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ORIGINAL RESEARCH

Prognostic value of the standardized uptake value maximum change calculated by dual-time-point ^{18}F-fluorodeoxyglucose positron emission tomography imaging in patients with advanced non-small-cell lung cancer

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Purpose: The purpose of this study was to investigate the prognostic value of the standardized uptake value maximum (SUVmax) change calculated by dual-time-point ^{18}F-fluorodeoxyglucose positron emission tomography (PET) imaging in patients with advanced non-small-cell lung cancer (NSCLC).

Patients and methods: We conducted a retrospective review of 115 patients with advanced NSCLC who underwent pretreatment dual-time-point ^{18}F-fluorodeoxyglucose PET acquired at 1 and 2 hours after injection. The SUVmax from early images (SUVmax1) and SUVmax from delayed images (SUVmax2) were recorded and used to calculate the SUVmax changes, including the SUVmax increment (ΔSUVmax) and percent change of the SUVmax (%ΔSUVmax). Progression-free survival (PFS) and overall survival (OS) were determined by the Kaplan–Meier method and were compared with the studied PET parameters, and the clinicopathological prognostic factors in univariate analyses and multivariate analyses were constructed using Cox proportional hazards regression.

Results: One hundred and fifteen consecutive patients were reviewed, and the median follow-up time was 12.5 months. The estimated median PFS and OS were 3.8 and 9.6 months, respectively. In univariate analysis, SUVmax1, SUVmax2, ΔSUVmax, %ΔSUVmax, clinical stage, and Eastern Cooperative Oncology Group (ECOG) scores were significant prognostic factors for PFS. Similar results were significantly correlated with OS, except %ΔSUVmax. In multivariate analysis, ΔSUVmax and %ΔSUVmax were significant factors for PFS. On the other hand, ECOG scores were only identified as independent predictors of OS.

Conclusion: Our results demonstrated the prognostic value of the SUVmax change in predicting the PFS of patients with advanced NSCLC. However, SUVmax change could not predict OS.

Keywords: dual-time-point ^{18}F-FDG PET/CT, non-small-cell lung cancer, prognosis, survival

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Introduction

Lung cancer is the most common malignancy and the leading cause of cancer-related death worldwide. Almost 70%–75% of patients with non-small-cell lung cancer (NSCLC) have advanced stage III or IV disease when first diagnosed.[1] Although much progress has been made in recent years, the prognosis of advanced NSCLC remains poor. A reliable prediction of prognosis in patients with advanced NSCLC also remains challenging. Moreover, despite the careful evaluation of clinical prognostic factors,

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such as stage, performance status, and treatment, survival varies from patient to patient.[2] A more accurate prognostic assessment incorporating all features of tumors, such as biological or molecular information, is needed.

Because ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) could reflect the aggressiveness of the tumors by the uptake of ^{18}F-FDG, two studies have evaluated prognosis using PET.[3,4] Studies reported in the literature have indicated that the ^{18}F-FDG uptake, determined by the standardized uptake value maximum (SUVmax) in the primary tumors of NSCLC, was prognostic. However, the findings of other studies were different.[5–7] The cause, in part, might be that single-time-point (STP) ^{18}F-FDG PET lacks dynamic information concerning ^{18}F-FDG accumulation in a lesion that reflected difficultly in tumor heterogeneity.

This obstacle was solved by dual-time-point (DTP) FDG PET, which was originally intended to differentiate between malignancy and benignity.[8,9] The underlying rationale was that FDG uptake and clearance showed discrepancies in different tissues.[10] In recent years, some studies have shown that dynamic changes in SUVmax calculated by DTP FDG PET could be useful to predict the tumor prognosis in patients. For example, the study by Sampath et al revealed that a high percent change in the SUVmax (%ΔSUVmax) could predict poor survival in pancreatic masses.[11] Moreover, Abgral et al confirmed that %ΔSUVmax is independently correlated with the progression-free survival (PFS) of patients with head and neck cancer.[12] Shimizu et al found that the %ΔSUVmax of intratumoral ^{18}F-FDG was significantly related to PFS in resectable NSCLC.[13] At the same time, however, other study had demonstrated that DTP ^{18}F-FDG PET might not have prognostic value in overall survival (OS) in patients with early-stage (stage I and II) NSCLC.[14]

To the best of our knowledge, few studies have evaluated the prognostic role of DTP ^{18}F-FDG PET in advanced NSCLC. The aim of the present study was to investigate whether DTP ^{18}F-FDG PET could predict the outcome in patients with advanced NSCLC.

Methods

Patients

We retrospectively reviewed the medical records of all patients with advanced NSCLC diagnosed by histologic or cytologic examination who underwent ^{18}F-FDG PET before any treatment for lung cancer at our institution from January 2009 to January 2014. Cases of known diabetes or of age younger than 18 years were excluded. The study was conducted with the approval of the Ethics Committee of Shandong Cancer Hospital and Institute, People's Republic of China, and the requirement for informed consent was waived because this was a retrospective study. Follow-up information until either death or October 2015 was obtained from the medical records.

^{18}F-FDG PET/CT imaging

All patients fasted and rested for at least 6 hours before FDG PET examination (Discovery LS PET/CT system; General Electric Healthcare, Milwaukee, WI, USA). After ensuring that the peripheral blood glucose level was $<$150 mg/dL, they were injected with 370 MBq (10 mCi) of ^{18}F-FDG. Computed tomography (CT) was performed with the following settings: 140 kV, 80 mA, a pitch of 6, a section thickness of 4.25 mm, a field of view of 50 cm, and a matrix size of 512×512. CT data were collected in the helical acquisition mode. The early scan was performed from the skull base to the upper thigh at 1 hour after the injection, and the delayed scan was acquired for the whole lung at 2 hours after the administration. PET images were reconstructed with CT-derived attenuation correction using the ordered subset expectation maximization algorithm. The attenuation-corrected PET images, CT images, and fused PET/CT images displayed as axial, sagittal, and coronal slices were reoriented on a Xeleris workstation (GE Healthcare).

^{18}F-FDG PET/CT analysis

The PET/CT datasets of early and delayed images were assessed independently by two nuclear medicine physicians who were blinded to the clinical and pathologic results. Disagreements were resolved by discussion to reach a consensus interpretation. Semiquantitative analysis of early and delayed images was performed by measuring the SUVmax of the lesions. SUVmax was defined as the highest pixel value related to the tumor burden in the present study and was calculated using the following equation: SUVmax = tumor maximum radioactivity concentration (Bq/mL)/injected dose (MBq)/body weight (g). The SUVmax increment (ΔSUVmax) was calculated by subtracting 1-hour SUVmax (SUVmax1) from 2-hour SUVmax (SUVmax2). %ΔSUVmax was calculated by dividing the ΔSUVmax.

Statistical analysis

The prognostic evaluation was based on PFS and OS. PFS was defined as the time from treatment to the objective progression of disease, and OS was calculated as the time from treatment to death or the last follow-up. Survival curves for PFS and OS were constructed using the

Kaplan–Meier method, and differences among the curves were evaluated by the log-rank test. The cutoff values for the SUVmax, ΔSUVmax, and %ΔSUVmax were chosen by identifying the threshold that was the most discriminative in terms of PFS and OS and yielded the minimum *P*-value in the log-rank test. Using the Kaplan–Meier method, univariate analysis was performed to evaluate all of the prognostic factors. The factors with significance in the univariate analysis were included in Cox proportional hazard models to conduct multivariate analyses. All of the statistical analyses were performed using SPSS Statistics version 20 (IBM Corporation, Armonk, NY, USA). A *P*-value <0.05 was regarded as indicating statistical significance.

Results

Clinical characteristics

We retrospectively reviewed 115 consecutive patients who underwent DTP ^{18}F-FDG PET before treatment from January 2009 to January 2014 at the Shandong Cancer Hospital and Institute, People's Republic of China. The baseline characteristics of the patients are presented in Table 1. The median age was 63 years (range: 32–89 years) with 74 (64.35%) males and 41 (35.65%) females. The number of patients with an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 was 38 (33.04%), 49 (42.61%), or 28 (24.35%), respectively. Histopathologically, there were 65 (56.52%) adenocarcinoma and 50 (43.48%) squamous carcinoma cases. There were 65 (56.52%) cases in stage III, including 24 (20.87%) in stage IIIA and 41 (35.65%) in stage IIIB, and 50 (43.48%) cases in stage IV. Eighteen (15.65%) cases previously received surgery with or without neoadjuvant therapy, including 16 (13.91%) treated with lobectomy with systematic lymph node dissection and two (1.74%) with segmentectomy. Fifty (43.48%) cases previously received chemotherapy or targeted. Forty-seven (40.87%) cases previously received radiation therapy or chemoradiation therapy, including 38 (33.04%) treated with three-dimensional conformal radiotherapy and nine (7.83%) with intensity-modulated radiotherapy. The median follow-up period was 13.5 months (range: 8–26 months). The median PFS and OS for the cohort were 3.8 and 9.6 months, respectively.

Table 1 Baseline characteristics of the 115 patients

Clinical feature	N	Percentage
Sex		
Male	74	64.35
Female	41	35.65
Age		
Median	63	
≤60	50	43.48
>60	65	56.52
ECOG scores		
0	38	33.04
1	49	42.61
2	28	24.35
Histological subtype		
Adenocarcinoma	65	56.52
Squamous carcinoma	50	43.48
Clinical stage		
Stage IIIA	24	20.87
Stage IIIB	41	35.65
Stage IV	50	43.48
T stage		
T1	16	13.91
T2	58	50.44
T3	27	23.48
T4	14	12.17
N stage		
N0	0	0
N1	14	12.17
N2	54	46.96
N3	47	40.87
Treatment		
Surgery (with or without neoadjuvant therapy)	18	15.65
Chemotherapy or targeted therapy	50	43.48
Radiation or chemoradiation therapy	47	40.87

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Parameters derived from DTP ^{18}F-FDG PET

The patients had a median SUVmax1 of 9.5 (range: 3.4–25.1) and SUVmax2 of 13.3 (range: 4.2–29.2). The median ΔSUVmax was 3.4 (range: 0.2–8.4), and the median %ΔSUVmax was 32.2% (range: 3.77%–85.94%). The exact cutoff values for the Kaplan–Meier analysis (SUVmax1 =9.3, SUVmax2 =11.1, ΔSUVmax =3.05, and %ΔSUVmax =29.55) were chosen because they were the most discriminative with minimum *P*-values in the log-rank test.

Prognostic values of the parameters derived from DTP ^{18}F-FDG PET

In the univariate analysis using the Kaplan–Meier method to estimate PFS, the cutoff values of SUVmax1, SUVmax2, ΔSUVmax, and %ΔSUVmax were identified as 9.3, 11.1, 3.05, and 29.55, respectively. SUVmax1 (P=0.003), SUVmax2 (P=0.011), ΔSUVmax ($P<0.001$), %ΔSUVmax (P=0.003), clinical stage (P=0.05), and ECOG scores (P=0.013) were significant prognostic factors for PFS. Similar results were significantly correlated with OS, except the %ΔSUVmax (P=0.76). The data from the univariate analyses of factors affecting PFS and OS are presented in

Table 2 Univariate Kaplan–Meier analysis of PFS and OS in patients with advanced NSCLC

Factor	PFS			OS		
	Median	95% CI	*P*-value	Median	95% CI	*P*-value
SUVmax1			0.003			0.002
≤9.3	46	3.799–5.401		10.1	8.61–11.59	
>9.3	3.2	2.861–3.539		8.9	7.995–9.805	
SUVmax2			0.011			<0.001
≤11.1	4.9	3.921–5.879		12.8	8.394–17.206	
>11.1	3.5	3.113–3.887		9.1	8.37–9.38	
ΔSUVmax			<0.001			<0.001
≤3.05	4.9	4.365–5.435		10.3	8.873–11.727	
>3.05	3.1	2.749–3.451		8.9	8.804–9.757	
%ΔSUVmax			0.003			0.76
≤29.55	4.6	3.887–5.313		9.1	8.119–10.081	
>29.55	3.2	2.686–3.714		9.6	8.743–10.457	
ECOG scores			0.013			<0.001
0	3.8	2.592–5.008		10.3	9.243–11.357	
1	4.3	3.5–5.1		10.2	9.103–11.297	
2	2.9	2.122–3.678		7.7	7.312–8.088	
Clinical stage			0.05			0.009
Stage III	4.3	3.594–5.006		9.6	8.362–10.838	
Stage IV	3.6	3.086–4.114		9.3	8.386–10.214	
Treatment			0.087			0.106
Surgery	4.6	3.716–5.484		9.3	7.217–11.383	
Chemotherapy	3.8	3.052–4.548		9.9	8.358–11.442	
Radiation	4.1	3.374–4.826		9.6	8.148–11.052	

Abbreviations: PFS, progression-free survival; OS, overall survival; NSCLC, non-small-cell lung cancer; CI, confidence interval; SUVmax1, standardized uptake value maximum from early images; SUVmax2, SUVmax from delayed images; ΔSUVmax, SUVmax increment; %ΔSUVmax, percent change of SUVmax; ECOG, Eastern Cooperative Oncology Group.

Table 2. All of the prognostic factors with significance in the univariate analysis were included in the Cox proportional hazards model to evaluate their interaction and joint effect on PFS and OS. In the multivariate analysis, the ΔSUVmax (P=0.014) and %ΔSUVmax (P=0.018) were the only significant prognostic factors for PFS. Figure 1 shows different PFS values in the two groups according to the cutoff values of the ΔSUVmax and %ΔSUVmax. In addition, the ECOG score (P<0.001) was the only significant prognostic factor for OS in the multivariate analysis. The data from the multivariate analyses of factors affecting PFS and OS are presented in Table 3. Figure 2 shows an example of patients in the same stage with different ΔSUVmax and %ΔSUVmax values but different PFS and similar OS values.

Discussion

In NSCLC, STP ^{18}F-FDG PET has been used for prognosis prediction.[15] To quantify a lesion on PET, the most commonly used parameter is the SUVmax, which reflects the voxel with the highest radioactivity concentration. Two studies have supported the use of STP ^{18}F-FDG PET for predicting the outcome in patients with NSCLC.[3,16] The proposed mechanism was that poor prognosis was associated with the overexpression of glucose transporters and upregulation of hexokinase enzyme activity as reflected by the increased accumulation of FDG in malignant tumors.[17,18] Moreover, ^{18}F-FDG uptake showed a moderately positive correlation with tumor cell proliferation in lung cancer patients.[19] However, other study findings indicated that the method of STP ^{18}F-FDG PET might be unreliable.[5,7] Recently, a large, prospective, multicenter study by Machtay et al revealed that the pretreatment SUVmax was not associated with survival in patients with locally advanced NSCLC.[20]

Compared with STP ^{18}F-FDG PET, DTP ^{18}F-FDG PET could offer information concerning the dynamics of glucose metabolism. The underlying mechanism is that FDG uptake and clearance depend on the time interval between intravenous FDG administration and imaging.[10] An increased cell proliferation rate and enhanced expression of hexokinase type-II and glucose transporter-1 might contribute to increased FDG uptake in tumor cells on delayed imaging.[21,22] Based on the faster washout of glucose from benign tissues than in malignant lesions, DTP FDG PET imaging has emerged as a possible strategy for differentiating malignant from benign FDG-avid lesions. Recently, DTP FDG PET was also used to evaluate the prognosis of NSCLC. However, to

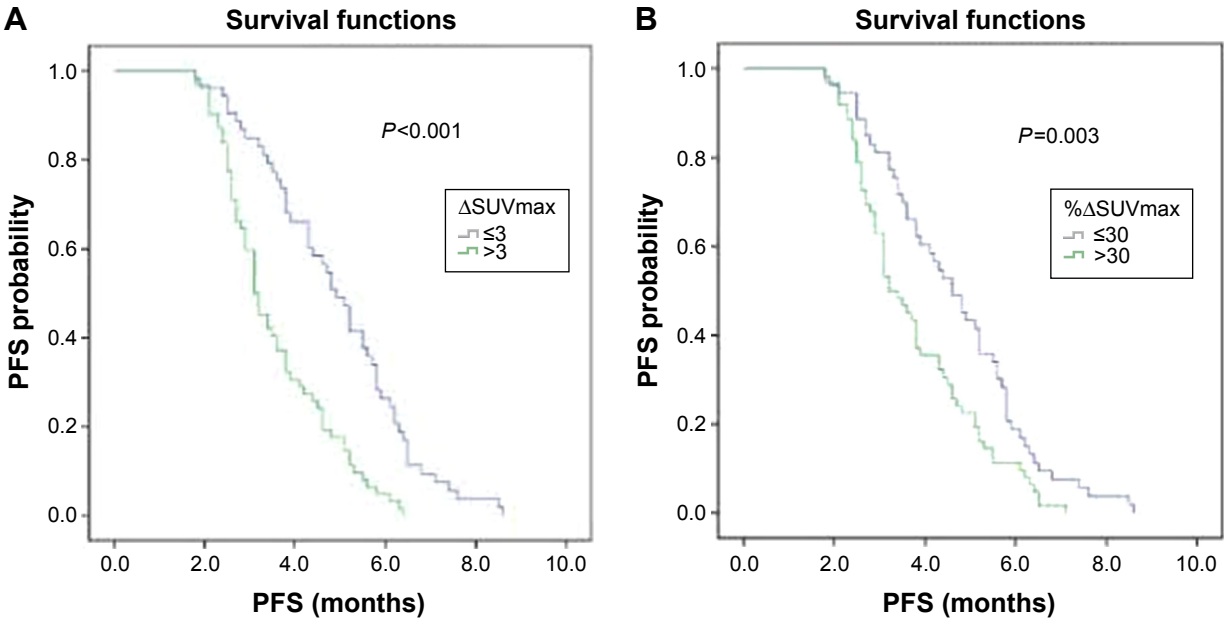

Figure 1 PFS of the patients according to ΔSUVmax (**A**) and %ΔSUVmax (**B**).
Abbreviations: PFS, progression-free survival; ΔSUVmax, SUVmax increment; %ΔSUVmax, percent change of ΔSUVmax.

the best of our knowledge, there is no special study concerning advanced NSCLC.

Although the study from Shimizu et al demonstrated that DTP FDG PET of the primary tumor in early-stage NSCLC could be useful to predict the PFS of the patients,[13] to our best knowledge, it was a small-sample size study on PFS and OS of advanced NSCLC. We found the prognostic value of dynamic changes in the SUVmax calculated from DTP FDG PET of the primary tumor of advanced NSCLC. The current study revealed that the semiquantitative indexes of the ΔSUVmax and %ΔSUVmax could predict PFS in advanced NSCLC. The analysis of dynamic changes in SUVmax could be associated with neoplasm aggressiveness. Haberkorn et al found that the degree of ^{18}F-FDG accumulation correlated significantly with the proliferation rate.[23] In other words, a positive correlation between ^{18}F-FDG uptake and the fraction of proliferating cells more likely reflected the aggressiveness of tumors.[24] Houseni et al also revealed similar results, in which the %ΔSUVmax was proved as a strong prognostic factor in patients with lung adenocarcinoma.[25] Moreover, Chen et al suggested that the ΔSUVmax of the primary lung tumor was a promising prognostic factor for

Table 3 Multivariate Cox regression analysis of PFS and OS in patients with advanced NSCLC

Factor	PFS		OS	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
ΔSUVmax	1.798 (1.127–2.869)	0.014		
%ΔSUVmax	1.785 (1.105–2.883)	0.018		
ECOG scores			1.79 (1.361–2.355)	<0.001

Abbreviations: PFS, progression-free survival; OS, overall survival; NSCLC, non-small-cell lung cancer; RR, relative risk; CI, confidence interval; ΔSUVmax, SUVmax increment; %ΔSUVmax, percent change of SUVmax; ECOG, Eastern Cooperative Oncology Group.

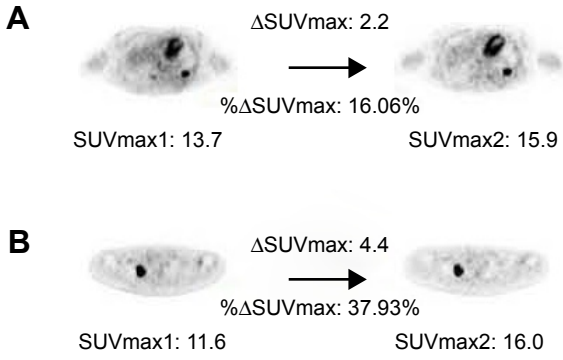

Figure 2 Transaxial PET images of two patients with stage IIIB, T2N3M0, NSCLC which had similar SUVmax from early images (SUVmax1) and delayed images (SUVmax2).
Notes: Histopathologically, it was a moderately differentiated adenocarcinoma in both cases. ΔSUVmax for patient in (**A**) and (**B**) was 2.2 and 4.4, respectively. %ΔSUVmax for patient in (**A**) and (**B**) was 16.06% and 37.93%, respectively. PFS for patient in (**A**) and (**B**) was 5.5 and 2.7 months, respectively. OS for patient in (**A**) and (**B**) was 11.9 and 11.6 months, respectively.
Abbreviations: PET, positron emission tomography; NSCLC, non-small-cell lung cancer; SUVmax, standardized uptake value maximum; SUVmax1, SUVmax from early images; SUVmax2, SUVmax from delayed images; ΔSUVmax, SUVmax increment; %ΔSUVmax, percent change of SUVmax; PFS, progression-free survival; OS, overall survival.

NSCLC.[26] They believed that the ΔSUVmax was better than the %ΔSUVmax because a higher initial SUVmax1 caused a lower %ΔSUVmax, and a higher initial SUVmax1 was associated with a poor prognosis. However, in this study, we found that a change in the SUVmax, including %ΔSUVmax and ΔSUVmax, was significant. However, for early-stage NSCLC, the %ΔSUVmax might not have a prognostic value for OS and PFS.[27] The contrasting result could be explained by the different cutoff values calculated for the SUVmax1 and SUVmax2.

Currently, no data have been published on the definitive SUVmax cutoff value for the prediction of survival likely because of the different clinical stages of the patients studied. In most cases, the cutoff value was determined by either the median or the so-called best cutoff point determined from the data, which would vary from one study population to another.[28] Because different cutoff values yielded different results, we selected cutoff values of the ΔSUVmax and %ΔSUVmax as those that were the most discriminative with minimum *P*-values in the log-rank test.

The results of the current study also showed that, compared with age, sex, histologic type, T stage, N stage, clinical stage, treatment, and parameters from ^{18}F-FDG DDP PET/CT, ECOG scores provided more significant survival information regarding patients with advanced NSCLC. ECOG score other than the SUVmax or SUVmax change was the only significant prognostic factor for OS. It showed that PET could not predict the prognosis of advanced NSCLC. The latter finding was different from that in a prior report.[13] Our focus was an advanced NSCLC, for which the treatment was more complex. Given the large discrepancies in therapeutic approaches, multimodal therapeutic modalities, such as surgery with or without neoadjuvant therapy, chemotherapy alone or targeted therapy, radiotherapy with or without chemotherapy, or support treatment, were proposed to treat advanced NSCLC.[29,30] Therefore, OS was difficult to be accurately predicted only from PET imaging. However, ECOG scores reflected the basic status of the patient, and was an important factor that affected the choice of treatment and treatment response.

The study possessed some limitations. First, despite the lack of a standard delayed time after ^{18}F-FDG injection, we adopted 2 hours as the common acquisition time used in several studies.[31] Different delayed acquisition times might yield different results. Therefore, additional investigation of the best acquisition time for delayed imaging is needed. Second, the cellular and molecular mechanisms of the dynamic changes in the SUVmax were unclear; thus, we should continue the study for a more detailed explanation. Third, because this was a single-center, retrospective study, a prospective, multicenter study is necessary to verify our results.

Conclusion

Our results demonstrated the prognostic value of the SUVmax change calculated by ^{18}F-FDG PET in patients with advanced NSCLC. This predictor was proved to be powerful for PFS in the Cox regression model but could not predict OS. A larger prospective study is still needed to confirm these results.

Disclosure

The authors report no conflicts of interest in this work.

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