OPEN

Original article

Nuclear Medicine Communications

Feasibility of semiquantitative 18F-fluorodeoxyglucose PET/computed tomography in patients with advanced lung cancer for interim treatment evaluation of combining immunotherapy and chemotherapy

Linping Ke[a,b], Leilei Wu[b,c], Jinming Yu[b] and Xue Meng[b]

Objective **This study aimed to investigate the prognosis value of 18F-fluorodeoxyglucose PET/computed tomography (^{18}F-FDG PET/CT) in advanced lung cancer patients with immunotherapy combined with chemotherapy.**

Methods **Fifty-one advanced lung cancer patients were included in this retrospective study, who underwent ^{18}F-FDG PET/CT imaging before four cycles of immunotherapy combined with chemotherapy at our institution between January 2018 and January 2020. The following PET/CT parameters were calculated: standardized uptake value SUVmax, SUVmean, SUVpeak, SUVsd, metabolic tumor volume (MTV), total lesion glycolysis (TLG), MTV25%, MTV42%, MTV50%, MTV75%, global lung glycolysis (GLG), target-to-background ratio (TBR), SUVpeakwb, MTVwb, TLGwb, SUVmeanwb, SUVmaxwb. Logistics regression analyses were used for assessing the association between baseline metabolic parameters and response to treatment. Kaplan–Meier estimator curves and the log-rank test were constructed for survival analyses.**

Results **According to RECIST, nine patients (18%) showed partial response, 25 (49%) had SD, and 17 (33%) had progressive disease. The mean ± SD of SUVmax, SUVpeak, MTV were lower in clinical benefit (CB) group than no-clinical benefit (no-CB) group (all $P < 0.05$). Median PFS was 3.7 months in no-CB group and 9.9 months in CB group ($P < 0.001$). Multivariate logistic analysis indicated that SUVmax and histology were independent factors significantly related to the evaluation of therapeutic efficiency. Furthermore, SUVmax is an independent predictor of efficacy in non-small cell lung cancer.**

Conclusion **SUVmax can be used to predict interim treatment response of immunotherapy combination with chemotherapy for advanced lung cancer. Moreover, the combination of SUVmax and histology may predict treatment response with acceptable reliability. However, a large prospective multicenter trial is still needed to examine the above finding for lacking limited evidence.**

Nuclear Medicine Communications 2021, **42**:1017–1023

Keywords: fluorodeoxyglucose, immunotherapy, lung cancer, PET/CT, prognosis, SUVmax

[a]Department of Clinical Medicine, Weifang Medical University, Weifang, [b]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences and [c]Department of Radiation Oncology, School of Medicine, Shandong University, Jinan, Shandong, China

Correspondence to Xue Meng, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Shandong, China
Tel: +86 0531 67627082; fax: +86 0531 67627083;
e-mail: mengxuesdzl@163.com

Received 23 October 2020 **Accepted** 22 March 2021

Introduction

According to the latest estimate by GLOBOCAN, lung cancer has the highest rate of incidence and mortality in 2018 [1]. Primary lung cancers include 80–85% non-small-cell lung cancer (NSCLC) [2], approximately 80% of newly diagnosed NSCLC patients, who are diagnosed at an advanced stage (stage IIIB, 22%; stage IV, 56%) [3]. Along with advances in modalities of cancer treatment, immunochemotherapy has attracted great attention in recent years due to compared with traditional surgery, chemotherapy, and radiotherapy, which has posed survival benefits for advanced lung cancer [4–6]. However, the benefit of combining immunotherapy and chemotherapy in advanced lung cancer therapy is still unclear.

As there are currently some biomarkers of clinical evaluation for programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) checkpoint blockade in advanced lung cancer, such as PD-L1 status [7,8] or total mutational burden (TMB) [9,10] it is generally believed that patients with higher PD-L1 expression (>50%) had better response to immune checkpoint inhibitor (ICI) [11–13] and PD-L1 expression may be a robust predictive biomarker for immunotherapy monotherapy. However, for immunotherapy, PD-L1 expression could not completely

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.nuclearmedicinecomm.com.

0143-3636 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. DOI: 10.1097/MNM.0000000000001428

predict benefit of therapy, and a part of patients with high PD-L1 levels do not respond [14]. Nevertheless, following questions existed for above biomarkers: (1) an invasive procedure, which is not suitable for monitoring the patients' condition; (2) not accurate enough, because not all patients induce the same treatment response. Thus, there is an urgent need to find reliable novel biomarkers for early identification of tumor response to chemotherapy combined with immunotherapy [11–13].

18F-fluorodeoxyglucose PET/computed tomography (^{18}F-FDG PET/CT) is an advanced imaging examination, which became widely used for radiation therapy treatment planning, response monitoring and prognostication for locally advanced NSCLC [15–17]. Moreover, PET/CT imaging can reflect not only tumor size and tumor burden, but also growth and proliferation of tumor cells, which provides a number of parameters to evaluate the response to treatment [18]. Although limited in number, a number of studies recently have outlined the potential role of ^{18}F-FDG PET/CT in the evaluation of treatment response to immunotherapeutic agents in lung cancer [19,20]. But few articles are now available to explore the value of ^{18}F-FDG PET/CT in assessing the early response to immunotherapy combination with chemotherapy in lung cancer. The purpose of this study is to evaluate the role of ^{18}F-FDG PET/CT semiquantitative parameters in interim effects for combining chemotherapy and ICIs in advanced lung cancer.

Materials and methods

Study population

This study was approved by the Institutional Review Board of our institution (Jinan, China). All patients provided informed consent before treatment. There were 51 eligible patients in this retrospective study at our institution from January 2018 to January 2020, who underwent ^{18}F-FDG PET/CT before receiving ICIs plus chemotherapy. The inclusion criteria included were the following: (1) histologically or cytologically diagnosed lung cancer; (2) according to TNM staging system of American Joint Committee on Cancer (AJCC) 8th, stage III or IV; (3) received four cycles PD-1/PD-L1 inhibitors plus chemotherapy; (4) ECOG PS of 0 to 1; (5) older than 18 years. Follow-up was obtained via CT scan after four cycles of therapy for treatment response evaluation. The clinical pathological characteristics of age, sex, smoking status, pathologic type and the clinical staging were collected for each patient by review of the medical records.

Image acquisition

^{18}F-FDG PET/CT scans were obtained prior to start the combined immunotherapy and chemotherapy treatment within 3 months. PET/CT images were acquired by a dedicated scanner (GEMINI TF Big Bore; Philips Healthcare) in the Department of Nuclear Medicine and PET-CT Centre. All subjects were advised to fast for at least 6 h and have serum glucose levels of less than 11 mol/l before receiving 370 MBq (10 mCi) of FDG administered intravenously. After resting in a lounge chair for at least 1 h, the patients went through 5 min whole-body Emission scanning from the head to the thighs. During PET scanning, all subjects were asked to slow and shallow breath. The reconstructed images were obtained by ordered-subset expectation maximization (OSEM) after transmission data from CT were attenuation corrected. Thereafter, the attenuation-corrected images of PET and CT, as well as fused PET/CT images in the transverse, coronal, and sagittal planes were observed on a dedicated workstation (Xeleris; GE Healthcare).

Images calculation and analysis

Two nuclear medicine physicians with more than 15 years working experience analyzed the PET/CT images by MIM software (MIM, 6.2.8, Cleveland, OH, USA) independently. According to CT scans and PET/CT fusion images, regions of interest (ROIs) were outlined in the axial, sagittal and coronal planes, using an automated contouring program with a fixed standardized uptake value (SUV) threshold of 2.5 (Fig. 1s in Supplementary, Supplemental digital content 1, *http://links.lww.com/NMC/A192*) [21].^{18}F-FDG uptake of the normal organs and the high activity structures because of inflammation such as stomach, intestine, vessels and heart was removed in the ROI. The following FDG-PET metabolic information were obtained by MIM software: SUVmax, SUVmean, the largest possible mean value of a 1 cm^3 of ROI (SUVpeak),the SD of SUV (SUVsd), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). In addition to the above parameters, MTV25%, MTV42%, MTV50% and MTV75% were also calculated, which meant total tumor volume with an absolute threshold of 25, 42, 50 and 75%, respectively. The sectional lung glycolysis (sLG) was calculated through multiplying the sectional lung volume by the sectional SUVmean (sSUVmean) of ROI. Furthermore, the global lung glycolysis (GLG) was obtained by summing the sLG of all slices [22]. In order to obtain target-to-background ratio (TBR), drawing five ROIs of similar diameter on the normal liver, and then calculated the average of their SUVmean. Thereafter, the TBR were computed by dividing the SUVmax of tumor with SUVmean of the liver [23]. The sum of the individual SUVmax, SUVmean, SUVpeak, MTV, and TLG of all measured lesions represented the whole-body burden values (SUVmaxwb, SUVmeanwb, SUVpeakwb, MTVwb, and TLGwb).

Evaluation of response to combination treatment

Based on RECIST (Response Evaluation Criteria in Solid Tumor) [24], the response to therapy was defined as complete response (CR), partial response (PR) and stable disease (SD), as well as progressive disease (PD) according to every 2–3 weeks clinical and radiological follow-up.

Table 1 Characteristics of all patients

Variables	Values[a]
Number of patients	51
Age (years)	62 (37–78)
Height (cm)	167 (144–181)
Weight (kg)	65 (32.5–92.5)
Gender	
Male	35(69)
Female	16(31)
Histology	
Adenocarcinoma	28(55)
Squamous cell carcinoma	14(27)
Small cell carcinoma	9(18)
TNM stage	
T stage	
TX	3(6)
T1	7(14)
T2	21(41)
T3	7(14)
T4	13(25)
N stage	
N0	8(16)
N1	2(4)
N2	16(31)
N3	25(49)
M stage	
M0	14(27)
M1	37(72)
Overall stage	
IIIA	7(14)
IIIB	7(14)
IV	35(72)
Drinking status	
Never-drinker	36(71)
Drinker	15(29)
Smoking status	
Never-smoker	26(51)
Smoker	25(49)
Hypertension	
Yes	10(20)
No	41(80)
Diabetes	
Yes	10(20)
No	41(80)
Tumor location	
RUL	10(20)
RML	3(6)
RLL	8(16)
LUL	21(41)
LLL	9(18)

LLL, left lower lung; LUL, left upper lung; NA, not available; RLL, right lower lung; RML, right middle lung; RUL, right upper lung; TNM, tumor, node and metastasis.[a]Median (interquartile range) or number (%).

Some research showed that SD following immunotherapy has similar survival rates comparing with those associated with response [25–27]. Therefore, clinical benefit (CB) was identified as patients with CR, PR and SD and no-clinical benefit (no-CB) was patients with PD [28,29].

Statistical analyses

The reasons of statistical analysis were described as the following: The difference of all ^{18}F-FDG PET/CT parameters in two response groups (CB and no-CB) were compared by independent sample student *t*-test. Concomitantly, thanks to limited patient number, univariate and multivariate logistic regression analysis with upward elimination method were used to further assess the relationship between parameters of ^{18}F-FDG PET/CT and efficacy of chemoimmunotherapy. For descriptive purposes, the median value of PET/CT measurement was regarded as the cutoff point. Overall survival was computed from the beginning of combination therapy of chemotherapy with immunotherapy until death for any cause or the date of last contact. Progression-free survival (PFS) was defined as the end of combination treatment with immunotherapy and chemotherapy until disease progression or death from any cause. Kaplan–Meier analyses and the log-rank test were used to quantify the associations about survival. SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. P-value < 0.05 was considered statistically significant.

Results

Characteristics of the patients

This study analyzed 51 advanced lung cancer patients (35 men, 16 women; median age 62 years, range 37–78 years). The histologic subtype was adenocarcinoma in 28, squamous cell carcinoma (SCC) in 14, small cell lung carcinoma (SCLC) in nine patients. There were 35 with stage IV and 16 with stage III. Moreover, chemotherapeutic drugs of the combination treatment of immunotherapy and chemotherapy, combination chemotherapy was delivered in 26 cases (51%) with platinum-based chemotherapy and single agent [24 (96%) of 25 in the taxane, 1 (4%) of 25 in the gemcitabine] in 25 cases (49%), respectively. Immunotherapeutic agents mainly included pembrolizumab (22%, 11/51), sintilimab (33%, 17/51) and camrelizumab (16%, 8/51). The proportion of smokers and no-smokers is also similar with 49% and 51%, respectively (Table 1). The median follow-up was 10.0 months (range 1.37–29.43 months), median PFS was 7.8 months (range 1.2–21.57 months).

Treatment response

Of note, after completion four cycles of the combined administration, 9 (18%) of 51 patients in PR and 25 (49%) in SD, 17 (33%) in PD. Particularly, the mean ± SD of SUVmax, SUVpeak and MTV was higher in no-CB group than CB group (15.03 ± 6.79 vs. 11.10 ± 5.01, 11.13 ± 5.34 vs. 7.84 ± 4.69, 115.56 ± 139.85 vs. 52.56 ± 76.66, respectively; all $P < 0.05$). At the same time, GLG and MTVwb were also higher in no-clinical benefit group than clinical benefit group, but this was marginally statistically significant (2830.04 ± 880.40 vs. 2365.57 ± 794.29, $P = 0.058$; 116.57 ± 139.19 vs. 61.55 ± 79.76, $P = 0.078$; respectively (Table 2).

Subgroup analysis found that in non-small cell lung cancer, all parameters in the CB group have lower mean ± SD

Table 2 *t*-test for all 51 patients

Parameters	Clinical benefit (32) (mean ± SD)	No-clinical benefit (19) (mean ± SD)	*P*-value (*t*-test)
SUVmax	11.10 ± 5.01	15.03 ± 6.79	0.022
SUVpeak	7.84 ± 4.69	11.13 ± 5.34	0.026
SUVmean	4.89 ± 1.86	5.53 ± 1.97	0.255
SUVsd	2.30 ± 1.30	2.83 ± 1.48	0.191
MTV	52.56 ± 76.66	115.56 ± 139.85	0.042
TLG	333.92 ± 737.82	685.34 ± 792.98	0.116
MTV25%	44.19 ± 60.34	77.50 ± 78.10	0.249
MTV42%	24.92 ± 39.23	45.11 ± 49.64	0.114
MTV50%	17.48 ± 33.43	32.15 ± 31.73	0.129
MTV75%	4.76 ± 9.76	7.32 ± 7.01	0.333
GLG	2365.57 ± 794.29	2830.04 ± 880.40	0.058
TBR	4.48 ± 2.16	5.28 ± 3.07	0.284
SUVpeakwb	9.03 ± 5.26	11.65 ± 5.81	0.105
MTVwb	61.55 ± 79.76	116.57 ± 139.19	0.078
TLGwb	361.24 ± 742.07	687.53 ± 791.36	0.145
SUVmeanwb	5.53 ± 3.15	5.71 ± 2.11	0.830
SUVmaxwb	28.95 ± 25.23	31.75 ± 16.85	0.669

GLG, global lung glycolysis; MTV, metabolic tumor volume with SUV 2.5; MTVwb, whole-body metabolic tumor volume; SUVpeak, peak standardized uptake value; SUVpeakwb, whole-body peak standardized uptake value; SUVmean, mean standardized uptake value; SUVmeanwb, whole-body mean standardized uptake value; SUVmax, maximum standardized uptake value; SUVmaxwb, whole-body maximum standardized uptake value; SUVsd, SD of standardized uptake volume; TBR, tumor-to-background ratio; TLG, total lesion glycolysis; TLGwb, whole-body total lesion glycolysis.

Table 3 *t*-test for non-small-cell lung cancer patients

Parameters	Clinical benefit (31) (mean ± SD)	No-clinical benefit (11) (mean ± SD)	*P*-value (*t*-test)
SUVmax	11.50 ± 5.54	17.21 ± 5.87	0.006
SUVpeak	8.20 ± 4.95	12.42 ± 5.11	0.021
SUVmean	4.87 ± 1.89	5.67 ± 1.51	0.222
SUVsd	2.34 ± 1.36	3.00 ± 1.20	0.157
MTV	53.87 ± 78.83	98.88 ± 80.53	0.114
TLG	345.70 ± 755.65	639.48 ± 614.57	0.254
MTV25%	44.44 ± 61.21	64.68 ± 47.64	0.327
MTV42%	25.36 ± 40.41	43.03 ± 43.13	0.228
MTV50%	17.90 ± 34.03	29.10 ± 29.63	0.339
MTV75%	5.18 ± 10.47	5.75 ± 6.41	0.868
GLG	2466.79 ± 850.56	2821.73 ± 911.02	0.250
TBR	4.57 ± 2.31	5.94 ± 3.49	0.149
SUVpeakwb	9.33 ± 5.61	13.05 ± 5.42	0.064
MTVwb	62.53 ± 81.79	100.63 ± 78.86	0.188
TLGwb	369.64 ± 759.29	643.27 ± 611.11	0.289
SUVmeanwb	5.51 ± 3.20	5.98 ± 1.78	0.650
SUVmaxwb	28.33 ± 25.53	32.57 ± 10.15	0.597

GLG, global lung glycolysis; MTV, metabolic tumor volume with SUV 2.5; MTVwb, whole-body metabolic tumor volume; SUVpeak, peak standardized uptake value; SUVpeakwb, whole-body peak standardized uptake value; SUVmean, mean standardized uptake value; SUVmeanwb, whole-body mean standardized uptake value; SUVmax, maximum standardized uptake value; SUVmaxwb, whole-body maximum standardized uptake value; SUVsd, SD of standardized uptake volume; TBR, tumor-to-background ratio; TLG, total lesion glycolysis; TLGwb, whole-body total lesion glycolysis.

values than in the no-CB group, but only the difference between parameters SUVmax and SUVpeak is statistically significant (17.21 ± 5.87 vs. 11.50 ± 5.54, 12.42 ± 5.11 vs. 8.20 ± 4.95, respectively; all $P < 0.05$) (Table 3).

Statistical analyses

In univariate logistics analysis, SUVmax, SUVpeak, MTV was significantly associated with response to therapy [odds ratio (OR), 0.876; $P = 0.033$ and OR, 0.887; $P = 0.029$, OR, 0.938; $P = 0.045$, respectively]. Multivariate analysis demonstrated that there is a significant association between treatment efficacy and SUVmax as well as pathological types (OR, 0.842; $P = 0.011$, OR, 0.098; $P = 0.014$, respectively), which reveals that pathology and SUVmax were predictors of response to treatment. However, no statistical significant were found between other variables and treatment efficacy (Table 4).

In NSCLC Patients, univariate and multivariate analysis reflects that SUVmax is an independent prognostic factor of treatment response (OR, 0.845; $P = 0.016$; Table 5).

Of the 51 subjects enrolled for the study, the median follow-up was similar between no-CB group and CB group [9.9 months (range 1.37–21.37 months) vs.11.0 months (range 2.2–29.4 months)]. At data cutoff (on 1 August 2020), 13 (76%) of 17 patients in no-CB group and 9 (26%) of 34 patients in CB group met a PFS event. Median PFS was 3.7 months [95% confidence interval (CI): 3.3–4.1] in the no-clinical benefit group and 9.9 months (95% CI: 9.1–10.9) in the clinical benefit group ($P < 0.001$; Fig. 1). Nine (18%) of 17 patients in the no-clinical benefit group and 6 (26%) of 34 patients in the clinical benefit group had died.

In the subgroup, according to the median value, 51 patients were divided into SUVmax ≤ 11.99 (n = 26) and SUVmax > 11.99 (n = 25). Median PFS was 16.9 months (95% CI: 13.8–20) in SUVmax ≤ 11.99 and 9.8 months (95% CI: 5.2–14.3) in SUVmax > 11.99 ($P = 0.158$; Fig. 2).

With respect to the pathological analysis, they were divided into three groups. Median PFS was 16.9 months (95% CI: 7.0–26.8) in adenocarcinoma group, 14.8 months (95% CI: 4.3–25.3) in SCC group and 3.6 months (95% CI: 3.2–4.0) in SCLC group ($P = 0.042$; Fig. 3).

Discussion

The primary goal of this investigation was to explore the relationship between ^{18}F-FDG PET/CT metabolic parameters and response to immunochemotherapy. We found that SUVmax was potential predictor of the evaluation of therapeutic efficiency (OR 0.842; $P = 0.011$). Additionally, logistic analysis also revealed that histology was able to predict response to therapy (OR 0.098; $P = 0.014$). Although many studies have shown that the combination treatment of immunotherapy and chemotherapy had brought survival benefits for advanced patients with lung cancer [4–6], the benefit of combining these two therapeutic methods remain indistinct. In this study, we found that SUVmax may best predict the efficacy of combination therapy, which will enable clinicians to adjust their therapeutic strategies in a timely fashion for those patients who did not benefit from treatment, consequently improving the clinical outcome of therapy.

In a previous study, metabolism increases demonstrated that prognosis of lung cancer patients is poor [30]. We found that the mean ± SD of ^{18}F-FDG PET/CT in no-CB

Table 4 Results of univariate analysis and multivariate analysis

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex (male vs. female)	1.231 (0.277–5.477)	0.785		
Age (years) (>62 vs. ≤62)	0.416 (0.104–1.664)	0.215		
Smoking status (never-smoker vs. smoker)	0.543 (0.140–2.104)	0.377		
Histology (adenocarcinoma vs. squamous cell carcinoma vs. small cell carcinoma)	0.167 (0.033–0.849)	0.031	0.098(0.015–0.626)	0.014
SUVpeak	0.876 (0.775–0.989)	0.033		
SUVmax	0.887 (0.797–0.988)	0.029	0.842 (0.738–0.961)	0.011
MTV	0.938 (0.881–0.999)	0.045		
GLG	1.000 (0.999–1.000)	0.231		
MTVwb	0.994 (0.988–1.001)	0.102		

CI, confidence interval; OR, odds ratio; GLG, global lung glycolysis; MTV, metabolic tumor volume with SUV 2.5; MTVwb, whole-body metabolic tumor volume; SUVmax, maximum standardized uptake value; SUVpeak, peak standardized uptake value.

Table 5 Results of univariate analysis and multivariate analysis in non-small-cell lung cancer patients

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex (male vs. female)	1.270 (0.276–5.839)	0.759		
Age (years) (>62 vs. ≤62)	0.907 (0.800–1.029)	0.131		
Smoking status (never-smoker vs. smoker)	1.125 (0.283–4.472)	0.867		
SUVpeak	0.850 (0.734–0.985)	0.031		
SUVmax	0.839 (0.728–0.966)	0.015	0.845 (0.732–0.968)	0.016

CI, confidence interval; OR, odds ratio; SUVmax, maximum standardized uptake value; SUVpeak, peak standardized uptake value.

group was higher in all semiquantitative parameters evaluated from pretreatment scans compared with CB group. Chemotherapy might be synergistic with immunotherapy through release of potentially immunogenic tumor antigens [31,32]. The tumor metabolic information of ^{18}F-FDG PET/CT is actively associated with tumor-related immune cells [33,34]. Immunotherapy plus chemotherapy might activate the increase of immunogenic tumor antigens compared to immunotherapy alone, which further promoted the FDG uptake on tumor lesion.

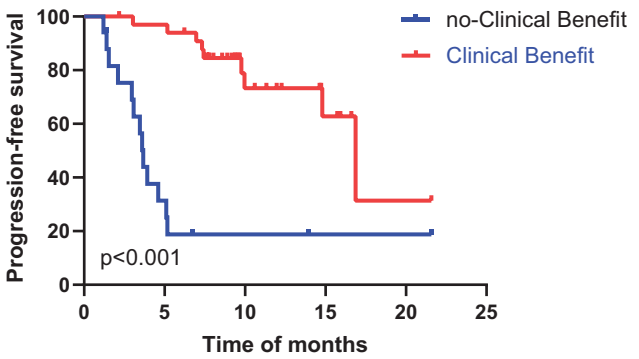
Benz MR *et al.* demonstrated that ^{18}F-FDG PET/CT was a validated tool in the evaluation of treatment response in lung cancer [30,35,36]. Sharma *et al.* [23] found that pretreatment parameters of ^{18}F-FDG PET/CT were equipped to predict the response of chemotherapy with acceptable reliability in advanced NSCLC patients. However, no relationship was found between SUVmax and response to chemotherapy. A report demonstrated that the entire tumor burden (such as SUVmaxwb, MTVwb, TLGwb) evaluated by ^{18}F-FDG PET/CT can predict response to immunotherapy alone in patients with advanced lung cancer; however, it also not showed the correlation between SUVmax and response to immunotherapy monotherapy [20]. However, in this study, multivariate analyses revealed SUVmax in PET/CT were predictors of response to treatment in patients with advanced lung cancer. First, the difference could be influenced by the type of treatment modality. Moreover, we have also evaluated many additional semiquantitative parameters, which, as per our results, is useful in identifying clinical benefit from no-clinical benefit. No such single study can be found in the literature evaluating the role of so many parameters in patients with lung cancer.

Furthermore, a preliminary analysis found an antithetical correlation between PET/CT baseline parameters (SUVmax and SUVmean) and the response to immunotherapy in patients with NSCLC [37]. For the past few years, SUVmax was used in the several literature to evaluate treatment (surgery, radiotherapy and chemotherapy) response and prognosis in lung cancer, even immunotherapy [23,37,38]. The results obtained from our study do agree with the above-mentioned study. It is likely because SUVmax can provide information on tumor lesion aggressiveness, which is the one associated with highest metabolic for all lesions, representing the most active areas of tumor and the most fast proliferative capacity of tumor cells, appeared to be most sensitive to treatment.

We also explored the gap between response to chemotherapy combined with immunotherapy and clinical features and found a statistically significant correlation between SUVmax and pathology with the treatment response. PFS benefits were observed in the subgroup, but patients in the group of SUVmax ≤ 11.99 vs. SUVmax > 11.99 showed no statistically significant. It was found that lung cancer patients with adenocarcinomas had longer PFS than SCC and SCLC. In the present study, pathology was a predictor of response to chemotherapy combined with immunotherapy in patients with advanced lung cancer, suggesting response to combination therapy might be associated with pathology and intratumoral heterogeneity.

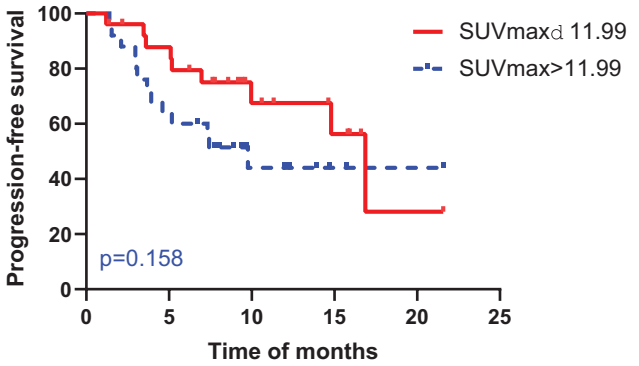
Our study had some limitations. The study included a small sample size and relatively homogeneous incorporated patients (patients in our study are clinically stage III or IV disease at inclusion). Apart from this, owing to a considerably small sample size, the analysis of survival data for this study was not performed, which might question this observation. Furthermore, a larger sample size was required for the study of patients with lung cancer to more accurately evaluate and define the value of these semiquantitative parameters for response evaluation.

Fig. 1



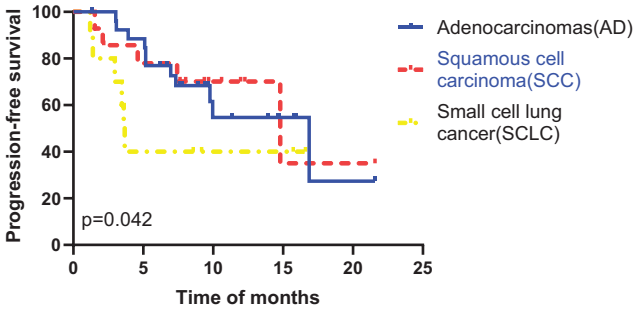
Kaplan–Meier plots for progression-free survival in the no-clinical benefit (no-CB) group and clinical benefit (CB) group population.

Fig. 2



Kaplan–Meier plots for progression-free survival in the SUVmax ≤ 11.99 vs. SUVmax > 11.99 population. SUVmax, maximum standardized uptake value.

Fig. 3



Kaplan–Meier plots for progression-free survival in the adenocarcinomas (AD) vs. squamous cell carcinoma (SCC) vs. small cell lung cancer (SCLC) population.

Conclusion

Our data suggest that SUVmax as an imaging biomarker can be used to predict interim treatment response of immunotherapy combination with chemotherapy for advanced lung cancer patients. Moreover, ^{18}F-FDG PET/CT parameters in combination with clinical features (SUVmax and histology) may predict treatment response with acceptable reliability. However, this evidence is clearly still very limited and further large prospective multicenter trials are needed to examine the role of ^{18}F-FDG PET/CT semiquantitative parameters, to find a suitable biomarker for evaluating response to immunotherapy combined with chemotherapy.

Acknowledgements

This study is supported by the Innovation Project of Shandong Academy of Medical Sciences (2019-04), and the Academic Promotion Program of Shandong First Medical University (2019ZL002), National Natural Science Foundation of China (81972864), Academic Promotion Program of Shandong First Medical University (2019RC002), Science and Technology Support Plan for Youth Innovation Teams of Universities in Shandong Province (2019KJL001) and Science and Technology Plan of Jinan (201907113).

Author contributions statement: M.X. and Y.J. contributed conception and design of the study; K.L. and W.L. organized the database; K.L. performed the statistical analysis; K.L. and M.X. and Y.J. wrote the first draft of the article. All authors contributed to article revision, read and approved the submitted version.

Conflicts of interest

There are no conflicts of interest.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, 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; **68**:394–424.

2 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**:74–108.

3 Scagliotti GV, Bironzo P, Vansteenkiste JF. Addressing the unmet need in lung cancer: the potential of immuno-oncology. *Cancer Treat Rev* 2015; **41**:465–475.

4 West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, *et al.* Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; **20**:924–937.

5 Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, *et al.*; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378**:2078–2092.

6 Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, *et al.*; KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018; **379**:2040–2051.

7 Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, *et al.* Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. *New Engl J Med* 2012; **366**:2443–2454.

8 Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, *et al.*; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389**:255–265.

9 Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med* 2017; **377**:2500–2501.
10 Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, *et al*. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; **348**:124–128.
11 Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther* 2015; **14**:847–856.
12 Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med* 2012; **366**:2517–2519.
13 Merelli B, Massi D, Cattaneo L, Mandalà M. Targeting the PD1/PD-L1 axis in melanoma: biological rationale, clinical challenges and opportunities. *Crit Rev Oncol Hematol* 2014; **89**:140–165.
14 Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. *Lancet Oncol* 2016; **17**:e542–e551.
15 Salavati A, Duan F, Snyder BS, Wei B, Houshmand S, Khiewvan B, *et al*. Optimal FDG PET/CT volumetric parameters for risk stratification in patients with locally advanced non-small cell lung cancer: results from the ACRIN 6668/RTOG 0235 trial. *Eur J Nucl Med Mol Imaging* 2017; **44**:1969–1983.
16 Simone CB II, Houshmand S, Kalbasi A, Salavati A, Alavi A. PET-based thoracic radiation oncology. *PET Clin* 2016; **11**:319–332.
17 Geiger GA, Kim MB, Xanthopoulos EP, Pryma DA, Grover S, Plastaras JP, *et al*. Stage migration in planning PET/CT scans in patients due to receive radiotherapy for non-small-cell lung cancer. *Clin Lung Cancer* 2014; **15**:79–85.
18 Czernin J, Allen-Auerbach M, Schelbert HR. Improvements in cancer staging with PET/CT: literature-based evidence as of September 2006. *J Nucl Med* 2007; **48** (Suppl 1):78s–88s.
19 Jreige M, Letovanec I, Chaba K, Renaud S, Rusakiewicz S, Cristina V, *et al*. 18F-FDG PET metabolic-to-morphological volume ratio predicts PD-L1 tumour expression and response to PD-1 blockade in non-small-cell lung cancer. *Eur J Nucl Med Mol Imaging* 2019; **46**:1859–1868.
20 Evangelista L, Cuppari L, Menis J, Bonanno L, Reccia P, Frega S, Pasello G. 18F-FDG PET/CT in non-small-cell lung cancer patients: a potential predictive biomarker of response to immunotherapy. *Nucl Med Commun* 2019; **40**:802–807.
21 Luan X, Huang Y, Gao S, Sun X, Wang S, Ma L, *et al*. 18F-alfatide PET/CT may predict short-term outcome of concurrent chemoradiotherapy in patients with advanced non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2016; **43**:2336–2342.
22 Jahangiri P, Pournazari K, Torigian DA, Werner TJ, Swisher-McClure S, Simone CB II, Alavi A. A prospective study of the feasibility of FDG-PET/CT imaging to quantify radiation-induced lung inflammation in locally advanced non-small cell lung cancer patients receiving proton or photon radiotherapy. *Eur J Nucl Med Mol Imaging* 2019; **46**:206–216.
23 Sharma A, Mohan A, Bhalla AS, Vishnubhatla S, Pandey AK, Bal CS, Kumar R. Role of various semiquantitative parameters of 18F-FDG PET/CT studies for interim treatment response evaluation in non-small-cell lung cancer. *Nucl Med Commun* 2017; **38**:858–867.
24 Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, *et al*. iRECIST: guidelines for response criteria foruse in trials testing immunotherapeutics. *LancetOncol* 2017; **18**:e143–e152.
25 Hodi FS, Butler M, Oble DA, Seiden MV, Haluska FG, Kruse A, *et al*. Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. *Proc Natl Acad Sci U S A* 2008; **105**:3005–3010.
26 Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, *et al*. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; **15**:7412–7420.
27 Dougan M, Dranoff G. Immune therapy for cancer. *Annu Rev Immunol* 2009; **27**:83–117.
28 Anwar H, Sachpekidis C, Winkler J, Kopp-Schneider A, Haberkorn U, Hassel JC, Dimitrakopoulou-Strauss A. Absolute number of new lesions on 18F-FDG PET/CT is more predictive of clinical response than SUV changes in metastatic melanoma patients receiving ipilimumab. *Eur J Nucl Med Mol Imaging* 2018; **45**:376–383.
29 Sachpekidis C, Anwar H, Winkler J, Kopp-Schneider A, Larribere L, Haberkorn U, *et al*. The role of interim 18F-FDG PET/CT in prediction of response to ipilimumab treatment in metastatic melanoma. *Eur J Nucl Med Mol Imaging* 2018; **45**:1289–1296.
30 Ma W, Wang M, Li X, Huang H, Zhu Y, Song X, *et al*. Quantitative 18F-FDG PET analysis in survival rate prediction of patients with non-small cell lung cancer. *Oncol Lett* 2018; **16**:4129–4136.
31 Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. *Nat Rev Immunol* 2008; **8**:59–73.
32 Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013; **39**:1–10.
33 Appelberg R, Moreira D, Barreira-Silva P, Borges M, Silva L, Dinis-Oliveira RJ, *et al*. The Warburg effect in mycobacterial granulomas is dependent on the recruitment and activation of macrophages by interferon-γ. *Immunology* 2015; **145**:498–507.
34 Palsson-McDermott EM, O'Neill LA. The Warburg effect then and now: from cancer to inflammatory diseases. *Bioessays* 2013; **35**:965–973.
35 Benz MR, Evilevitch V, Allen-Auerbach MS, Eilber FC, Phelps ME, Czernin J, Weber WA. Treatment monitoring by 18F-FDG PET/CT in patients with sarcomas: interobserver variability of quantitative parameters in treatment-induced changes in histopathologically responding and nonresponding tumors. *J Nucl Med* 2008; **49**:1038–1046.
36 Lee SH, Rimner A, Gelb E, Deasy JO, Hunt MA, Humm JL, Tyagi N. Correlation between tumor metabolism and semiquantitative perfusion magnetic resonance imaging metrics in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2018; **102**:718–726.
37 Grizzi F, Castello A, Lopci E. Is it time to change our vision of tumor metabolism prior to immunotherapy? *Eur J Nucl Med Mol Imaging* 2018; **45**:1072–1075.
38 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; **8**:51630–51640.