Journal of Cancer Research and Clinical Oncology (2019) 145:1361–1367
https://doi.org/10.1007/s00432-019-02848-9

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Prognostic significance of metabolic parameters measured by ^{18}F-FDG PET/CT in limited-stage small-cell lung carcinoma

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Received: 9 December 2018 / Accepted: 14 January 2019 / Published online: 21 March 2019

Abstract

Purpose Metabolic parameters measured by [^{18}F]-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) are important prognostic factors in several types of cancers. We evaluated the predictive value of tumor metabolic parameters measured by ^{18}F-FDG PET/CT in limited-disease small-cell lung cancer (LD-SCLC).

Methods This retrospective study included 30 LD-SCLC patients who underwent standard chemotherapy after radiotherapy with ^{18}F-FDG PET/CT. The maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and blood glucose-corrected values were used to evaluate metabolic parameters in primary tumors.

Results For the median follow-up of 41.1 months, median overall survival (OS) was 75.0 months [95% confidence interval (CI) 20.9–129.1 months], and median progression-free survival (PFS) was 9.5 months (95% CI 6.8–12.1 months). Two-year OS was 78.6%, and PFS was 32.7%. OS analysis indicated that MTV and TLG were significant predictors of OS following standard treatment. High glucose-corrected SUV_{max} (glu-SUV_{max}) was related to shorter median PFS. On multivariate analysis, MTV was an independent factor of OS, and glu-SUV_{max} was significantly related to PFS.

Conclusions MTV and glu-SUV_{max} measured on pretreatment ^{18}F-FDG PET/CT were independent prognostic factors for LD-SCLC patients after chemoradiotherapy with curative intent. These metabolic markers need validation in larger prospective studies but may be useful in the clinical care of LD-SCLC patients.

Keywords Small-cell lung cancer · FDG PET/CT · Prognosis · Survival · Metabolic parameter

Introduction

Small-cell lung cancer (SCLC) consists of 15–20% of primary lung cancers (Parkin et al. 2005). The standard treatment for patients with good performance status and limited disease SCLC (LD-SCLC) is concurrent chemoradiotherapy (Pignon et al. 1992). Compared with non-SCLC, SCLC has a shorter doubling time, an elevated growth fraction, and earlier development of extensive metastases, all of which lead to frequent relapse and reduced survival, despite initially favorable responses to treatment (Simon et al. 2004). Presently, tumor stage is the most important prognostic factor of SCLC over other clinical factors [e.g., performance status, weight loss, serum lactate dehydrogenase (LDH)], which is classified LD and extensive disease (ED) (Yip and Harper 2000; Zhu et al. 2011). However, the stage system is insufficient for predicting survival in certain patients (Micke et al. 2002). In addition, the clinical response to treatment for LD-SCLC shows substantial interindividual variation (Jiang et al. 2016). Thus, more discriminative prognostic

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markers are needed, allowing for better stratification for appropriate therapy and more accurate predictions of treatment outcome and survival.

For SCLC, ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is the main imaging tool for staging and influences patient management and early assessment of tumor response. ^{18}F-FDG PET/CT results with maximum standardized uptake value (SUV_{max}) have been suggested as a valuable prognostic gauge (Brink et al. 2004; Azad et al. 2010; Yamamoto et al. 2009; Kamel et al. 2003; Pandit et al. 2003; Onitilo et al. 2008; Lee et al. 2009; Zhu et al. 2011; Park et al. 2014). While volumetric metabolic factors such as metabolic tumor volume (MTV) or total lesion glycolysis (TLG) are investigated for independent prognostic parameters in other kinds of cancer (Lee et al. 2010, 2014; Dibble et al. 2012; Seol et al. 2010), evidence for their clinical value in SCLC patients is limited (Zhu et al. 2011; Oh et al. 2012; Park et al. 2014) Previous studies investigated patients with ED as well as LD and had limitation due to heterogeneous groups with different clinical stages. Furthermore, blood glucose level should be considered for metabolic factor analysis with PET/CT considering that blood glucose decreased FDG uptake by tumor cells through competitive inhibition (Lee et al. 2011). Glucose-corrected SUV_{max} has been reported to have better accuracy in predicting outcome than SUV_{max} in other cancers (Lee et al. 2011). However, the significance of glucose-corrected metabolic parameters has not yet been evaluated in SCLC patients.

The objective of this study was to assess the prognostic role of ^{18}F-FDG PET/CT pretreatment metabolic parameters and glucose-corrected values in LD-SCLC patients who underwent concurrent chemoradiotherapy.

Methods

Patients

This was a retrospective study of 83 consecutive SCLC patients who underwent pretreatment ^{18}F-FDG PET/CT at Seoul National University Bundang Hospital (Seongnam-si, Korea) from May 2009 to October 2012. Of these patients, we retrospectively enrolled 30 with limited-stage cancer who met the following inclusion criteria: (1) histologically or cytologically confirmed diagnosis of primary SCLC; (2) sufficient clinical information in the medical chart; and (3) treatment with at least two cycles of chemotherapy. Excluded from analysis were 53 patients with inadequate PET imaging or medical records. The remaining 30 patients were analyzed to assess clinicopathological characteristics, tumor responses, and survival outcomes using a predesigned data-collection format. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1402-238-107).

Treatment and response evaluation

Patients were treated with two cycles of induction chemotherapy, followed by definitive three-dimensional, conformal, involved field radiotherapy and concurrent chemotherapy. The chemotherapy regimen was etoposide plus cisplatin (EP) or irinotecan plus cisplatin (IP). The EP regimen was etoposide 100 mg/m^2 (days 1–3) and cisplatin 75 mg/m^2 (day 1). The IP regimen was irinotecan 60 mg/m^2 (days 1 and 8) and cisplatin 60 mg/m^2 (day 1). Cycles of combination chemotherapy were administered at 3-week intervals. Chest irradiation was administered after two cycles of induction chemotherapy. Patients received 1.8 Gy once daily in 30 fractions. Patients with LD-SCLC who showed complete or partial response after chemoradiotherapy were treated with prophylactic cranial irradiation of 25 Gy in 2.5-Gy fractions. Response evaluation was performed with a CT scan every two cycles, according to the guidelines of the Response Evaluation Criteria in Solid Tumor Committee version 1.0 (Therasse et al. 2000).

PET/CT imaging

Patients fasted for at least 6 h before ^{18}F-FDG PEC/CT. Median blood glucose was 98.5 mg/dL (range 85.0–142.0 mg/dL). Approximately 5.18 MBq/kg ^{18}F-FDG was intravenously injected 50 min before imaging. Using a dedicated PET/CT scanner (DVCT, GE Healthcare, Milwaukee, WI, USA) after an initial low-dose CT (120 kVp, tube current modulation), a PET scan was obtained from the skull base to proximal thighs, with an acquisition time of 2.5 min per bed position in three-dimensional mode. PET images were reconstructed with ordered-subset expectation maximization with attenuation correction using vendor-provided software (VUE Point High Definition, GE Healthcare, Milwaukee, WI, USA).

Data analysis and statistical methods

^{18}F-FDG PET-CT images were evaluated by two nuclear medicine physicians using an Advantage Workstation 4.5 (GE Healthcare, USA). Maximum standard uptake value (SUV_{max}), mean SUV and MTV of PET images were evaluated using volume viewer software. Tumors were measured with a spherical volume of interest (VOI) that included the entire lesion in the axial, sagittal, and coronal planes. Using CT images, ^{18}F-FDG uptake of normal organs such as stomach, intestine, and liver was not counted in the VOI. SUV_{max} of the VOI was assessed as (decay-corrected activity/tissue volume)/(injected dose/lean body weight). MTV was defined

as total tumor volume with SUV 2.5 or greater, and MTV and mean SUV of the VOI were mechanically analyzed. TLG was computed as (mean SUV) × (MTV). SUV_{max} corrected for blood glucose level (glu-SUV_{max}) was estimated as (SUV_{max}) × (blood glucose level)/100. Glucose-corrected TLG (glu-TLG) was also estimated using glucose-corrected SUV_{max}. Values corresponding to the 75th percentile of SUV_{max}, MTV, TLG, glu-SUV_{max}, and glu-TLG were used as arbitrary cutoffs. The 75th percentile values better discriminated patients according to the main clinical outcome endpoints compared to other cutoffs.

Overall survival (OS) was defined as the time interval between the date of ^{18}F-FDG PET/CT and the date of death from any cause, date of last contact, or last date known to be alive. Progression-free survival (PFS) was evaluated from the date of ^{18}F-FDG PET/CT until the date of first recurrence or death. Survival time was calculated using the Kaplan–Meier method and survival differences between groups assessed by log-rank test. Multivariate Cox regression analyses assessed prognostic significance of ^{18}F-FDG PET/CT variables and clinical factors that were significant in univariate analyses. We used both forward stepwise methods and a block entry method (all variables entered together in a single block). The forward stepwise method was chosen because many individual ^{18}F-FDG PET/CT parameters are highly correlated. Stepwise regression solves the problem of multicollinearity because two highly correlated characteristics generally are not both entered in the model (Braun et al. 2011). SPSS 20.0 for Windows software was used for statistical analysis.

Results

Patient characteristics

The clinical characteristics of the 30 patients are described in Table 1. The median age was 65 years (range 37–76 years). Initial chemotherapy regimens were mainly EP (80%). Follow-up data were available through June 2016, and the median follow-up time was 41.1 months [95% confidence interval (CI) 31.7–50.4 months]. Median OS was 75.0 months (95% CI 20.9–129.1 months), and median PFS was 9.5 months (95% CI 6.8–12.1 months). Two-year OS and PFS were 78.6% and 32.7%, respectively.

Tumor response

Tumor response for concurrent chemoradiotherapy was evaluable in 29 patients after treatment, while one patient showed disease progression after induction chemotherapy. The objective tumor response rate for CCRT was 96.5%, with six complete responses and 22 partial responses. Stable disease was observed in one case (3.5%). No significant difference was seen in response to CCRT according to metabolic parameters.

Table 1 Patient characteristics

Characteristics	Number of patients (%)
Total	30 (100)
Age (years)	
< 65	16 (53.3)
≥ 65	14 (46.7)
Sex	
Male	29 (96.7)
Female	1 (3.3)
Performance status (ECOG)	
0, 1	30 (100)
≥ 2	0 (0)
Blood glucose (mg/dL)	
< 110	22 (73.3)
≥ 110	8 (26.7)
Albumin (g/dL)	
< 4.0	22 (73.3)
≥ 4.0	8 (26.7)
Hgb (g/dL)	
< 13.0	25 (83.3)
≥ 13.0	5 (16.7)

ECOG Eastern Cooperative Oncology Group, *Hgb* hemoglobin

Metabolic parameters for survival

High MTV and TLG were associated with significantly shorter OS. Median OS for MTV < 166.6 mL vs. MTV ≥ 166.6 mL was 75.0 months (95% CI not calculated) vs. 22.2 months (95% CI 7.9–36.7) ($P < 0.001$). Median OS for TLG < 780.3 g vs. TLG ≥ 780.3 was 75.0 months (95% CI not calculated) vs. 22.3 months (95% CI 5.7–38.8) ($P < 0.001$) (Fig. 1a, b; Table 2). Median OS for high SUV_{max} was shorter than for low SUV_{max}, but the difference was not significant. SUV_{max} < 10.1 vs. SUV_{max} ≥10.1 was 75.0 months (95% CI 20.9–129.0) vs. 22.3 months (95% CI 2.6–41.9) ($P = 0.066$). Median OS for glu-SUV_{max} and glu-TLG was associated with higher risk of death. Median OS for glu-SUV_{max} < 10.1 vs. glu-SUV_{max} ≥10.1 was 75.0 months (95% CI 21.6–128.9) vs. 22.3 months (95% CI 2.5–41.9) ($P = 0.047$). Median OS for glu-TLG < 856.0 g vs. glu-TLG ≥ 856.0 g was 75.0 months (95% CI not calculated) vs. 22.3 months (95% CI 1.6–42.9) ($P < 0.001$). No other clinical factors of age, sex, performance status, or tumor response were predictors of OS in univariate analysis. In multivariate analysis for OS, MTV was confirmed as an independent predictor. High MTV patients had higher risk of

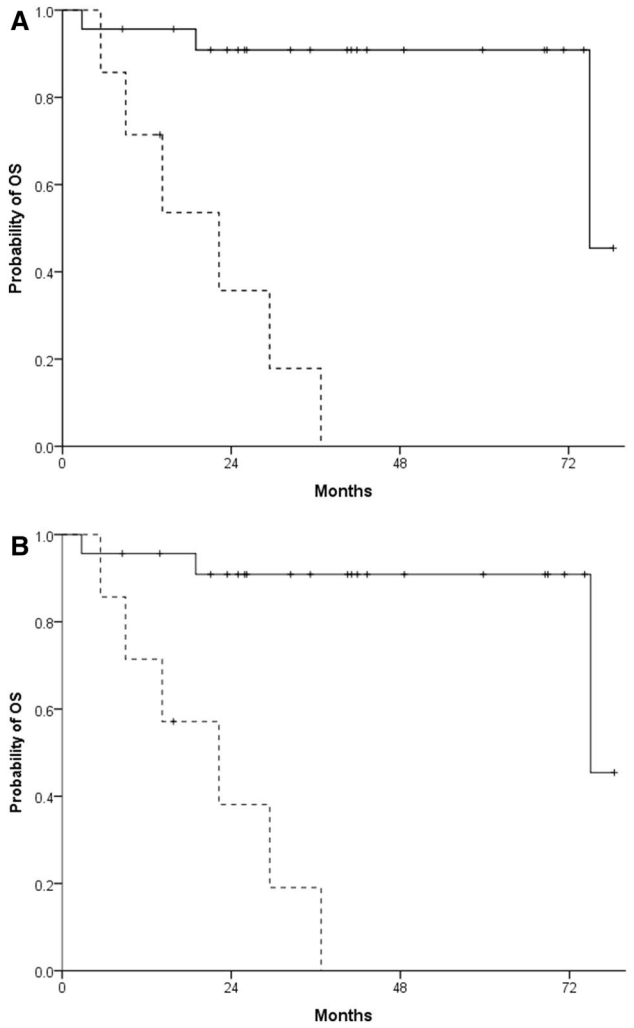

Fig. 1 Overall survival curves according to metabolic parameters. **a** Patients with low MTV (continuous line) had better OS than those with high MTV (dashed line). **b** Patients with low TLG (continuous line) showed longer OS than those with high TLG (dashed line)

death than low MTV patients, with an adjusted hazard ratio of 16.7 (95% CI 3.26–85.1, $P=0.001$).

For PFS analysis, glu-SUV_{max} was associated with significantly shorter PFS. Median PFS for glu-$SUV_{max} < 10.1$ vs. glu-$SUV_{max} \geq 10.1$ was 19.6 months (95% CI 6.6–36.7) vs. 8.37 months (95% CI 0.83–15.9) ($P=0.011$) (Fig. 2). Median PFS for high SUV_{max} was shorter than for low SUV_{max}, though the difference was not significant. $SUV_{max} < 10.1$ vs. $SUV_{max} \geq 10.1$ was 13.2 months (95% CI 0–28.5) vs. 8.37 months (95% CI 0.84–15.8) ($P=0.06$). No other factors of age, sex, performance status, tumor response, MTV, TLG, or glu-TLG were identified as predictors in univariate analysis of PFS. In multivariate analysis of PFS, glu-SUV_{max} was confirmed as an independent predictor. High glu-SUV_{max} patients had a higher risk of recurrence/progression than patients with low glu-SUV_{max}, with an adjusted hazard ratio of 3.38 (95% CI 1.24–9.18, $P=0.017$). No significance difference was observed in OS or PFS according to sex, age, performance status, serum albumin, or hemoglobin.

Discussion

This study explored the prognostic value of specific metabolic parameters from pretreatment ^{18}F-FDG PET/CT of patients with LD-SCLC treated with chemoradiotherapy as the primary treatment. Our results showed that MTV of SCLC lesions was a significant prognostic factor of OS, and glu-SUV_{max} was a significant prognostic factor of PFS. To our knowledge, this is the first study to report the clinical worth of glu-SUV_{max} for predicting survival of LD-SCLC patients.

Conservatively, tumor volume measured by CT is used to characterize tumors (Zhu et al. 2011). However, CT-based tumor volume does not perfectly represent tumor size or burden, because tumors do not always have a uniform shape and can have necrotic portions with nonviable tissues. Functional imaging, which can obtain metabolic data on malignant tissues, can more precisely reflect tumor burden. SUV_{max} is used to evaluate outcomes in patients with SCLC (Lee et al. 2009; Pandit et al. 2003; Azad et al. 2010). Although convenient to measure and commonly used, SUV_{max} has limitations. It gives a single-pixel value representing the most intense ^{18}F-FDG uptake by the tumor and may not be a sufficient surrogate marker of tumor biology (Dibble et al. 2012). It may not reveal the heterogeneous nature of the tumor and is affected by statistical noise and pixel size (Soret et al. 2007). MTV and TLG represent the extent of FDG uptake for the entire tumor and have been proposed as better prognostic parameters of clinical results than SUV_{max} (Zhu et al. 2011; Dibble et al. 2012). Our study showed that MTV, TLG, glu-SUV_{max}, and glu-TLG were significantly associated with OS. Only MTV was a significant independent prognostic factor of OS on multivariate analysis. However, analysis of PFS showed that glu-SUV_{max} was significantly associated with PFS in both univariate and multivariate analyses. This result could be explained by the inhibitory effect of glucose on tumor FDG uptake, which is seen for other cancer types. Langen et al. (1993) reported that FDG uptake in lung cancer decreases in response to elevated plasma glucose. In head and neck cancer patients, decreased FDG uptake is seen after glucose loading (Lindholm et al. 1993). Adding glucose level to metabolic parameters seems to offset the underestimation of FDG uptake, revealing the true tumor FDG uptake (Lee et al. 2006).

An essential question in assessing tumor biology is whether total MTV or the maximally active portion of the tumor is more important for predicting outcome. Our results showed that MTV was strongly associated with OS,

Table 2 Significant prognostic factors of OS and PFS

Variables	OS				PFS			
	Median (months)	Univariate	Multivariate		Median (months)	Univariate	Multivariate	
		P	HR (95% CI)	*P*		*P*	HR (95% CI)	*P*
SUV_{max}		0.066				0.06		
< 10.1	75.0				13.2			
≥ 10.1	22.3				8.3			
MTV (mL)		< 0.001	16.7 (3.26–85.1)	0.001		0.23		
< 166.6	75.0				9.7			
≥ 166.6	22.2				7.4			
TLG (g)		< 0.001				0.19		
< 780.3	75.0				10.5			
≥ 780.3	22.3				7.4			
Glu-SUV_{max}		0.047				0.011	3.38 (1.24–9.18)	0.017
< 10.1	75.0				19.6			
≥ 10.1	22.3				8.3			
Glu-TLG (g)		< 0.001				0.18		
< 856.0	75.0				10.5			
≥ 856.0	22.3				7.4			

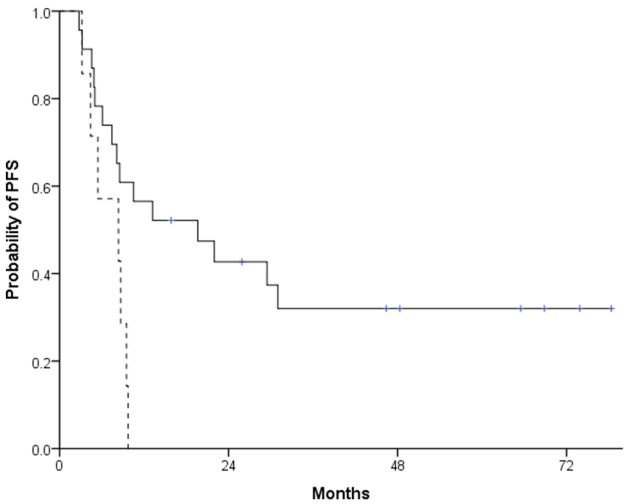

Fig. 2 Progression-free survival curves according to glu-SUV_{max}. Patients with low glu-SUV_{max} (continuous line) had better PFS than those with high glu-SUV_{max} (dashed line)

probably because this volume-based parameter reflects overall tumor burden. SUV_{max} was more highly related to PFS, presumably because SUV_{max} may represent current disease activity. Relationships among pretreatment metabolic parameters, disease progression, and survival may be quite different depending on the intrinsic biological characteristics of tumor cells, treatment modality, and chemotherapeutic agents.

New treatment strategies by MTV and SUV_{max} are required for subgroups of patients with LD-SCLC, who are at higher risk for death or progression. LD-SCLC patients with high MTV and/or SUV_{max} relapsed more frequently with distant metastasis and needed more enhanced systemic chemotherapy than patients with low MTV and/or SUV_{max}. Combinations of chemoradiotherapy and induction chemotherapy using non-cross resistant drugs or chemoradiotherapy and consolidation chemotherapy with novel agents may help these high-risk patients with the LD-SCLC (Han et al. 2005; Ready et al. 2015).

This study had several limitations such as its retrospective nature. In addition, some medical data such as LDH were missing for some patients, although LDH is rarely elevated in LD-SCLC (Osterlind 2000). SUV_{max} is usually measured with high reproducibility; however, it is vulnerable to image noise (Nahmias and Wahl 2008; Lodge et al. 2012). In addition, the partial-volume effect strongly depends on tumor size (Soret et al. 2007). In patients with tumors smaller than 2.0 cm, partial-volume effects can affect ^{18}F-FDG uptake by tumors, resulting in undervaluing of MTV and TLG. Despite these limitations, this study is noteworthy because the patient population was homogenous, including only patients with LD-SCLC who received chemoradiotherapy as an initial treatment.

In conclusion, MTV and glu-SUV_{max} measured on pretreatment ^{18}F-FDG PET/CT were independent and significant prognostic factors in LD-SCLC patients after chemoradiotherapy with curative intent. Patients with low MTV or glu-SUV_{max} had significantly better OS and PFS than patients with high MTV or glu-SUV_{max}, respectively. These biomarkers need to be validated in larger prospective studies

but may be valuable for treatment stratification of LD-SCLC patients.

Compliance with ethical standards

Conflict of interest Author H.C. declares that he/she has no conflict of interest. Author S.J.L. declares that he/she has no conflict of interest. Author J.L. declares that he/she has no conflict of interest. Author J.S.L declares that he/she has no conflict of interest. Author Y.J.K declares that he/she has no conflict of interest. Author W.W.L declares that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent The requirement for informed consent was waived in view of the retrospective nature of the study.

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