European Journal of Cancer 101 (2018) 181–190

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

2-Deoxy-2-[fluorine-18] fluoro-D-glucose uptake on positron emission tomography is associated with programmed death ligand-1 expression in patients with pulmonary adenocarcinoma

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Received 30 January 2018; received in revised form 16 June 2018; accepted 20 June 2018

KEYWORDS
^{18}F-FDG PET;
PD-L1;
Lung cancer;
Adenocarcinoma;
Immunohistochemistry;
HIF-1α

Abstract 2-Deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) positron emission tomography (PET) is a useful modality for the assessment of tumour glucose metabolism by upregulation by hypoxia. Little is known whether the uptake of ^{18}F-FDG within cancer cells is linked to the expression of programmed death ligand-1 (PD-L1), a predictor of anti–PD-1 antibody. We conducted a clinicopathological study to assess the expression of PD-L1 and tumour-infiltrating lymphocytes (TILs) in patients with surgically resected pulmonary adenocarcinoma (AC) who received preoperative ^{18}F-FDG PET. A total of 315 patients with lung AC who received ^{18}F-FDG PET were enrolled in the study. Tumour specimens were stained by immunohistochemistry for glucose transporter 1 (Glut1), hypoxia-inducible factor-1α (HIF-1α), PD-L1, CD4 and CD8. We assessed whether the uptake of ^{18}F-FDG was correlated with clinicopathological variables. PD-L1 was highly expressed in 60% of all patients with AC, and the expression level was significantly correlated with ^{18}F-FDG uptake, glucose metabolism and hypoxia. PD-L1 and the maximum standardised uptake value (SUV_{max}) were identified as independent prognostic predictors by multivariate analysis. In particular, PD-L1 could be a

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https://doi.org/10.1016/j.ejca.2018.06.022

significant marker for predicting worse outcomes in AC patients with high ^{18}F-FDG uptake but not in those with low ^{18}F-FDG uptake. According to the epidermal growth factor receptor (*EGFR*) mutation status, the expression of PD-L1 was significantly correlated with SUV_{max} in patients with *EGFR* mutation, whereas, PD-L1 was a significant predictive negative factor in those with wild-type *EGFR*. ^{18}F-FDG uptake was significantly correlated with PD-L1 expression, and the latter was closely linked to the presence of glucose metabolism and hypoxia in patients with pulmonary AC.

1. Introduction

2-Deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) with positron emission tomography (PET) is a diagnostic modality used to differentiate malignant and benign lesions [1]. Several researchers have reported that ^{18}F-FDG PET is useful for the monitoring of the efficacy of chemotherapeutic agents and predicting the outcome after any therapy in patients with several human neoplasms [2,3]. Moreover, ^{18}F-FDG PET/computed tomography (CT) has been previously reported to be suitable for the examination of early response in patients with non–small-cell lung cancer (NSCLC) [3]. The mechanism for ^{18}F-FDG uptake within cancer cells requires the presence of glucose metabolism, hypoxia and angiogenesis, and the uptake level of ^{18}F-FDG is closely linked to the expression of these markers [4]. Recently, we have reported that ^{18}F-FDG PET is precise and useful for prediction of the early therapeutic efficacy of nivolumab, an immune checkpoint inhibitor developed as an anti–programmed death-1 (PD-1) antibody [5–7]. Although the expression level of programmed death ligand-1 (PD-L1) is reportedly related to the therapeutic efficacy of anti–PD-1 antibody [8], recent studies demonstrated the relationship between the level of ^{18}F-FDG uptake and PD-L1 expression in patients with NSCLC [9,10]. In addition, the expression of PD-L1 is closely linked to those of glucose transporter 1 (Glut1) and hypoxia-inducible factor 1α (HIF-1α) in patients with pulmonary pleomorphic carcinoma and renal cell carcinoma [11,12]. Zhang *et al.* described the close correlation between the maximum standardised uptake value (SUV_{max}) on ^{18}F-FDG uptake with the expression of PD-L1 in 84 patients with surgically resected pulmonary squamous cell carcinoma [10]. Takada *et al.* also reported that the SUV_{max} was significantly higher in patients with NSCLC with PD-L1 protein expression compared with that in patients without PD-L1 protein expression; in addition, high SUV_{max} was identified as an independent predictor of PD-L1 positivity by multivariate analysis in 579 surgically resected primary lung cancers [9]. However, little is known about the relationship between the immune environment, including PD-L1 expression, and ^{18}F-FDG uptake and between PD-L1 expression and the expression level of Glut1 and HIF-1α in NSCLC, especially pulmonary adenocarcinoma (AC).

In this context, we conducted a clinicopathological study to assess the expression of PD-L1 and tumour-infiltrating lymphocytes (TILs) in patients with surgically resected pulmonary AC who received preoperative ^{18}F-FDG PET and assessed their correlation with glucose metabolism by Glut1 and hypoxia by HIF-1α using immunohistochemistry (IHC).

2. Material and methods

2.1. Patients

From June 2006 to November 2013, 315 consecutive patients with NSCLC who received preoperative ^{18}F-FDG PET for assessment before surgery by either lobectomy or pneumonectomy with mediastinal lymph node dissection at Gunma University Hospital were registered in the present study. As postoperative adjuvant chemotherapy, platinum-based regimens, S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) and oral tegafur (a fluorouracil derivative drug) were administered to 27, 15 and 55 patients, respectively. No chemotherapy or radiotherapy was performed on any patient before surgery. The study protocol was approved by the institutional review board and followed the guidelines of the Declaration of Helsinki. The tumour specimens were histologically classified according to World Health Organization criteria. The stages of pathological tumour-node-metastasis were established using the International System for Staging Lung Cancer adopted by the American Joint Committee on Cancer and the Union Internationale contre le Cancer [13]. The follow-up duration for censored cases ranged from 3 to 130 months (median: 58 months).

2.2. Immunohistochemical staining

For PD-L1, immunohistochemical staining was performed according to the procedures described previously [4,5,14]. Rabbit monoclonal antibodies against PD-L1 (E1L3N; 1:200 dilution; Cell Signaling Tech-