuvant chemotherapy. They showed that, 80% or more decrease in the SUVmax , could predict a complete pathologic response with a 90% sensitivity and 100% specificity(14). We also found that; SUVmax reduction was correlated with histologic response in our patient cohort.

Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been investigated as measures of metabolic tumor burden more recently. These PET-CT indexes represent the overall malignant process in the whole body that incorporates both tumor volume and metabolic activity. Lee et al., performed the first study which assess the prognostic value of baseline whole-body MTV in 19 patients with stage I-IV lung cancer. They found that higher MTV values on PET-CT scan before therapy was associated with increased risk of progression and of death. They included patients with any stage (15). Although, we included in stage III patients, we also have shown that higher MTV and TLG reduction rates are associated with better histologic response.

The performance of total tumor burden to predict clinical outcome was also shown in early stage patients. Kim et al., evaluated MTV and TLG values in preoperative PET-CT to predict recurrence free and overall survival in 91 surgically resected NSCLC patients (16). They demonstrated that, patients with smaller MTV and lower TLG showed longer RFS and OS. These indices were found to have better predictive value than SUVmax for recurrence and death.

Hyun et al evaluated stage III 194 NSCLC patients treated with or without surgical resection and showed that MTV and TLG were both had significant prognostic impact in the surgical group but not in the nonsurgical group, whereas SUVmax was not a significant prognostic factor in either group (17).

Conclusion

TLG and MTV reduction rates were predictive for histopathologic tumor regression in NSCLC patients who were treated with neoadjuvant chemotherapy. Large scale prospective trials are needed to confirm these findings.

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Ethical issues: All Authors declare, Originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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