

Increased ^{18}F -FDG uptake within the reticuloendothelial system in patients with active lung cancer on PET imaging may indicate activation of the systemic immune response

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Abstract

The reticuloendothelial system (RES) cells are in the defense against certain pathogens, and in the removal of dying cells, cell debris, microorganisms, and malignant cells. Liver, spleen, and bone marrow represent the major organs with high RES activity. *We hypothesized* that in subjects with active lung cancer, the metabolic activity of these organs would be greater than that of the subjects with no active tumor. *We have studied* two groups of subjects who had undergone ^{18}F -FDG-PET imaging for clinical purposes. The first group consisted of 39 subjects (20 women, 19 men, mean age 64.8 ± 10.2 years) with benign lung nodules as demonstrated by ^{18}F -FDG-PET imaging. The second group consisted of 30 subjects (18 women, 12 men; mean age 65.1 ± 11 years) who were known to have active lung cancer with or without distant metastases as seen on ^{18}F -FDG-PET imaging. The subjects in the second group did not have any evidence of liver, spleen, bone marrow, or heart involvement on ^{18}F -FDG-PET images. We measured the mean SUV of the liver, spleen, bone marrow, heart, and of the contralateral unaffected lung, and compared the average SUV for these organs between the two groups. *We found that* the mean SUV of the liver, bone marrow, and spleen were significantly greater in subjects with evidence of active primary or metastatic lung cancer compared with those of subjects who had benign lung nodules and no evidence of active malignant disease. There was a statistically significant difference between mean SUV for organs noted above between the two groups ($P < 0.05$). In contrast, mean SUV for the heart and contralateral normal lung did not show any significant difference between the two groups. *In conclusion*, the mean SUV for the major organs of RES, liver, spleen, and bone marrow were higher in subjects with active lung cancer with or without metastases than in those without active malignancy. We believe these differences in SUV may indicate a differential activation of the systemic immune response, related to the presence or absence of active lung cancer, which can be detected and quantified non-invasively through ^{18}F -FDG-PET imaging.

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Introduction

The liver, spleen, and bone marrow represent the organs with the highest reticuloendothelial system (RES) activity. The monocyte-macrophage group of cells in these organs plays an active role in the defense against certain pathogens, aiding in the removal of dying cells, cell debris, microorganisms, and malignant cells. This group of cells is an integral part of both the inductive phase of the immune response and of cell-mediated immune reactions. In addition, it probably plays a role in the defense against tumors that arise spontaneously [1].

Fluorine-18-2-fluoro-2-deoxy-D-glucose (^{18}F -FDG) positron emission tomography (PET) has been successfully used for diagnosing, staging, and monitoring response to treatment for a variety of malignancies [2]. It is now evolving into a powerful imaging modality that can effectively be used for diagnosis and monitoring of therapeutic response in a variety of non-neoplastic disease conditions [3]. As a functional/molecular imaging modality, ^{18}F -FDG-PET may play a role in detecting the presence and the degree of systemic immune response occurring in the RES organs against active malignancy.

Therefore, we hypothesized that in subjects with active lung cancer, the metabolic activity of the major organs that contain RES (liver and spleen) or the participate in the RES cells production (bone marrow) will be greater than that of subjects without active malignancy.

Subjects and methods

Institutional review board approval for this retrospective study was obtained prior to study initiation. This study was Health Insurance Portability and Accountability Act compliant as well, and an approved waiver for informed patient consent was utilized.

Subjects studied

We included two groups of subjects in this retrospective study. Both groups had undergone ^{18}F -FDG-PET imaging for clinical purposes. The first group consisted of 39 subjects (20 women, 19 men, mean age 64.8 ± 10.2 years) who were undergoing evaluation for pulmonary lung nodules and who did not have any evidence of active disease (positive results) on ^{18}F -FDG-PET imaging. The second group consisted of 30 subjects (18 women, 12 men; mean age 65.3 ± 10.1 years) who were known to have active lung cancer with or without distant metastases as seen on ^{18}F -FDG-PET imaging (Fig. 1). Of the 30 patients, 18 had non-small cell lung carcinoma (NSCLC) (6 adenocarcinomas, 6 squamous cell carcinomas, and 6 unspecified). The histological information was not available for the remaining 12 patients with lung cancer. The subjects in the second group did not have any evidence of involvement of the liver, spleen, bone marrow, or heart on ^{18}F -FDG-PET images. The subjects in the first group did not have chemotherapy, but the ones in the second group, for the restaging purposes, have had previous chemotherapy.

The ^{18}F -FDG-PET imaging technique

At the time of ^{18}F -FDG injection all patients had fasted for at least 4h and had blood sugar levels of less than 150mg/dL. Image acquisition for the whole body emission scan started at a mean time point of 60 min after injection of 2.52MBq/kg body weight of ^{18}F -FDG. PET imaging was performed on a dedicated PET only scanner (Allegra; Philips Medical Systems, Bothell WA). Emission scanning covered the neck, chest, abdomen, pelvis, and upper thighs. Images were acquired using 4 or 5 emission frames of 25.6cm length each with an overlap of 12.8cm, covering a total craniocaudal length of 64-76.8cm. Image reconstruction was performed with an iterative ordered-subsets expectation maximization algorithm with 4 iterations and 8 subsets. Attenuation-corrected images were obtained by applying transmission maps with a ^{137}Cs source interleaved with the emission scans.

Image analysis

PET image analysis was performed on a dedicated workstation. We measured the standardized uptake value (SUV) of the liver, spleen, bone marrow, unaffected lung contralateral to the side of pathology, and heart on the ^{18}F -FDG-PET images by placing regions of interest (ROI) around each organ on all transaxial slices (Fig. 2). Mean SUV of each organ from each transaxial slice were recorded, and were subsequently averaged for each organ noted above. These average values were considered as the mean SUV for the whole organs. We then compared the mean SUV for each organ noted above between the two groups.

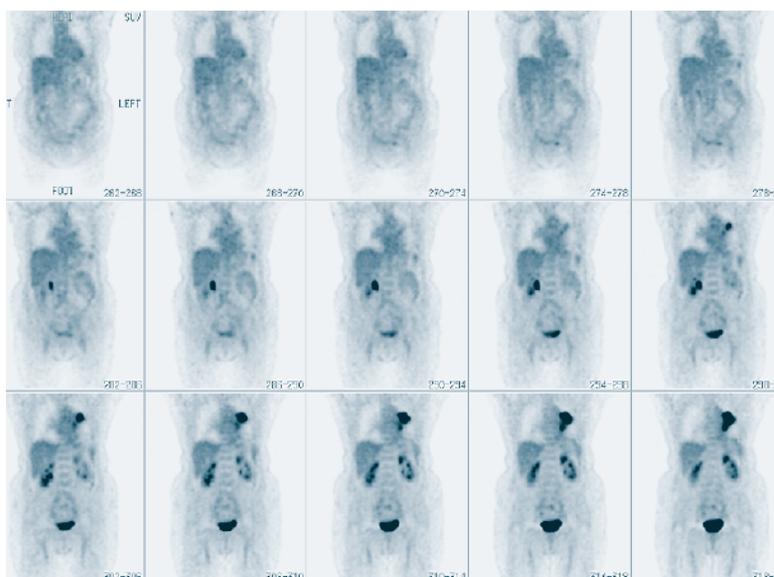


Figure 1. A 85 years old woman with lung cancer. On the coronal slices there is an intensely ^{18}F -FDG-avid tumor in the left lung and an ^{18}F -FDG-avid left hilar lymph node.

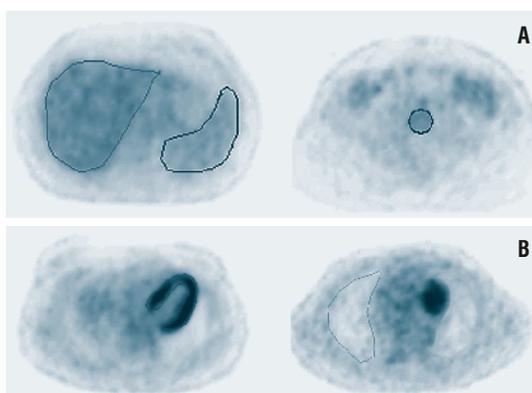


Figure 2. Mean SUV were determined by placing ROIs along all transaxial slices through liver, spleen, bone marrow (2a), heart, and contralateral unaffected lung (2b), respectively, and calculating the average of these measurements for each organ.

Statistical analysis

All data acquired from quantitative analysis were recorded into a computerized database (Microsoft Excel 2002; Microsoft Corporation, Redmond, WA). Student's unpaired t-test was used to assess for statistically significant differences between SUV amongst the two groups using a P value of < 0.05 as the threshold for statistical significance.

Results

The mean SUV of the liver, spleen, and bone marrow were significantly greater in subjects with evidence of active primary or metastatic lung cancer compared with subjects who had benign lung nodules and no evidence of active malignancy on ^{18}F -FDG-PET imaging. There was a statistically significant difference of mean SUV of the liver, spleen, and bone marrow between the two groups ($P < 0.05$). In contrast, the mean SUV of the heart and contralateral unaffected lung did not show any statistically significant difference between the two groups. The mean and standard deviation values for mean SUV of the liver, spleen, bone marrow, heart, and contralateral unaffected lung for both groups are given in Table 1.

Table 1. Organ SUV (Means and Standard Deviations)

	Liver	Spleen	Bone marrow	Heart	Lung
Subjects without active malignancy	1.9 ± 0.4	1.6 ± 0.3	1.5 ± 0.3	3.6 ± 2.0	0.5 ± 0.2
Subjects with active primary or metastatic lung cancer P values	2.1 ± 0.4 P < 0.05	1.9 ± 0.8 P < 0.05	1.8 ± 0.3 P < 0.05	3.1 ± 1.5 P = ns	0.5 ± 0.2 P = ns

Discussion

The immune system is comprised of a collection of mechanisms within a living organism that aims to protect against disease by certain pathogens including tumor cells [4-6]. The RES is a part of the immune system, which consists of phagocytic cells, primarily macrophages, located in reticular connective tissue. These cells accumulate in the lymph nodes and spleen, and also in the liver as Kupffer cells [7-8]. Kupffer cells, which are specialized macrophages, play an important role in clearing pathogenic substances, including tumor cells, from the circulation [9]. The liver is continuously exposed to a large antigenic load that includes pathogens, toxins, and tumor cells, and therefore has the local immune mechanisms required to cope with this diverse immunological challenge [10].

The spleen plays a significant role in host defense as well, contributing to both humoral and cell-mediated immunity. Circulating monocytes are converted into fixed macrophages within the red pulp of the spleen, which account for the remarkable phagocytic activity of the spleen. In the spleen, there is the selective slowing of blood cell flow relative to plasma flow. During this process of slow flow through the spleen, there is contact with splenic macrophages, allowing for removal of cellular debris and senescent blood cells [11].

Bone marrow is a central lymphoid organ where cells of the RES are produced, is one of the largest organs in the body, approaching the size and weight of the liver, and is also one of the most active. The bone marrow mononuclear phagocytic system is a continuum of cells beginning with the monoblast and promonocyte through to the monocyte and to larger tissue macrophages and multinucleate giant cells. The activity and the composition of these cells vary with the level of maturation, with changes in cellular environment, and with various cellular activities [12].

The significance of our findings is that increased SUV may in the RES of patients with active lung cancer be a manifestation of metabolic activation of the RES as part of the systemic immune response against active malignancy. This is plausible as increased activity and numbers of macrophages would lead to increased phagocytic processes against tumor cells, requiring an increase in cellular energy consumption, leading to an increase in glucose utilization, as well as ¹⁸F-FDG uptake. Furthermore, the increase in synthesis of these cells in the bone marrow would require an increase in energy consumption as well, associated with a higher metabolic activity in the bone marrow. As such, quantitative measurement of the degree of ¹⁸F-FDG uptake in the organs of the RES in patients

with active lung cancer may be useful to non-invasively prognosticate clinical outcome.

Limitations of this study include a retrospective study design with a small sample size, involving patients with a mixture of different histologies and stages of lung cancer. Furthermore, histopathological analysis of tissue samples from the RES organs was not

performed, although it is extremely unlikely that metastatic disease would cause diffuse increased ¹⁸F-FDG uptake in the liver, spleen, and bone marrow simultaneously. One other limitation of our study is that information regarding use of chemotherapy or bone marrow stimulatory therapy (e.g., G-CSF) in patients with metastatic lung cancer prior to the date of ¹⁸F-FDG-PET scanning was not available.

In conclusion, the mean SUV for the major organs of the RES (liver, spleen, and bone marrow) on ¹⁸F-FDG-PET imaging were greater in subjects with active lung cancer with or without metastases than in those without active malignancy. These differences in the metabolic activity of the major organs of the RES may indicate a differential activation of the systemic immune response that is related to the presence or absence of active lung cancer, which can be detected and quantified non-invasively through ¹⁸F-FDG-PET imaging. Further research will be required to determine whether detection of increased metabolism within the RES on ¹⁸F-FDG-PET imaging has any relationship to the stage of disease or to clinical outcome in the setting of active lung cancer.

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