Prognostic value of total lesion glycolysis in stage IIIB/IV non–small cell lung cancer

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ABSTRACT

Although positron emission tomography–computed tomography (PET/CT) is widely used for staging, there are limited data available to describe exactly the role of PET/CT metabolic and quantitative parameters for the prediction of disease outcome. A total of 145 patients diagnosed with histology-proven lung carcinoma in the advanced stage were included. According to the exclusion criteria remaining 76 patients (41 of them were adenocarcinoma EGFR wild-type, 35 were squamous non-small cell lung cancer (NSCLC)) were analyzed. Maximum standardized uptake value (SUV(max)) of a primary lesion was only statistically significant parameter with progression-free survival (PFS) in regression analyses in the whole study population as well as for overall survival (OS). According to the tumor histology, squamous cell carcinoma group did not have any significant PET CT parameters for PFS and OS, but adenocarcinoma group had significant PET CT parameters which were primary lesion of SUV max, SUV mean, total lesion glycolysis (TLG), mediastinal TLG and whole body TLG. In adenocarcinoma group, patients with lower than median TLG values had significantly increased overall survival than patients having higher median whole body TLG values (median OS was 11 vs 6.5 months, P = 0.031, HR 2.1), also they had more PFS without statistical significance (median PFS 6.5 vs 4 months, P = 0.3 HR 1.2). The present study showed that PET/CT metabolic parameters give some prognostic information other than staging of NSCLC, but this information was only significant in EGFR-wild type adenocarcinoma. For squamous cell carcinoma, we need to find any driver targets.

1. Introduction

Lung cancer is the most common cause of cancer deaths and the second most common gender unrelated cancer in the World.[1] Although non-small cell lung cancer (NSCLC) is very deadly cancer, it has limited prognostic and predictive factors. The treatment and prognosis of NSCLC are related to the stage and with increasing stage prognosis gets worse, being worst in stage IV.[2] Computed tomography has been using as a primary imaging technique for the diagnosis and staging for lung cancer. However, it has very limited role to assess for metastatic disease and metabolic pattern of cancer. Currently PET CT is the method of choice for the evaluation of metastatic involvement and it offers the added metabolic information regarding the maximum glucose uptake in malignant tissues. However there are some limitations to PET CT such as falsely elevated FDG uptake because of inflammation, granulomatous diseases or false negative results that can mask residual viable tumor in a bulky lesion, even there is complete metabolic response according to the SUVmax values.[3,4]

Although PET/CT is widely used for staging, there are limited data available on the utility of metabolic and quantitative parameters of glucose metabolism for the prediction of disease outcome.[5,6] In this study we aimed to investigate the prognostic and predictive importance of metabolic parameters such as SUVmax, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) in different histologic subtypes of NSCLC.

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2. Materials and methods

2.1. Patients

This was a retrospective study of a single cancer center. A total of 145 patients diagnosed with histology-proven NSCLC were included at the beginning of study and following inclusion and exclusion criteria, remaining 76 patients (41 with adenocarcinoma EGFR wild type, 35 with squamous NSCLC) in advanced stage (≥stage IIIB) were included in the study. The inclusion criteria's were 1) patients with inoperable stage IIIA/B at diagnosis and stage IV patient lung adenocarcinoma or squamous cell carcinoma, 2) patients without history of prior chemotherapy 3) patients without mutations such as EGFR, ALK and ROS-1. Those patients with active infections and symptomatic brain metastases, those with other histologic subtype described above and who have any contraindication to chemotherapy or radiotherapy were excluded. Median follow up period was 16 months. For the assessment of clinical stage American Joint Committee on Cancer Staging System was used (refere Each patient's stage was determined by the consensus reached in our tumor board conference. The study protocol was approved by our institutional review board.

In the adenocarcinoma group, patients were treated with pemetrexed ± platinum combination chemotherapy as a first line option and patients diagnosed with squamous cell carcinoma were treated with either taxane-based or gemcitabine-based regimens. The most common chemotherapy regimen was taxane and platinum combination in squamous cell carcinoma group. Patients in stage III were treated with chemoradiotherapy.

Exclusion criteria were 1) active infections, 2) Granulomatosis disease or rheumatologic disease.

2.2. FDG PET/CT imaging

FDG PET screening was performed before the treatment and after 3 months of the treatment of NSCLC. All patients had at least 6 h fast period before the FDG PET protocol. The serum glucose levels checked before the FDG administration and all participants' glucose levels were lower than 180 mg/dL and not allowed higher than 140 mg/dL during the procedure. Totally 370 MBq (10 mCi) of FDG was administered IV within supine position and thereafter patients were stable for 1 h. Subsequently, scanning was completed from the head to the upper thighs (Biograph mCT; Siemens) with 3 min for each position. The position of patients in the CT was "arms up" position. Low-dose CT imaging protocol used for attenuation correction of PET data. PET/CT images were achieved by using standard algorithm. The attenuation-corrected for CT images, FDG, and PET/CT fusion in all section for maximum intensity projection.

2.3. PET/CT analysis

2.3.1. Visual assessment

PET/CT images were analyzed by the same blinded physician. The foci of FDG uptake was identified as representing a tumor if the accumulation of FDG was obviously increase relative to comparable normal contralateral or surrounding soft tissues and liver activity in the abdomen. All images were evaluated for local tumor site and all metastatic sites as lymph nodes, bone and other distant metastases. Staging had done according to the TNM classification as early-, locally advanced- and metastatic stages.[7,8]

2.4. Quantitative assessment

After determining the tumors, commercial software (Siemens Medical Solutions) was used for semi automatically represent the tumor borders with a threshold of 40% of the maximal SUV for lesions. We checked the results with the fused tomography slides to determine if the adjustment was needed. All MTV and SUV were determined by attenuation-corrected 18F-FDG PET images. The regions of interest (ROI) were specified as primary lesion and metastatic sites of the tracer uptake in targeted lesions. Tumor volumes were calculated with the exact threshold for the MTV, and TLG computation. Verges of the target lesions were automatically produced, and the voxels presenting SUV intensity higher than 2.5 level within contouring margin to define the MTV.[9,10] The SUVmean and SUVmax of the primary tumor, mediastinal lymph node metastases and other distant metastases (liver, adrenal etc.) were termed "SUVmean.T" and "SUVmax.T"; "SUVmean. LN and SUVmax". "LN; SUVmean.DM" and "SUVmax.DM" respectively. The whole-body SUVmean was determined from the average voxel counts within all the tumor regions "SUVmean.WB". The metabolic volumes of the primary tumor and total tumor (defined as the sum of the signal intensities of the primary tumor plus the metastatic lesions) were determined as "MTV.T" and "total MTV.WB", respectively. The TLG was calculated by the MTV multiplying the SUVmean.[10]

2.5. Statistical analysis

Progression-free survival (PFS) was defined as the time between the diagnosis and progression of disease. Overall survival (OS) was calculated as the time between the diagnosis and death and/or last follow-up. To have a suitable cutoff point for whole-body MTV, whole-body TLG, lung MTV, lung TLG, and SUVmax, the receiver operating characteristic curve have been used. Kaplan-Meier method was used for survival curves for PFS and OS, and log rank tests were used to determine the differences between groups. We analyzed prognostic factors with Cox regression analyses including whole-body TLG, whole-body MTV, lung TLG, lung MTV, SUVmax, sex, age, performance status, histologic subtype, T stage, N stage, clinical stage, and treatment method for univa3riate and multivariate prediction of PFS. All statistical tests were done with SPSS 21 inc USA, and a two-tailed P value of <0.05 was considered to be statistically significant.

3. Results

A total of 145 patients diagnosed with histology-proven NSCLC were included and after inclusion and exclusion criteria's there were 76 patients with a mean age of 64 (34-84) years old. Most of the patients were male (68/8). Forty-one patients were diagnosed with adenocarcinoma of lung and 35 patients with squamous cell carcinoma of lung. The general characteristics of the study population were summarized in Table 1. In each group 4 patients had liver metastasis, 5 patients had adrenal gland metastasis in adenocarcinoma group and 3 patients had adrenal gland metastasis in squamous cell carcinoma group, 6 patients in adenocarcinoma group and 5 patients in squamous cell carcinoma group had bone metastases, respectively. In adenocarcinoma group, twenty-eight patients were treated with pemetrexed ± platinum combination chemotherapy and the remaining 13 patients were treated with either taxane-based or vinorelbine-based regimens. The most common chemotherapy regimen was taxane and platinum combination in squamous cell carcinoma group (27/35). The mean OS of patients who had adenocarcinoma and squamous cell carcinoma was not statistically significantly different (7.2 (1.5-23) months vs 8(1-22) months, respectively, $P = 0.8$) as well as PFS (5.2(1-20) months vs 6(5-14) months, respectively, $P = 0.8$).

According to the PET CT parameters, we analyzed SUV max, mean and MTV for primary lesion of lung as well as mediastinal

Table 1
Characteristics features of the study population.

Characteristic	Adenocarcinoma	Squamous	P
N	41	35	
Age,years	62 ± 12	69 ± 9	0.012
Male/Female	35/6	33/2	0.2
Creatine,mg/dL	0.98 ± 0.3	1.03 ± 0.39	0.59
AST, IU/L	19 ± 9	19 ± 10	0.1
ALT, IU/L	17 ± 10	22 ± 11	0.38
LDH, IU/L	269 ± 100	233 ± 70	0.1
WBC, mm3	8600 ± 2000	8800 ± 3100	0.7
PLT,mm3	285000 ± 87000	283000 ± 75000	0.8
Hb, gr/dL	12.3 ± 2.2	12.5 ± 1.8	0.6
PFS,months	5.2 (1-20)	6 (5-14)	0.8
OS,months	7.2(1.5–23)	8 (1-22)	0.8

N:Number of patient, LDH: lactate dehydrogenase, WBC: White blood cell, PLT: Platelets, Hb: Hemoglobin, PFS: Progression free survival, OS: Overall survival.

lymph nodes, adrenal and liver metastases and then TLG of each lesions and then whole body TLG was calculated. Quantitative results representing metabolic tumor were shown in Table 2. When these metabolic parameters were compared between the adenocarcinoma and squamous cell carcinoma, TLG whole body, primary lesion of SUV max, and SUV mean values were found to be significantly higher in squamous cell carcinoma compared to adenocarcinoma group. No evidence of statistical difference was noted between the other parameters, either lymph nodes or metastatic lesions. .

When we focused on the relationship between survival rate and the metabolic tumor rate, Cox regression analyses showed that the SUV max of primary lesion was the only statistically significant parameter related to PFS in the whole study population ($P = 0.013$), as well as for OS ($P = 0.015$). Assessment of tumor histology with regard to these parameters indicated that squamous cell carcinoma group did not have any significant PET CT parameters for PFS and OS. On the other hand in adenocarcinoma group primary lesion SUV max, SUV mean, TLG, mediastinal TLG and whole lesions TLG results found to be significantly related to PFS and OS (P values were, 0.02, 0.038, 0.01, 0.02 and 0.012, respectively). For OS analyses, only TLG whole lesions, mediastinal lymph node TLG and primary lesion TLG were significantly correlated (P values were 0.028, 0.027 and 0.041, respectively).

In adenocarcinoma group, patients with lower than median TLG values had significantly increased overall survival than patients having higher median TLG values (median OS was 11 vs 6.5 months, $P = 0.031$, HR 2.1, also they had more PFS without statistical significance (median PFS 6.5 vs 4 months, $P = 0.3$ HR 1.2). In patients with squamous cell carcinoma, there were no significant differences between the groups for OS and PFS (median OS 9 vs 7,7 months, $P = 0.66$, median PFS 5,5 vs 6 months, $P = 0,9$), which were showed in Fig. 1 A,B,C, and D.

4. Discussion

In the present study we showed that metabolic tumor parameters of the PET/CT were clinically more valuable and significant in adenocarcinomas without driver mutations than squamous cell NSCLC. While primary lesion of SUV max, SUV mean, and TLG, mediastinal TLG and whole body TLG were significantly correlated with PFS and TLG of whole body, TLG of mediastinal lymph nodes and TLG of primary lesion were significantly correlated with OS in adenocarcinoma patients but, there was no significant correlation of any parameter with either PFS or OS in patients with squamous cell cancer. In stage IIIB and IV patients diagnosed with NSCLC, prognostic and predictive information of PET/CT remains uncertain, mostly used parameter SUV max was practical but unfortunately does not reflect the whole tumor burden and may change in many situations such as with inflammation and with size of tumor.[11,12] In recent years, metabolic tumor volume and tumor lesion glycolysis gives more information about tumor metabolic activity and showed promising outcome results in NSCLC patients.[13,14] These new parameters need to be investigated more about their clinical usage because they may need a long time for reporting and experience.

Only few but growing data have reported the prognostic and predictive value of volumetric parameters of PET CT in advanced stage NSCLC. Liao et al. investigated correlation between the OS with MTV and TLG of whole body in 92 stage IV NSCLC patients.[15] They found a significant correlation with OS and MTV and TLG of whole body whereas there was no significant correlation with SUV, MTV and TLG of metastatic lesion and lymph nodes. In this study 20 patients were diagnosed with adenocarcinoma histology and 21 patients had squamous cell, remaining 51 patients had large cell and not-otherwise specified carcinoma so they did not reveal the relation with histologic subtypes of the lung cancer and volumetric parameters. Yoo et al. also published a similar study and they found that lower values of primary lesion of MTV and TLG values had significantly longer PFS than those with higher values.[16] In contrast, SUV, MTV, and TLG whole body did not have any significant correlation. Their study population included 57 patients with stage IV NSCLC, 7 of them had squamous cell histology and 50 had adenocarcinoma (25% EGFR mutation positive, 75% EGFR wild type). These two studies showed that volumetric PET-CT parameters have some considerable findings but they also have some conflicting results. We know well that lung cancer is a heterogeneous disease and has complex histology as well as prognosis. NSCLC has mainly 4

Table 2
Comparison of PET CT parameters.

| PET CT parameters	Adenocarcinoma	Squamous	P
SUVmax primary lesion	11 ± 5	16.7 ± 7	0.002
SUVmean primary lesion	6.8 ± 3	10 ± 4	0.003
TLG primary lesion	185(15-2180)	370 (11-1475)	0.08
SUVmax mediastinal lymph nodes	6,7 ± 4	6.6 ± 2	0.28
SUVmean mediastinal lymph nodes	3,5 ± 2	3 ± 2	0.28
TLG mediastinal lymph nodes	11 (0-1380)	26 (0-933)	0.51
SUVmax Liver	7.5 ± 3	13 ± 5	0.5
SUVmean Liver	4.6 ± 2	8 ± 3	0.5
TLG Liver	93(0-2300)	146(0-3670)	0.6
SUVmax Adrenal	6(0-9)	9 (0-18)	0.8
SUVmean Adrenal	3.6 (0-6)	5 (0-8)	0.8
TLG Adrenal	33 (0-58)	28 (0-1030)	0.8
TLG whole body	292 (12.6–3290)	677 (14.6–4540)	0.046

TLG: total lesion glycolysis.
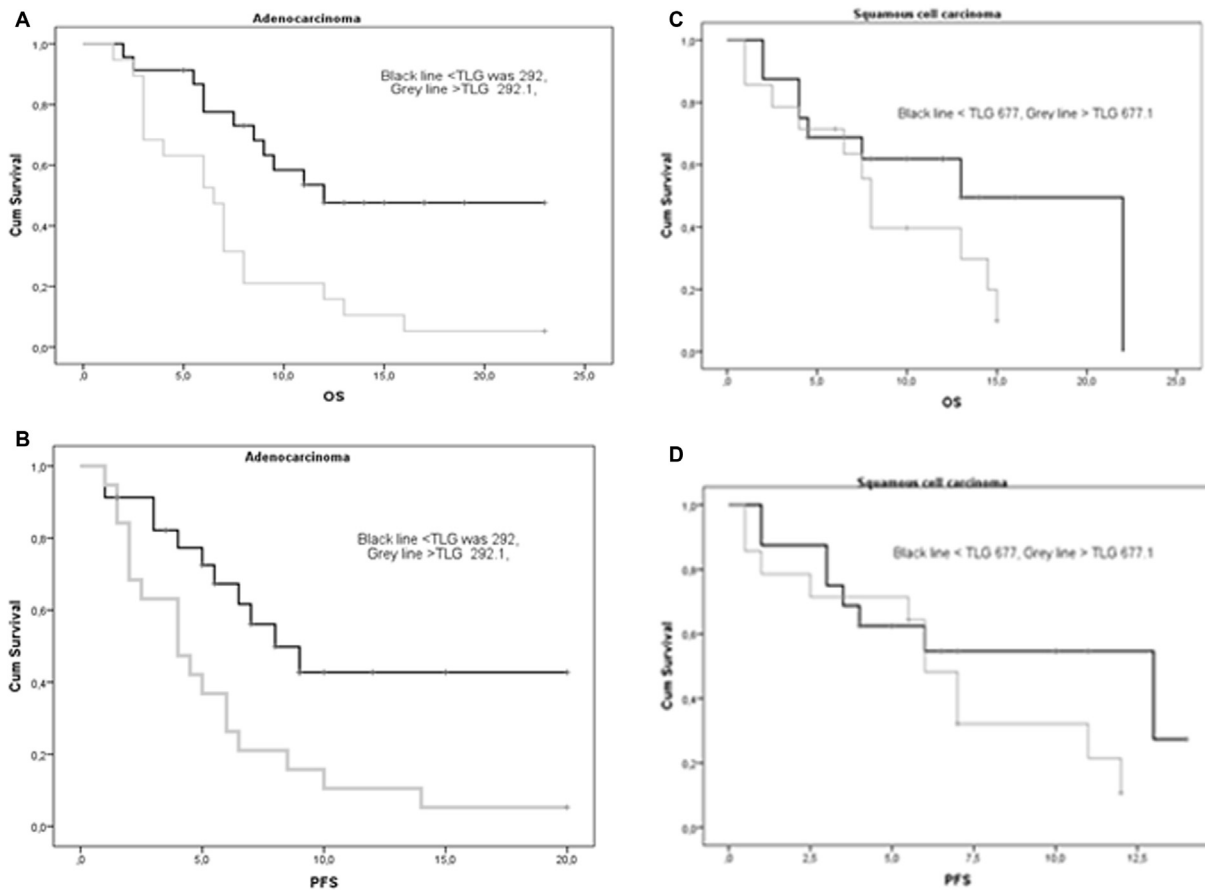
Fig. 1. Legend: Kaplan−Meier curves for overall survival (OS) and progression free survival (PFS) adjusted to TLG levels which above (high) and below (low) the median values in patients with adenocarcinoma (Fig. 1A and B). Kaplan−Meier curves for OS and PFS according to TLG levels which above and below the median values of Squamous cell carcinoma (Fig. 1C and D).

major subtypes (adenocarcinoma, squamous cell carcinoma, large cell and NOS) and in addition there are many driver mutations (EGFR, ALK, and ROS 1 etc.).[17] Briefly we can speculate that, this heterogeneous structure of the tumor may explain the conflicting results. With SUV max we can only measure a single voxel value, whereas MTV and TLG may measure the whole tumor volumetric metabolism either in primary lesion or in all measurable lesions. Nonetheless it cannot give a certain prognostic finding because metabolic behavior of the histologic subtypes of the lung cancer may differ. Also we cannot be sure of which of the metastatic site may affect the survival in advanced stage lung cancer. Brain metastases have a poor prognosis, but NSCLC mostly metastasizes to liver, adrenal gland, and bones, so it is not known clearly which of them or whether amount of tumor volume have the determinative value for survival.

As we discussed above a homogeneous study population included 56 NSCLC (25 wild type, 31 mutants) patients in the study published by Ho et al.[18] They assessed MTV and TLG and the main result of the study was that TLG in whole measurable lesions is an independent predictor of OS in EGFR mutation-negative patients with advanced lung adenocarcinoma. Patients with high TLG had a very short median OS compared to patients with low TLG (10.0 ± 2.0 vs 24.7 ± 4.4 months, respectively) but there was no significant correlation in patients with EGFR mutation-positive NSCLC. Our study included more EGFR wild type adenocarcinoma NSCLC patients and our results were consistent with the results of Ho et al. We also could not find any significant correlation in

squamous cell NSCLC with MTV and TLG similar to EGFR mutant patients. Moreover our study had a new finding for the literature; TLG of mediastinal lymph node was prognostic in adenocarcinoma without EGFR mutation but not in squamous cell carcinoma.

So, why there was no association between TLG and OS in patients with squamous cell carcinoma? Biological behavior of tumor cells is not solely regulated by the genotype of cancer cells, but it is also modified by the microenvironment of tumor.[19] Schuurbiers et al. investigated mRNA and some metabolic markers of protein expression such as glucose transporter 1 (GLUT1), carbonic anhydrase IX (CAIX), and monocarboxylate transporters (MCT) and TLG of lesion in patients with early and locally advanced stage NSCLC. They found that mRNA and protein expression of metabolic markers, with the exception of MCT4, and TLG were higher in squamous cell carcinomas than in adenocarcinomas and high TLG was associated with a worse DFS only in adenocarcinomas.[20] Biologic behavior can be modified using glucose for NSCLC subtypes. Adenocarcinoma of lung has a high metastatic potential, whereas the course of squamous cell histology usually was locally advanced.[21] In the present study there was no statically significant difference due to metastatic rates but adenocarcinoma patients were a homogenous group because they included only EGFR, ALK wild type tumors but squamous cell carcinoma patients were not homogenous. So we need to find driver targets in patients with squamous cell NSCLC.

Our study have some major limitations; such as there are limited number of patients and only driver mutations wild type

adenocarcinoma were included in the study, so we could not compare the adenocarcinoma patients with or without mutations. We analyzed data retrospectively data but all patients were followed up by the same oncologist for prognosis and survival. In addition, squamous cell carcinoma did not have any distinctiveness for pathologic characteristics such as EGFR, ALK mutations.

In conclusion our study showed that PET/CT metabolic parameters give some prognostic information other than staging of NSCLC, but this information was significant only in EGFR, ALK wild type adenocarcinoma. For squamous cell carcinoma we need to find any driver targets to better understand PET/CT metabolic parameters relationship with prognosis.

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