Int J Clin Exp Med 2018;11(2):1133-1140
www.ijcem.com /ISSN:1940-5901/IJCEM0059841

Original Article

The study of the correlation between quantitative ^{18}F-FDG PET/CT metabolic parameters and the early treatment response for non-small cell lung cancer with chemoradiotherapy

Hongbin Deng[1,2*], Changsheng Ma[2*], Jinghao Duan[2], Judong Luo[2], Yong Yin[2]

[1]School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan 250022, Shandong, China; [2]Shandong Cancer Hospital Affiliated to Shandong University, Jinan 250117, Shandong, China. [*]Equal contributors.

Received June 19, 2017; Accepted November 27, 2017; Epub February 15, 2018; Published February 28, 2018

Abstract: Objective: This study was to investigate the correlation of pretreatment ^{18}F-FDG PET/CT metabolic parameters and the early treatment response to chemoradiotherapy in patients with non-small cell lung cancer (NSCLC). Methods: PET/CT images of 61 patients with locally advanced NSCLC (31 patients with adenocarcinoma and 30 with squamous cell carcinoma) were collected at Shandong Cancer Hospital. All patients accepted chemoradiotherapy. The gross tumor volume (GTV) was delineated on PET/CT images with standard uptake values (SUVs) > 2.5. SUV volume histograms, maximum SUV (SUV_{max}), mean SUV (SUV_{mean}), metabolic tumor volume (MTV), total lesion glycolysis (TLG) and area under the curve of the cumulative SUV volume histogram (AUC-CSH) were extracted. The correlations between the metabolic parameters and three months after treatment for early treatment response were analyzed. Results: AUC-CSH, SUV_{max}, SUV_{mean}, MTV, and TLG correlated with the early treatment response in lung adenocarcinoma patients. For squamous cell carcinoma, all parameters were associated with the early treatment response except for MTV, and all the results was same to the One-way ANOVA analysis. Multivariate Linear regression analysis, SUV_{max} was an independent prognostic factor for the early treatment response in adenocarcinoma cases (standardized coefficient =-0.708, P=0.000). AUC-CSH was an independent prognostic factor for squamous cell carcinoma (standardized coefficient =0.733, P=0.000). We used the ROC curve to analyze the efficacy of the parameters to predict the treatment response. Receiver-operating characteristic curve (ROC) analysis showed that the cut-off threshold of SUV_{max} for adenocarcinoma was 8.650, with 76.5% sensitivity and 100% specificity, and the cut-off threshold of AUC-CSH for squamous cell carcinoma was 0.4715, with 83.3% sensitivity and 100% specificity. Conclusions: Quantitative metabolic parameters are valuable for predicting the early treatment response in NSCLC, and special parameters should be applied for different pathological types of NSCLC.

Keywords: PET/CT, quantitative parameters, chemoradiotherapy, treatment response, NSCLC

Introduction

Lung cancer is one of the most common malignant tumors with the highest rates of morbidity and mortality worldwide [1]. In 2008, there were 1.61 million new cases and 1.38 million deaths from lung cancer [2]. Non-small cell lung cancer (NSCLC) accounts for up to 85% of all lung cancers, with adenocarcinoma and squamous cell carcinoma making up 50% and 30% of cases, respectively. For patients with inoperable NSCLC, radiotherapy and chemoradiotherapy play very important roles. The 5-year survival rates of patients with stage I-II and III NSCLC are only 50% and 20%, respectively. The main cause of death is local progression and distant metastasis [3]. Early and accurately prediction of the treatment response can be detected in patients with high risk of recurrence and clinical intervention timely.

Although many studies have investigated the predictive value of pretreatment tumor characteristics, there are currently no standardized methods for predicting the response to therapy early in the course of treatment. FDG-PET/CT provides a potential advantage over other morphological imaging. It is rapid, non-invasive, in

vivo and quantitative method of glucose metabolism which precedes changes in tumor size and can possibly reflect drug effects at a cellular level. It might also be a powerful tool for measurement of treatment response, which may enable a distinction between patients who are going to benefit from treatment. In recent years, ^{18}F-FDG PET has been used to assess the treatment response and predict patient outcome [4]. ^{18}F-FDG PET/CT images reflect both morphological changes of the tumor as well as the metabolic activity inside the tumor, which makes this the main method used to quantitatively analyze heterogeneity in tumor metabolism [5].

Traditional parameters, such as the maximum standard uptake value (SUV_{max}) and mean standard uptake value (SUV_{mean}), have some limitations in predicting the early treatment response [6]. Several studies have reported that quantitative and semi-quantitative parameters of FDG-PET, including metabolic tumor volume (MTV), gross total lesion glycolysis (TLG) and cumulative area under the curve area (AUC-CSH), are more important for predicting prognosis [7, 8].

The cumulative volume histogram (CSH) of SUV is a new method to quantitatively analyze intratumor heterogeneity. This method allows the area under the CSH (AUC-CSH) curve to be quantified as a percentage of the total tumor volume exceeding a percentage threshold of SUV_{max}, with lower AUC-CSH values corresponding to higher degrees of heterogeneity [9]. Kang SR et al. retrospectively reviewed 116 pretreatment FDG PET/CT scans of patients with inoperable stage III NSCLC and found that the AUC-CSH was the most significant independent prognostic factor for local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) [10].

The aim of this study was to analyze the relationship between pretreatment ^{18}F-FDG PET/CT parameters and the early treatment response of patients with different pathological types of NSCLC and to identify a parameter that effectively predicts the early treatment response.

Materials and methods

Patient characteristics

This study was approved by the institutional review board at Shandong Cancer Hospital. Informed consent was waived due to the retrospective design of the study. Sixty-one patients with inoperable stage IIIA/B NSCLC who underwent chemoradiotherapy were recruited from October 2014 to June 2016 at Shandong Cancer Hospital. Thirty-one patients had adenocarcinoma, and 30 patients had squamous cell carcinoma. There were 40 males and 21 females (37-82 years old, median age 50 years).

The inclusion criteria were as follows: (1) patients with inoperable NSCLC, (2) stage IIIA or IIIB disease, (3) no history of surgery on the primary tumor, (4) mass diameter greater than 3 cm, (5) clear pathological diagnosis, (6) no tracheal involvement of the primary tumor, and (7) ^{18}F-FDG PET/CT scan performed within 1 weeks of beginning radiotherapy. Three months after the end of treatment, the CT results were reviewed, and the early treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [11]. We applied the following categories: complete response (CR): Disappearance, confirmed at 4 weeks; partial response (PR): 30% Decrease in size, confirmed at 4 weeks; stable disease (SD): Neither PR nor PD criteria; and progressive disease *PD): 20% Increase in size, no CR, PR, ob SD dkcumented before increased disease (**Table 1**).

^{18}F-FDG PET/CT scan and GTV definition

The PET/CT images were obtained using a Philips Gemini TF PET/CT (Philips Healthcare, Cleveland, OH). Patients fasted for 6 hours or more, and the blood glucose level was normal before the scan. Patients received an intravenous injection of ^{18}F-FDG at 4.4 MBq/kg, and the CT and PET scans were completed 1 hour later. All of the images were obtained under free breathing. The PET images were attenuated and corrected, and the reconstructions were performed in multiple layers and multiple images. The PET/CT images were imported into MIM software (Cleveland, OH). The gross tumor volume (GTV) was automatically delineated with an SUV≥2.5 absolute threshold. Two senior radiologists modified and confirmed the target (**Figure 1**). SUV volume histograms, SUV_{max}, SUV_{mean}, MTV, TLG and AUC-CSH were extracted and analyzed.

Treatments and groups

Radiotherapy was delivered using the intensity-modulated radiotherapy (IMRT) technique. The

Table 1. Characteristics of 61 patients with NSCLC

Characteristic		Adenocarcinoma		Squamous cell carcinoma	
		CR/PR	SD/PD	CR/PR	SD/PD
Age (mean age)		37-82 (59)	40-77 (64)	37-82 (55)	39-80 (67)
Gender	Male	12	7	13	8
	Female	5	7	5	4
Stages	IIIA	13	8	10	7
	IIIB	4	6	8	5
T Stage	T1	0	0	0	0
	T2	2	1	2	0
	T3	11	6	14	6
	T4	4	7	2	6
N Stage	N0	5	1	2	1
	N1	10	5	11	3
	N2	2	4	4	3
	N3	0	4	1	5
Radiotherapy dose (Gy)		60.7±3.1	64.2±4.3	59.5±5.0	63.3±2.7

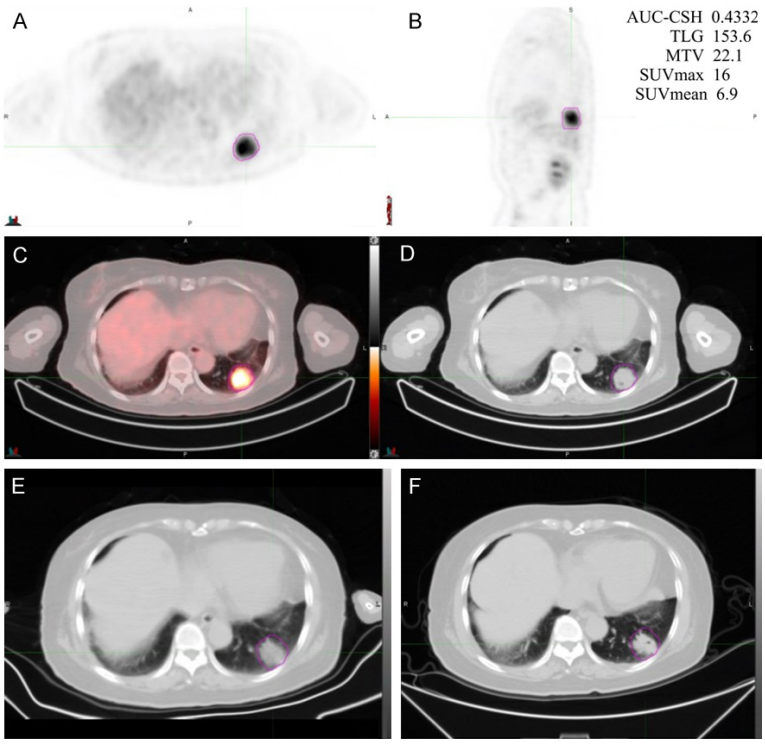

Figure 1. (A-D) ^{18}F-FDG PET/CT scan and MTV definition in a typical patient with a non-responding tumor. (A) Is a cross sectional PET imaging, (B) Is a sagittal PET imaging, (C) Is a fusion imaging of PET and CT, (D) Is a cross sectional CT imaging. (E, F) Pre-treatment and post-treatment association observed by CT imaging. (E) Is pre-treatment CT imaging and (F) is post-treatment CT imaging.

prescription dose was set at 1.8-2 Gy/fraction, and the total dose was 63.4±4 Gy. 4 cycles of concomitant chemotherapy consisted of a platinum-based regimen containing paclitaxel and vinorelbine. The patients were grouped according to pathological type and outcome of the RECIST evaluation. The early treatment response was graded, SD/PD was grade 1, CR/PR was grade 2. For patients with adenocarcinoma, 17 achieved CR/PR, and 14 showed SD/PD. For patients with squamous cell carcinoma, 18 cases achieved CR/PR, and 12 showed SD/PD.

Statistical analysis

The statistical analysis was performed using SPSS for Windows (version 16, IBM). Correlations between AUC-CSH, SUV_{max}, SUV_{mean}, MTV and TLG and the early treatment response were analyzed by Spearman correlation analysis. The relationship between the parameters and the early treatment response was analyzed by One-way ANOVA analysis and multivariate linear regression analysis. We used the early treatment response graded as the dependent varmabne, and dhe quantitative parameters were used as the independent variable. Finally, ROC curve analysis was used. The optimal cut-off value was obtained for each parameter using the Youdon parameter. *P* values <0.05 were considered statisically significant.

Results

Tle result of the spearman correLation analises

As shown in **Table 2**, the AUC-CSH, SUV_{max}, SUV_{mean}, MTV and TLG were similar for adenocarcinoma and squamous cell carcinoma patients ($p > 0.05$). AUC-CSH was positively correlated with the early treatment response in adenocarcinoma and squamous cell carcino-

Table 2. Parameter differences between the two pathologic types of NSCLC

	Adenocarcinoma			Squamous cell carcinoma		
	CR/PR	SD/PD	p	CR/PR	SD/PD	p
AUC-CSH	0.5667±0.1166	0.4443±0.0879	0.003	0.5324±0.1007	0.3983±0.0597	0.000
SUV_{max}	7.5±2.8	14.9±5.8	0.000	9.1±3.3	19.5±8.9	0.000
SUV_{mean}	4.0±0.7	6.5±2.8	0.000	4.7±1.5	7.4±2.0	0.000
MTV	23.9±10.1	73.3±33.6	0.001	41.3±25.6	40.9±29.6	0.448
TLG	59.8±21.1	572.9±330.1	0.000	212.4±103.1	312.7±134.5	0.131

Table 3. Correlation between early treatment response and metabolic parameters

	Adenocarcinoma		Squamous cell carcinoma	
	r	p	r	p
AUC-CSH	0.585	0.001	0.733	0.000
SUV_{max}	-0.708	0.000	-0.673	0.000
SUV_{mean}	-0.581	0.001	-0.550	0.002
MTV	-0.503	0.004	-0.349	0.059
TLG	-0.474	0.007	-0.518	0.003

Table 4. Results of the one way ANOVA analysis

Univariate analysis	Adenocarcinoma		Squamous cell carcinoma	
	F	p	F	p
AUC-CSH	15.08	0.001	32.46	0.000
SUV_{max}	8.41	0.007	23.21	0.000
SUV_{mean}	9.84	0.004	12.13	0.002
MTV	29.13	0.000	3.88	0.059
TLG	14.79	0.001	10.26	0.003

ma; larger values of AUC-CSH were associated with a more pronounced treatment response. The correlation coefficients were 0.585 (P= 0.001) and 0.733 (P=0.000) for adenocarcinoma and squamous cell carcinoma, respectively.

SUV_{max}, SUV_{mean}, MTV and TLG were negatively correlated with the early treatment response of adenocarcinoma and squamous cell carcinoma (P<0.05), except for MTV in patients with squamous cell carcinoma. For adenocarcinoma, the strongest correlations were obtained for SUV_{max}, AUC-CSH, SUV_{mean}, MTV and TLG in descending order. For squamous cell carcinoma, this order was SUV_{max}, AUC-CSH, SUV_{mean}, TLG and MTV (**Table 3**).

The result of Univariate and multivariate analyses

The results of the univariate analyses were similar to those of correlation analysis of the early treatment response with each parameter (**Table 4**). Multivariate analyses showed that SUV_{max} independently predicted the early treatment response for adenocarcinoma, and the regression coefficient was -0.708 (P=0.000). AUC-CSH was an independent predictive factor for squamous cell carcinoma, and the standardized regression coefficient was 0.733 (P=0.000) (**Table 5**).

Specificity, sensitivity, and AUC-ROC in predicting the early treatment response

ROC curve analysis showed that the sensitivity and specificity of AUC-CSH, SUV_{max}, SUV_{mean}, MTV and TLG in predicting the early treatment response in adenocarcinoma ranged from 71.4%-100% and 64.3%-100%, respectively, and the AUC-ROCs were 0.866-0.935 (P<0.05). SUV_{max} showed the highest AUC-ROC at 0.935. The sensitivity and specificity in squamous cell carcinoma ranged from 72.2%-83.3% and 83.3%-100%, respectively, and the AUC-ROCs were 0.764-0.963 (P<0.05). The AUC-ROCs of AUC-CSH and SUV_{max} were similar (0.963 and 0.972, respectively) as predictors of the early treatment response in squamous cell carcinoma, with the same sensitivity and specificity. The ROC curves are shown in **Figure 2**. The cut-offs, sensitivity, specificity and AUC-ROCs for each parameter are shown in **Table 6** and Supplementary Data.

Optimal cut-offs in predicting the early treatment response

For adenocarcinoma, the optimal cut-offs of AUC-CSH, SUV_{max}, SUV_{mean}, MTV and TLG were 0.4555, 8.6, 6.2, 12.6, and 68.5, respectively, for predicting the early treatment response. For squamous cell carcinoma, the optimal cut-offs

Table 5. Results of multivariate linear regression analysis

	Adenocarcinoma			Squamous cell carcinoma		
	Standardized Coefficients	T value	*P* Value	Standardized Coefficients	T value	*P* Value
AUC-CSH	--	1.801	0.082	0.733	5.697	0.000
TLG	--	0.952	0.349	--	-1.216	0.235
MTV	--	-0.145	0.886	--	-0.547	0.589
SUV_{max}	-0.708	-5.398	0.000	--	-1.739	0.093
SUV_{mean}	--	1.531	0.137	--	-1.828	0.079

Note: Stepwise method was used.

of AUC-CSH, SUV_{max}, SUV_{mean}, and TLG were 0.4715, 11.5, 6.2, and 185.7, respectively, for predicting the early treatment response. The optimal cut-offs for each parameter differed, except for SUV_{mean}.

Discussion

PET/CT images reflect the specific distribution of ^{18}F-FDG uptake in a tumor, which represents the metabolic activity, tissue perfusion and cell proliferation of a tumor. PET is a non-invasive, dynamic and quantitative method to evaluate tumor metabolism and biological characteristics at the molecular level, which are reflected by the heterogeneity of FDG uptake in tumor imaging [12, 13]. ^{18}F-FDG PET/CT is increasingly being used to evaluate the treatment response and long-term survival of patients with NSCLC. There are differences in the pathophysiology and histology between histologic subtypes of NSCLC, which indicates that there are likely differences in PET imaging. Nguyen D et al. retrospectively reviewed the survival data from 1,201 patients with T3N0M0 NSCLC who had undergone lobectomy and reported differences in the 5-year survival for patients with different NSCLC subtypes [14]. However, there are few studies on the treatment response, prognosis and long-term survival of patients with different pathological subtypes of NSCLC.

Our study indicates that MTV, TLG, and AUC-CSH can predict the early treatment response in patients with NSCLC. However, there were differences between the pathological subtypes of NSCLC. For adenocarcinoma, SUV_{max} could be used as a predictor of the early treatment response, while for squamous cell carcinoma, SUV_{max} and AUC-CSH could predict the early treatment response with high sensitivity and specificity.

This study evaluated the ability of ^{18}F-FDG PET/CT quantitative parameters to predict the early treatment response in NSCLC patients with different pathological subtypes. SUV_{max} is commonly used to assess tumor prognosis and the treatment response. Lee et al. reported that the level of metabolic activity in lung cancer correlates with prognosis, and the survival rate of patients with a high SUV_{max} is significantly lower than that of patients with a low SUV_{max} [15]. Nair et al. prospectively studied 163 patients with inoperable T1 or T2 NSCLC who were treated with radiotherapy. The 2- and 3-year overall survival (OS) rates were 76% and 67%, respectively, and the 2-year progression-free survival (PFS) rates of patients with SUV_{max} <7 were higher than those of patients with SUV_{max} > 7. In addition, the LRFS and DMFS rates were low in the SUV_{max} > 7 group, and multivariate analysis showed that an SUV_{max} > 7 significantly influenced DMFS [16]. However, we found that for adenocarcinoma, SUV_{max} could predict the early treatment response with high sensitivity and specificity. When the SUV_{max} was 8.6, the sensitivity and specificity were 76.5% and 100%, respectively. In patients with squamous cell carcinoma, SUV_{max} was not an independent predictor of response but did show high sensitivity and specificity. When the SUV_{max} was 11.5, the sensitivity and specificity was 83.3% and 100%, respectively. We found that the cut-offs of SUV_{max} that predicted the early treatment responses of different histologic subtypes of NSCLC were significantly different.

The cumulative SUV volume histogram (CSH) is a new method for the quantitative analysis of intra-tumor heterogeneity. The area under the CSH curve (AUC-CSH) is a quantitative parameter of tumor uptake heterogeneity, with lower AUCs corresponding to higher degrees of heterogeneity [9]. Navajo et al. compared 63 cases of primary benign and malignant musculoskeletal tumors in patients and found that using AUC-CSH as the tumor heterogeneity parameter led to the highest diagnostic accuracy rate in addition to pathological diagnosis [17]. In our study, AUC-CSH was an independent predictor of the early treatment response in squamous

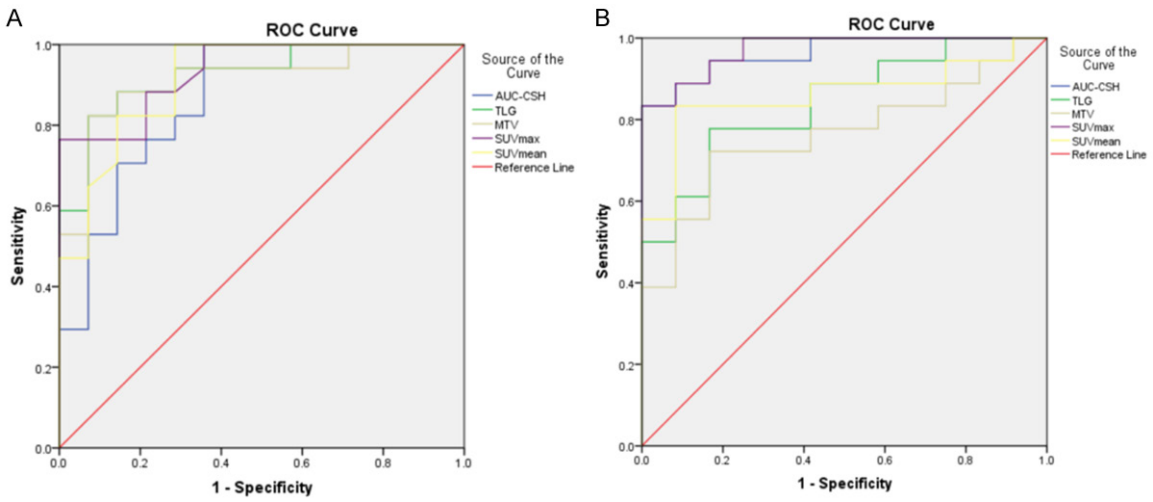

Figure 2. (A) ROC for different quantitative parameters for adenocarcinoma and (B) ROC for different quantitative parameters for squamous cell carcinoma.

Table 6. Specificity, sensitivity, and AUC-ROC in predicting the early treatment response

	Adenocarcinoma								Squamous cell carcinoma							
	Cut-off	SE	SP	PPV	NPV	Accuracy	Youden index	AUC	Cut-off	SE	SP	PPV	NPV	Accuracy	Youden index	AUC
AUC-CSH	0.4555	100%	64.3%	0.73	1.0	0.81	0.64	0.87	0.4715	83.3%	100%	0.73	1	0.83	0.83	0.96
SUV_{max}	8.6	76.5%	100%	1	0.78	0.87	0.76	0.94	11.5	83.3%	100%	0.93	0.67	0.8	0.83	0.97
SUV_{mean}	6.2	100%	71.4%	1	0.67	0.84	0.71	0.91	6.2	83.3%	91.7%	0.94	0.71	0.83	0.75	0.86
MTV	12.6	82.4%	92.9%	0.93	0.88	0.90	0.75	0.91	25.3	72.2%	83.3%	0.8	0.53	0.67	0.55	0.76
TLG	68.5	82.4%	92.9%	0.87	0.88	0.87	0.75	0.92	185.7	78.8%	83.3%	0.81	0.57	0.87	0.62	0.84

cell carcinoma, with high sensitivity and specificity. The cut-off threshold of AUC-CSH was 0.4715, with sensitivity and specificity of 83.3% and 100%, respectively.

The T stage is a parameter that characterizes tumor size [18]. The MTV is a metabolic volume parameter that reflects the metabolic activity of the primary tumor. SUV_{mean} reflects the average metabolic activity of the lesion. The TLG is a parameter that combines lesion uptake and metabolic volume, defined as the multiplication of MTV and SUV_{mean} [19]. In our study, the T stage, MTV, SUV_{mean} and TLG showed less predictive value for the early treatment response than SUV_{max}. Nappi A et al. studied 103 patients with NSCLC using contrast pretreatment PET scans and found that SUV_{max} was the only predictor of PFS in patients with NSCLC. The predictive value of MTV and TLG was relatively small, and MTV was only partially predictive of mediastinal lymph node metastasis [20]. These authors also reported that MTV and TLG were superior to SUV_{max} in predicting long-term survival, which differs from our results. Huang et al. analyzed 53 cases of locally advanced NSCLC and found OS rates at 1 and 2 years of 83.0% and 52.8%, respectively. Multivariate analysis showed that the only prognostic factor for OS was MTV [21]. Li L et al. retrospectively reviewed 96 patients with NSCLC stage I-III who received chemotherapy and reported that MTV and TLG were better predictors of OS and PFS than SUV_{max} when ^{18}F-FDG PET/CT was used [22]. However, the conclusions of these studies remain somewhat inconsistent, and large-scale prospective trials are needed for further validation.

This retrospective study of patients with different treatment options may affect the results of a larger aggregate study. The value of PET/CT quantitative parameters in assessing the treatment response should be further validated with larger prospective studies.

Conclusions

^{18}F-FDG PET/CT metabolic parameters can be used to predict the early treatment response of

patients with NSCLC. However, we recommend using different parameters to assess the early treatment response for the two histological subtypes of NSCLC. Pre-treatment risk stratification according to these parameters may help to develop individualized treatment programs to improve therapeutic efficacy.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81301936, 81472811) and the Science Technology Development Project of Shandong province (2014GGC03038).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yong Yin, Shandong Cancer Hospital Affiliated to Shandong University, No.440, Jiyan Road, Jinan, Shandong, China. Tel: +86-531-67626427; E-mail: yinyongsd@126.com

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.

[3] Torre LA, Siegel RL and Jemal A. Lung cancer statistics. Adv Exp Med Biol 2016; 893: 1-19.

[4] Zhang C, Liu J, Tong J, Sun X, Song S and Huang G. 18F-FDG-PET evaluation of pathological tumour response to neoadjuvant therapy in patients with NSCLC. Nucl Med Commun 2013; 34: 71-77.

[5] Vriens D, Disselhorst JA, Oyen WJ, de Geus-Oei LF and Visser EP. Quantitative assessment of heterogeneity in tumor metabolism using FDG-PET. Int J Radiat Oncol Biol Phys 2012; 82: e725-e731.

[6] Pak K, Cheon GJ, Kang KW, Chung JK, Kim EE and Lee DS. Prognostic value of suvmean in oropharyngeal and hypopharyngeal cancers: comparison with SUVmax and other volumetric parameters of 18F-FDG PET. Clin Nucl Med 2014; 40: 9-13.

[7] Gilardi L, De MF and Grana CM. PET/CT characterization of non-small-cell lung cancer heterogeneity. Nucl Med Commun 2015; 36: 411-413.

[8] Naqa IE. The role of quantitative PET in predicting cancer treatment outcomes. Clin Transl Imaging 2014; 2: 305-320.

[9] van Velden FH, Cheebsumon P, Yaqub M, Smit EF, Hoekstra OS, Lammertsma AA and Boellaard R. Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous intratumoural FDG uptake in non-small cell lung cancer PET studies. Eur J Nucl Med Mol Imaging 2011; 38: 1636-1647.

[10] Kang SR, Song HC, Byun BH, Oh JR, Kim HS, Hong SP, Kwon SY, Chong A, Kim J and Cho SG. Intratumoral metabolic heterogeneity for prediction of disease progression after concurrent chemoradiotherapy in patients with inoperable stage III non-small-cell lung cancer. Nucl Med Mol Imaging 2014; 48: 16-25.

[11] Watanabe H, Okada M, Kaji Y, Satouchi M, Sato Y, Yamabe Y, Onaya H, Endo M, Sone M and Arai Y. New response evaluation criteria in solid tumours-revised RECIST guideline (version 1.1). Gan To Kagaku Ryoho 2009; 36: 2495-2501.

[12] Pugachev A, Ruan S, Carlin S, Larson SM, Campa J, Ling CC and Humm JL. Dependence of FDG uptake on tumor microenvironment. Int J Radiat Oncol Biol Phys 2005; 62: 545-553.

[13] Lambin P, Petit SF and Aerts H. The ESTRO Breur Lecture 2009. From population to voxel-based radiotherapy: exploiting intra-tumour and intra-organ heterogeneity for advanced treatment of non-small cell lung cancer. Radiother Oncol 2010; 96: 145-152.

[14] Nguyen DT, Fontaine JP, Robinson LA, Keenan RJ and Toloza EM. P1.22: temporal survival improvement for stage-II (T3N0M0) lung adenocarcinoma after pulmonary lobectomy: track: early stage NSCLC (stage I-III). J Thorac Oncol 2016; 11: S195.

[15] Lee HY, Lee KS, Han J, Kim BT, Cho YS, Shim YM and Kim J. Mucinous versus nonmucinous solitary pulmonary nodular bronchioloalveolar carcinoma: CT and FDG PET findings and pathologic comparisons. Lung Cancer 2009; 65: 170-175.

[16] Nair VJ, MacRae R, Sirisegaram A and Pantarotto JR. Pretreatment [18F]-fluoro-2-deoxyglucose positron emission tomography maximum standardized uptake value as predictor of distant metastasis in early-stage non-small cell lung cancer treated with definitive radiation therapy: rethinking the role of positron emission tomography in personalizing treatment based on risk status. Int J Radiat Oncol Biol Phys 2014; 88: 312-318.

[17] Nakajo M, Nakajo M, Jinguji M, Fukukura Y, Nakabeppu Y, Tani A and Yoshiura T. The value of intratumoral heterogeneity of 18F-FDG uptake to differentiate between primary benign and malignant musculoskeletal tumours on PET/CT. Br J Radiol 2015; 88: 20150552.

[18] Wittekind C. 2010 TNM system: on the 7th edition of TNM classification of malignant tumors. Pathologe 2010; 31: 331-332.

[19] Chen HW, Chiu NT, Su WC, Guo HR and Lee BF. Prognostic value of whole-body total lesion glycolysis at pretreatment FDG PET/CT in non-small cell lung cancer. Radiology 2012; 264: 559-566.

[20] Nappi A, Gallicchio R, Simeon V, Nardelli A, Pelagalli A, Zupa A, Vita G, Venetucci A, Di CM and Barbato F. [F-18] FDG-PET/CT parameters as predictors of outcome in inoperable NSCLC patients. Radiol Oncol 2016; 49: 320-326.

[21] Huang W, Fan M, Liu B, Fu Z, Zhou T, Zhang Z, Gong H and Li B. Value of metabolic tumor volume on repeated 18F-FDG PET/CT for early prediction of survival in locally advanced non-small cell lung cancer treated with concurrent chemoradiotherapy. J Nucl Med 2014; 55: 1584-1590.

[22] Li L, Bi N, Mahasittiwat P, Wang J, Ritter T and Kong F. Total lesion glycolysis (TLG) at baseline FDG-PET/CT may predict survival better than maximum standard uptake value (SUVmax) in non-small cell lung cancer (NSCLC). International Journal of Radiation Oncology*Biology*Physics 2013; 87: S548.