



Extra-thoracic tumor burden but not thoracic tumor burden on ^{18}F -FDG PET/CT is an independent prognostic biomarker for extensive-disease small cell lung cancer

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ARTICLE INFO

Article history:

Received 18 January 2013

Received in revised form 11 March 2013

Accepted 1 May 2013

Keywords:

Extensive disease small cell lung cancer

^{18}F -FDG PET/CT

Prognosis

Metabolic tumor volume

Oligometastases

Biomarker

ABSTRACT

Purpose: The aim of this study was to evaluate the relationship and difference in prognostic significance between whole-body tumor burden, thoracic tumor burden, and extra-thoracic tumor burden on ^{18}F -FDG PET/CT for patients with extensive-disease small cell lung cancer (ED-SCLC).

Materials and methods: We performed a retrospective, two-center analysis for patients with ED-SCLC who underwent pretreatment ^{18}F -FDG PET/CT. Metabolic tumor burden was estimated using whole-body metabolic tumor volume (MTV_{WB}), thoracic metabolic tumor volume (MTV_{TRX}), extra-thoracic metabolic tumor volume (MTV_{EXT}), and the number of extra-thoracic tumor foci. Uni- and multivariate analyses were performed using various clinical factors and the metabolic indices.

Results: A total of 91 patients were eligible for this study. MTV_{WB} showed stronger correlation with MTV_{EXT} than MTV_{TRX} ($r^2 = 0.804$ vs. 0.132 , $p < 0.001$, both), whereas no correlation was observed between MTV_{EXT} and MTV_{TRX} ($r^2 = 0.007$, $p = 0.428$). Patients with smaller MTV_{WB}, MTV_{EXT}, and extra-thoracic tumor foci showed longer survival than patients with larger MTV_{WB}, MTV_{EXT}, and extra-thoracic tumor foci, respectively, whereas the survival difference between patients with smaller MTV_{TRX} and those with larger MTV_{TRX} was not significant. Results of uni- and multivariate analyses showed that ECOG performance status (HR = 2.31, $p = 0.015$), initial chemotherapy cycles (HR = 0.24, $p < 0.001$), and the number of extra-thoracic tumor foci (HR = 2.75, $p < 0.001$) were independent prognostic factors for overall survival, and initial chemotherapy cycles (HR = 0.25, $p < 0.001$), and MTV_{EXT} (HR = 2.04, $p = 0.013$) were independent prognostic factors for progression-free survival.

Conclusion: These data provide evidence indicating that extra-thoracic tumor burden but not thoracic tumor burden is an independent prognostic biomarker for ED-SCLC, and support further exploration of novel treatment strategies targeting extra-thoracic tumor burden in order to improve the clinical outcomes of patients with ED-SCLC.

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1. Introduction

Small cell lung cancer (SCLC), accounting for 13–20% of all new cases of lung cancer, is an aggressive malignancy characterized by widespread dissemination at presentation with rapid doubling time [1]. SCLC is staged as either limited disease (LD) or extensive disease (ED) according to the suitability for thoracic radiotherapy. Over the past 20 years, ED-SCLC has mainly been treated with chemotherapy alone. Despite initial response rates of 60–70%,

the median duration of response for initial treatment is too short and the median survival time is only 9–11 months [1,2]. Prophylactic cranial irradiation (PCI) has recently been suggested as a promising treatment option for improvement of the clinical outcomes of patients with ED-SCLC [3], however, otherwise, only small advances have been made including molecular-targeted agents, thoracic radiotherapy, and extra-thoracic radiosurgery [4–7]. To reduce expenses and enhance the efficacy of upcoming clinical investigations, identification of more optimized biomarkers that can validate effectiveness of new treatment strategy and select patients who might benefit from it is essential.

^{18}F -fluorodeoxyglucose (FDG), an analog of glucose, is actively taken up within most tumor cells. Positron emission tomography/computed tomography (PET/CT) using ^{18}F -FDG, with its advantage for whole body assessment and quantification of tumor

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activity, has already been successfully applied in oncologic practice [8]. Metabolic tumor volume (MTV), defined as the volume of tumor tissues with increased FDG uptake, can estimate the total extent of activated tumor cells. Our group has reported optimistic results that whole-body metabolic tumor volume, which reflects systemic tumor burden including primary tumor, lymph nodes, and distant foci, could be a prognostic marker for both LD and ED-SCLC patients [9]. However, prior to its clinical translation, more detailed metabolic profiling that may allow better insight into tumor biology is required. Therefore, the aim of this study was to evaluate the prognostic significance of whole-body tumor burden, thoracic tumor burden, and extra-thoracic tumor burden on ^{18}F -FDG PET/CT for patients with ED-SCLC.

2. Materials and methods

2.1. Patients

Patients with pathologically proven ED-SCLC who underwent pretreatment ^{18}F -FDG PET/CT scan at two centers from January 2004 to December 2010 were retrospectively reviewed. ED was pathologically or clinically defined as disease extending to a contralateral hemithorax or extra-thoracic lesion. Patients who did not receive any treatment or did not have available follow-up data were excluded. For evaluation of the significance of extra-thoracic tumor burden, patients with intra-thoracic ED [N3 (contralateral supraclavicular involvement beyond the radiation field) and M1a (separate tumor nodule in contralateral lung/pleural metastasis/malignant pleural effusion) disease based on the 7th edition of the American Joint Committee on Cancer Staging (AJCC) for non-small cell lung cancer (NSCLC)] were also excluded for analysis. Routine staging work-up, including history and physical examination, complete blood cell counts and chemistry panel, CT of chest and upper abdomen, brain MRI, and ^{18}F -FDG PET/CT, were completed prior to initiation of therapy. The main treatment was based on chemotherapy consisting of platinum with either etoposide or irinotecan administered every three weeks for six cycles. PCI was recommended for patients who showed complete or partial remission after initial therapy. During follow-up, palliative radiotherapy to thorax, brain, or extra-thoracic metastasis was also added according to the patients' performance status and clinical situation. The standard response evaluation consisted of chest X-ray prior to each cycle and CT scan every two cycles of chemotherapy. Follow-up ^{18}F -FDG PET/CT scan was performed three weeks after the last cycle of chemotherapy or when disease progression or recurrence was suspected by standard examinations. All patients were followed up for at least nine months after diagnosis or until death. The local ethical committees approved the study and all enrolled patients gave written informed consent for ^{18}F -FDG PET/CT study.

2.2. Imaging acquisitions

Combined PET/CT scanners (Discovery ST System, GE Medical Systems, Milwaukee, WI, USA; Reveal RT HiREZ, Siemens, Knoxville, TN, USA) were used in performance of ^{18}F -FDG PET/CT studies. All patients fasted for at least 6 h prior to intravenous administration of ^{18}F -FDG. Patients' blood glucose levels were measured prior to injection of ^{18}F -FDG; if the level was over 8.3 mmol/L, then PET/CT was deferred. No oral or intravenous contrast material was administered. Image acquisitions for torso scanning were started approximately 1 h after injection of 7.4 MBq ^{18}F -FDG per kilogram of body weight. CT scan was performed for generation of an attenuation correction map for the PET scan using the following settings: 120 kVp; 10–130 mA; tube rotation time, 0.7 s per rotation; and

section thickness, 3.75 mm in discovery PET/CT unit and 130 kVp; 95 mA; tube rotation time, 0.8 s per rotation; and section thickness, 2.5 mm in reveal PET/CT unit. Immediately following CT acquisition, PET data were acquired in the same anatomic locations with a 15.7 cm axial field of view acquired in the 2D mode with 180 s/bed position. CT data were used for attenuation correction and the PET images were reconstructed using a conventional iterative algorithm, ordered-subsets expectation-maximization (OSEM).

2.3. Image analysis

An Advantage Workstation 4.4 (GE Medical Systems, Milwaukee, WI, USA), providing multiplanar reformatted images, was used in performance of image display and analysis. Maximum standardized uptake value (SUV_{max}) based on body weight and metabolic tumor volume were determined by the attenuation-corrected PET data using volume viewer software, as described in a previous study [9]: (1) automatic production of the boundaries of voxels presenting SUV intensity exceeding 3.0 encasing targeted metabolic tumor burden, (2) subtraction of normal organ, (3) subtraction of false-positive lesions. Thoracic metabolic tumor volume (MTV_{TRX}) was measured in the tumor within the thoracic cavity, including both lungs, pleura, mediastinum, and both hilar and supraclavicular lymph nodes. Extra-thoracic metabolic tumor volume (MTV_{EXT}) was measured in the tumor beyond the thoracic cavity. Whole-body metabolic tumor volume (MTV_{WB}) was calculated by the sum of MTV_{TRX} and MTV_{EXT}. The number of extra-thoracic tumor foci was estimated by the foci that present abnormal FDG uptake in any organ beyond the thoracic cavity. Due to high physiologic FDG uptake, brain was excluded for evaluation of extra-thoracic tumor burden.

2.4. Statistical analysis

SPSS 18 for Windows (SPSS Inc., Chicago, IL, USA) was used in performance of statistical analysis. For detailed classification for prognosis, median values of SUV_{max}, MTV, and the number of extra-thoracic tumor foci were used [9,10]. Pearson correlation coefficient was used for assessment of correlations between MTV_{WB}, MTV_{TRX}, and MTV_{EXT}. Survival time was derived from the date of ^{18}F -FDG PET/CT scan to the date of death/recurrence or last follow-up. Kaplan–Meier methods were used for production of overall survival (OS) and progression free survival (PFS) curves and the log-rank test was used for assessment of survival differences between groups. Cox regression analysis was used for development of uni- and multivariate models describing the association of the independent variables with OS and PFS. Independent variables analyzed included gender, age, smoking, comorbidity, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH), initial chemotherapy regimen, number of initial chemotherapy cycles received, thoracic radiotherapy, prophylactic cranial irradiation, palliative brain radiotherapy, palliative extra-thoracic radiotherapy, brain metastasis, brain-only metastasis, bone metastasis, distant nodal metastasis, liver metastasis, SUV_{WB}, SUV_{TRX}, SUV_{EXT}, MTV_{WB}, MTV_{TRX}, MTV_{EXT}, and the number of extra-thoracic tumor foci. A value of $p < 0.05$ was considered statistically significant. The 95% confidence interval (95% CI) was determined for each parameter.

3. Results

3.1. Patient characteristics

A total of 128 patients with ED-SCLC who underwent pretreatment ^{18}F -FDG PET/CT were scanned. Among them, 103 patients who received at least one cycle of chemotherapy with

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