Abstract

The purpose of this study was to evaluate differences in histological subtypes of lung cancer using \(^{18}\)F-FDG-PET 3-point imaging and kinetic analysis. Subjects comprised 44 patients with histologically proven lung cancer (squamous cell carcinoma (SCC), n=18; well-differentiated adenocarcinoma (WDA), n=9; poorly/moderately differentiated adenocarcinoma (non-WDA), n=17) who underwent \(^{18}\)F-FDG-PET/CT examinations at 1, 2h and 3 h after injection of 185MBq of \(^{18}\)F-FDG, approximately. Mean standardized uptake value (SUV) in each lesion was measured at each time point and the increase rate of SUV (IR\(_{\text{SUV}}\)) was calculated. SUV and IR\(_{\text{SUV}}\) were compared among the 3 groups. In addition, to estimate differences in kinetic parameters for each group, kinetic analysis based on a 3-compartment model was performed. Our results showed SUV differed significantly at every time point among the 3 groups. IR\(_{\text{SUV}}\) between 2 and 3 h post-injection (IR\(_{\text{SUV}}\)\(_{\text{2-3}}\)) differed significantly among the 3 groups, while both IR\(_{\text{SUV}}\)\(_{\text{1-3}}\) and IR\(_{\text{SUV}}\)\(_{\text{1-2}}\) were significantly higher in SCC than in WDA. In kinetic analyses, both K1 and k3 showed significant differences among the 3 groups, with highest values in SCC and lowest in WDA. In conclusion, \(^{18}\)F-FDG-PET 3-point imaging and kinetic analysis enabled the differentiation of histological subtypes in lung cancer, arising from differences in glucose transporter density and enzymatic activity of hexokinase.

Introduction

Positron emission tomography (PET) using 2-deoxy-2-fluorine-18-fluoro-D-glucose (\(^{18}\)F-FDG) is an established diagnostic tool for oncological imaging [1]. In particular, dual-point \(^{18}\)F-FDG-PET is reportedly useful for differentiating between malignant and benign lesions in various organs [2-9]. As for the differentiation of histological subtypes in malignancy, Mavi et al. (2006) [8] reported that differentiation between invasive and noninvasive ductal carcinoma in breast cancer was feasible using dual-point \(^{18}\)F-FDG-PET. Others reported a positive correlation between dual time point changes and degree of cellular differentiation in lung cancer [5], but failed to achieve histological differentiation between squamous cell carcinoma (SCC) and poorly/moderately differentiated adenocarcinoma (unpublished data). Uptake of \(^{18}\)F-FDG in malignancy is known to increase over the course of numerous hours [10], but the increment gradually becomes smaller. This indicates that the scan interval between 1 and 3h after injection of \(^{18}\)F-FDG as used by others may be inappropriate for such differentiation and a different scan interval may be more appropriate. Therefore, this study tried to achieve differentiation using emission scans between 1 and 3h after \(^{18}\)F-FDG injection.

As for the difference in factors that affect \(^{18}\)F-FDG uptake in different histological subtypes, some investigations using immunohistochemistry have been reported [11-15]. In this respect, we also tried to reveal differences in these factors using kinetic analysis based on a 3-compartment model, instead of immunohistochemistry.

Subjects and methods

Patients

Subjects comprised 44 patients with lung cancer (SCC, n=18; well-differentiated adenocarcinoma (WDA), n=9; moderately/poorly differentiated adenocarcinoma (non-WDA), n=17). Histological confirmation was achieved by surgery or transbronchial lung biopsy. Patient characteristics are shown in Table 1 in detail. Written informed consent was obtained from all patients participating in this study, which was approved by the institutional review board of the University of Fukui Hospital.
**Table 1. Patient characteristics**

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<th>SCC</th>
<th>non-WDA</th>
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<td>Patients</td>
<td>18</td>
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<td>9</td>
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<tr>
<td>Age (years)</td>
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*P<0.05 vs. WDA, non-WDA

**18F-FDG-PET/CT examination**

All patients underwent 18F-FDG-PET/CT examination using a PET/CT scanner (Discovery LS; General Electric Medical Systems, Waukesha, WI). Thirty-five transaxial images were acquired simultaneously per field of view with an interslice spacing of 4.25mm. This PET/CT scanner incorporates an integrated 4-slice multidetector CT scanner, which was used for attenuation correction. CT scanning parameters were as follows: Auto mA (upper limit, 40mA; noise index, 20); 140kV; section thickness, 5mm; table feed, 15mm; and pitch, 4.

After fasting for ≥6h, patients received intravenous administration of 185MBq of 18F-FDG, then image acquisition was started 1, 2, and 3h after injection. A whole-body emission scan was performed from the head to the inguinal region with 2min per bed position (7-8 bed positions) for 1- and 3h imaging. Emission scan only in the chest region (1 or 2 bed positions) for 1- and 3h was performed for 18h imaging. Emission scan was performed for 2h imaging. A transmission scan with CT was performed prior to imaging. Emission scan only in the chest region (1 or 2 bed positions) for 1- and 3h imaging.

Kinetic analysis based on the 3-compartment model of 18F-FDG proposed by others [16] was performed in all cases. In this analysis simulated input function generated from a standardized input function curve with body weight correction was used as reported by others [17] as neither arterial blood sampling nor dynamic scans on the left ventricle were performed in this study. Simulated input function was extrapolated until 3h post injection, with exponential fitting. With the simulated input function and individual tissue activity in each time point, a fitting procedure was performed. To simplify fitting parameters, the kinetic parameters were differentiated among the 3 groups.

**Statistical analysis**

Results are expressed as mean±SD. Differences in individual SUV, IR_SUV, and kinetic parameters among the 3 groups were compared using one-way ANOVA. Values of P<0.05 were considered statistically significant.

**Results**

Comparisons of SUV and IR_SUV among the 3 groups are shown in Figures 1 and 2, and Table 2. Serial changes to SUV in each group are demonstrated in Figure 1. Significant differences in SUV at each time point among the 3 groups were observed (Table 2). As for comparisons of IR_SUV, values were higher in SCC than in WDA for every time interval and IR_SUV was observed in all cases. In this analysis simulated input function generated from a standardized input function curve with body weight correction was used as reported by others [17] as neither arterial blood sampling nor dynamic scans on the left ventricle were performed in this study. Simulated input function was extrapolated until 3h post injection, with exponential fitting. With the simulated input function and individual tissue activity in each time point, a fitting procedure was performed. To simplify fitting parameters, the kinetic parameters were differentiated among the 3 groups.

**Discussion**

In the present study, SUV at each time point and IR_SUV were able to differentiate between histological subtypes of lung cancer. Others have already reported differentiation of histological subtypes of breast cancer using dual-point imaging [8]. In that report, invasive and noninvasive ductal cancers were differentiated by dual-point 18F-FDG-PET imaging. Among lung cancer patients, others reported that dual-point 18F-FDG-PET examination showed a positive correlation between SUV increase and degree of cellular differentiation [5].
However, unpublished data from the same patient population showed no significant difference in IR\textsubscript{SUV\textsubscript{1-3}} between SCC and non-WDA (50.4±24.3% in 15 SCCs, 41.3±18.9% in 10 non-WDAs). In the present study, IR\textsubscript{SUV\textsubscript{2-3}} was able to differentiate between SCC and non-WDA, although neither IR\textsubscript{SUV\textsubscript{1-2}} nor IR\textsubscript{SUV\textsubscript{1-2}} could. Others reported that 18\textsubscript{F}-FDG uptake in malignancy increases for many hours, with a gradually decreasing increment [10]. In fact, IR\textsubscript{SUV\textsubscript{1-2}} was smaller than IR\textsubscript{SUV\textsubscript{1-3}} in all groups in our study, and the IR\textsubscript{SUV\textsubscript{1-2}} component in IR\textsubscript{SUV\textsubscript{1-3}} may negatively affect the statistical significance.

Several reports have examined the differentiation of histological subtypes in lung cancer with single-point 18\textsubscript{F}-FDG-PET imaging [11-14, 19]. In those reports, 18\textsubscript{F}-FDG uptake was higher in SCC than in adenocarcinoma. In particular, others reported that SUV differed significantly between SCC, bronchioloalveolar cell carcinoma (BAC) and non-BAC, compatible with the present results [19]. In addition, to investigate factors affecting 18\textsubscript{F}-FDG uptake in lung cancer, correlations between 18\textsubscript{F}-FDG uptake and parameters obtained from immunohistochemistry have also been reported [11-15]. In those reports, 18\textsubscript{F}-FDG uptake in cancer cells correlated with amounts of glucose transporter-1 (Glut-1) and hexokinase-II (HK-II). In the present study, as no immunohistochemical examinations were performed, we tried to estimate the above parameters by kinetic analysis. Fluorine-18-FDG is usually transported into the cell via glucose transporter, metabolized to FDG-6-phosphate by hexokinase and trapped within the cell. Considering 18\textsubscript{F}-FDG kinetics using a compartment model, the 3-compartment model proposed by Phelps et al. was applied [16]. In this model, K1 and k3 represent glucose transporter density and hexokinase activity, respectively. As Glut-1 and HK-II are thought to be the main subtypes of glucose transporter and hexokinase in regulating glucose influx [11] and metabolism [20], respectively, differences in K1 and k3 for different histological subtypes in lung cancer represent differences in the amounts of Glut-1 and HK-II. Both K1 and k3 showed significant differences between SCC.
non-WDA, and WDA in this study, supporting previous immunohistochemical findings. In all groups, K1/k3 was similar and the rate-limiting step was indeterminable, again agreeing with previous findings [21]. In this kinetic analysis, some limitations exist. First, as the simulated input function, not a measured input function was used in this analysis, both K1 and k3 were only estimated values. However, the difference in cerebral metabolic rate of glucose calculated with simulated input function and that with measured input function was less than 3% [12], so the estimated values of K1 and k3 may not show a large degree of error compared with measured values. Second, to simplify fitting parameters, the ratio between influx and efflux of 18F-FDG (K1/k2) was fixed because the number of tissue activity points was small. Previous studies have reported K1/k2 as 4 [10], 0.55 [18], 0.47 [21] and 0.2 [22], showing a high degree of variability. We selected a value of 0.55 for this study, as this value was reproducible and seemed reliable.

To the best of our knowledge, this is the first report concerning the successful differentiation of histological subtypes in lung cancer with multi-point 18F-FDG-PET imaging and kinetic analysis. As for the clinical relevance of differentiating the histological subtypes, it seems not to have clinical relevance in pretreatment differentiation as the diagnosis will be made by histology regardless of the differentiation with imaging. However, when the chemo-/radio-therapy was applied in advanced stage lung cancer patients, the change of 18F-FDG uptake or kinetic parameter may vary between histological subtype and the response evaluation criteria in each histological subtypes may be required. From such viewpoint, histological differentiation with multi-point imaging is thought to have the clinical relevance although the further study will be required. Moreover, to confirm the validity of the kinetic parameters, direct comparison of the parameters and results of immunohistochemistry for amounts of Glut-1 and HK-II is required.

In conclusion, the present study was able to differentiate between histological subtypes of lung cancer using 18F-FDG-PET 3-point imaging and kinetic analysis. Differences in kinetic parameters between all groups were concordant with previously described results of immunohistochemistry.

The authors declare that they have no conflicts of interest.

Bibliography