# Tumor metabolism measured by partial volume corrected standardized uptake value varies considerably in primary and metastatic sites in patients with lung cancer. A new observation

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## Abstract

Fluorine-18 fluorodeoxyglycose -position emission tomography ($^{18}$F-FDG-PET) as an efficient staging tool for lung carcinoma; allows description and characterization of the primary tumor and of local and distant metastases in a single examination. One of the important limiting factors in quantification of metabolic parameters with PET is the partial volume effect. *Our aim* for this study was to delineate tumor (size) both in the primary and metastatic lesions in patients with lung cancer by using partial volume correction techniques. *Thirty two patients* with proven lung cancer who had $^{18}$F-FDG-PET and computerized tomography (CT) within the last 80 days were involved in this study. They were 18 women and 14 men, with age range 43-83 years. Maximum standardized uptake values (SUVmax) in primary and metastatic lesions for all patients were measured. The lesions were categorized into 4 different Groups according to their site. Partial volume corrections were applied using the CT sizes of lesions to obtain corrected SUVmax values. Average corrected SUVmax in each lesion site was calculated and compared between the 4 Groups. A total of 81 primary and metastatic lesions were included in this analysis. They were 28 mediastinal-hilar lymph node lesions, 26 lung lesions, 11 solid organ lesions, and 16 bone marrow lesions. The average uncorrected SUVmax for the primary lung lesions, mediastinal-hilar lymph node lesions, solid organ lesions, and the bone marrow lesions before application of partial volume correction formula were 7.2±3.2; 7.0±2.7; 6.3±3.4 and 7.0±3.4, respectively. The average corrected SUVmax for the lesions in the above mentioned regions were 11±6, 10±4, 13±7, and 18±13, respectively. A statistically significant difference was observed in the average SUVmax values between lung lesions and nodal lesions compared to the bone marrow lesions. *In conclusion,* our findings indicate that metabolic activities of lung cancer lesions vary depending on the sites of metastatic disease.

## Introduction

The most important prognostic indicator in lung carcinoma is the extent of cancer [1]. A careful diagnostic evaluation for defining the location and extent of primary and metastatic tumor sites is critical to implement an appropriate therapeutic regimen.

Positron emission tomography (PET) with fluorine-18-2-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG), frequently in combination with computed tomography (CT) is now the standard of care for the diagnosis of lung cancer disease since it describes the primary tumor as well as local and distant metastases in a single non-invasive examination with great accuracy as compared other conventional imaging procedures [2-5].

Standardized uptake value (SUV) is defined as the regional tissue radioactivity concentration normalized for injected dose and body weight [6]. This semi-quantitative measurement in the primary tumor, independent of size, is a marker of biologic behavior of lung cancer [7] and of several other malignancies.

One of the major limitations for the accurate quantification of SUV is the partial volume effect. This phenomenon leads to underestimation of regional radioactivity concentration obtained by measurement from reconstructed PET images. The error varies depending on the size of the lesion, with an accentuation of this effect noted as lesions become smaller [8]. Several methodologies and algorithms have been proposed and implemented in the literature to address this important problem [9-12].

To our knowledge, there are no published data in medical literature that assess tumor metabolism of the primary and metastatic lung cancer lesions by measuring and comparing their partial volume corrected SUV. With the help of recovery coefficients calculated from phantom experiments performed in our laboratory, we have carried out partial volume corrections of SUVmax of similar lesions. Subsequently, we assessed the variability of metabolism among primary and metastatic lung cancer lesions in different anatomical sites in the body through use of partial volume corrected SUV [13].

## Subjects and methods

Institutional review board approval for retrospective data collection and image analysis along with a HIPAA waiver were obtained from the Hospital of the University of Pennsylvania's (HUP) Institutional Review Boards, prior to study initiation.

### Subject population

Thirty two subjects with proven lung cancer, who had undergone whole body $^{18}$F-FDG-PET imaging and a diagnostic CT scan within the last 80 days (mean 35±23 days; median 30 days), and who had evidence of at least one primary and/or metastatic lesion on the PET scan were included in this retrospective study. Eighteen of these subjects were women, and 14 were men. The age range was 43-83 (mean 64±11 years). Despite an interval of up to 80 days in a few of the studies, the lesions did not grossly appear to change in size based on PET size estimates compared to CT size estimates.

### Image acquisition

PET imaging was performed using a dedicated whole-body full ring PET scanner (Allegro; Philips Medical Systems, Bothell WA, USA). All patients underwent whole body $^{18}$F-FDG-PET imaging according to the following protocol. At the time of intravenous $^{18}$F-FDG injection, all patients had already fasted for at least 4h and had serum glucose levels of <150mg/dL. Image acquisition for the whole-body scan started at a mean time point of 60min after injection of approximately 2.52MBq/kg of body weight of $^{18}$F-FDG. Imaging by $^{18}$F-FDG-PET of covered neck, thorax, abdomen, pelvis, and upper thighs, and was performed using 4 or 5 emission frames of 25.6cm length each, with an overlap of 12.8cm to cover an axial length of 64-76.8cm. Image reconstruction was performed with an iterative ordered-subset expectation maximization algorithm with 4 iterations and 8 subsets. Attenuation-corrected images were obtained by applying transmission maps, which were acquired after $^{18}$F-FDG injection with a cesium-137 source interleaved with the emissions scans.

### Calculation of lesional partial volume corrected SUVmax

The maximum $^{18}$F-FDG uptake was semi-quantitatively measured using SUVmax for each primary and metastatic lesion visualized on $^{18}$F-FDG-PET imaging in all patients. A background average SUV (SUVmean) measurement for each lesion was made using a region of interest (ROI) located at the same

transaxial level as the lesion but located away from the lesion (Fig. 1). For all primary and metastatic lesions, the greatest lesional diameter was measured using corresponding CT images. Most of the bone marrow lesions were mixed lytic and sclerotic. All of them had a structural correlate on CT, therefore we were able to see and measure all bone marrow lesions on CT.
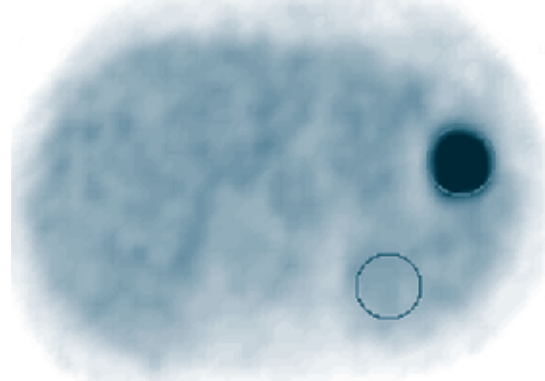


**Figure 1.** The maximum SUV was calculated using the axial slices. Region of interest (ROI) was placed around the lesion (arrow). Furthermore, in the same axial cut, another ROI was placed for the mean background activity.

Recovery coefficients (RC) derived from previous PET phantom experiments conducted in our laboratory were subsequently estimated based on maximum lesional diameters. In these prior experiments, a National Electrical Manufacturers Association (NEMA) image quality torso phantom containing six small radioactive spheres with diameters ranging from 1-3.7cm was filled with water, with a uniform activity concentration of $^{18}$F-FDG. The activity concentration ratios of these spheres with respect to the background were equal. For each sphere SUVmax, as well as SUVmean of the background were measured for calculation of RC, which account for "spill out" of radioactivity from sphere to background and for "spill in" of radioactivity from background to sphere. Logarithmic curves of RC versus sphere diameter were subsequently generated, and served as the basis for lesional RC estimation in the current study [14]. To calculate partial volume corrected SUV max for each lesion, we subtracted the background SUVmean from lesional SUVmax. We then divided this value by the RC that was estimated for that particular lesion size from the previously generated phantom data. Finally, we added back the previously subtracted background SUVmean. Using mathematical notation, *lesion partial volume corrected SUVmax=[(lesion SUVmax–background SUVmean)/RC] +background SUVmean* [15]. By using this mathematical formula, we were able to calculate the partial volume corrected SUVmax for every lesion.

### Analysis of lesions based on partial volume corrected SUVmax

We grouped the $^{18}$F-FDG avid lesions into four subgroups according to location. Lesions involving the lungs were designated as the first Group, and metastatic lesions involving the mediastinal-hilar lymph nodes, distant solid organs, and bone

marrow were considered the other three Groups. The lesion sizes for the first Group ranged between 1 to 8cm, for the second Group between 1.4 to 6cm, for the third Group between 2.7 to 4.2cm and for the fourth Group was 0.7 to 6cm. We measured the uncorrected SUVmax of all lesions in these sites, and calculated corresponding partial volume corrected values as well. Averages of partial volume corrected SUVmax for lesions in each of the four Groups were then computed. All data acquired from quantitative analysis were recorded into a computerized database (Microsoft Excel 2002; Microsoft Corporation, Redmond, WA). One way ANOVA testing using Microsoft Excel 2002; Microsoft Corporation, Redmond, WA, USA was then performed to assess for statistically significant differences on average partial volume corrected SUVmax, among the four Groups, where a P value of less than 0.05 was considered the threshold for statistical significance. We performed additional post hoc testing to determine which pairs of Groups were statistically significantly different in terms of average corrected SUVmax.

## Results

A total of 81 malignant lesions were detected. There were 26 lung lesions, 28 mediastinal-hilar lymph node lesions, 11 solid organ lesions: 9 in the liver and 2 in the spleen and 16 bone marrow lesions: 1 in the cervical spine, 2 in the thoracic spine, 1 in the lumber spine, 3 in the , 1 in the scapula, 4 in the ribs, and 4 in the pelvic bones.

Average uncorrected SUVmax for lung lesions, mediastinal-hilar lymph node lesions, solid organ lesions and bone marrow lesions were; 7.2±3.2, 7.0±2.7, 6.3±3.4, and 7.0±3.4, respectively (Fig. 2). No statistically significant difference on average uncorrected SUVmax was noted among the four Groups.

Average partial volume corrected SUVmax for the same four Groups listed above were 10.4±4.4, 11.2±6.0, 13.6±7.3, and 18.6±13.0, respectively (Fig. 3). A statistically significant difference on average uncorrected SUVmax was noted among the four Groups (P< 0.05).

There was no statistically significant difference between average partial volume corrected SUVmax of lung lesions and mediastinal-hilar lesions (P>0.05). The average partial volume corrected SUVmax of solid organ lesions was greater than those of lung lesions and mediastinal-hilar lesions and less than that of bone marrow lesions without statistical significance (P>0.05) (Fig. 4 and 5). Average partial volume corrected SUVmax of bone marrow lesions was statistically signifi-
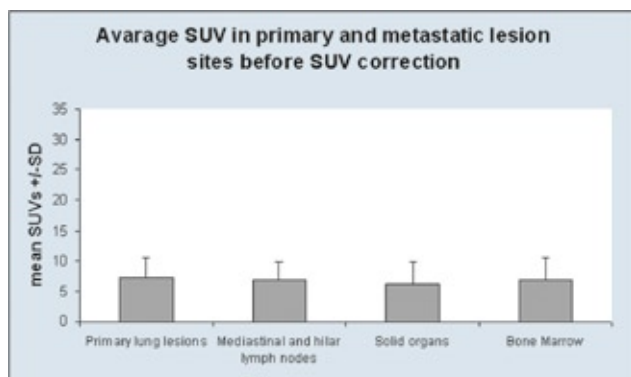


**Figure 2.** SUV values before partial volume correction for different lesion locations.
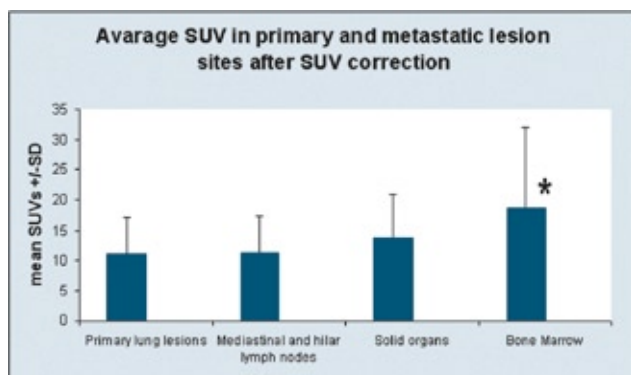


**Figure 3.** SUV values after partial volume correction for different lesion locations. Average partial volume corrected SUVmax of bone marrow lesions was statistically significantly greater than those of lung lesions (P<0.05) and mediastinal-hilar lesions *.
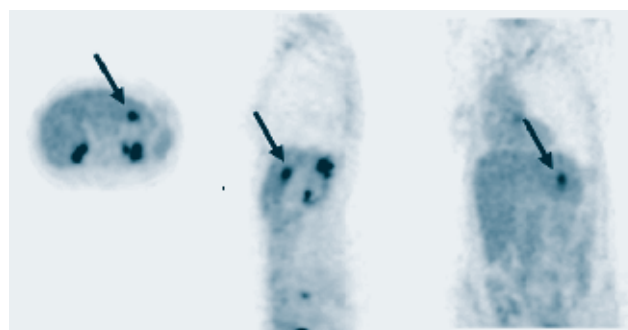


**Figure 4.** Transverse, sagittal, and coronal slices of ^{18}F-FDG-PET images. There is a focus of ^{18}F-FDG avid lesion in the left lobe of the liver. The maximum SUV for this lesion before correction was 9.1. The mean background SUV for the liver was 2.2. After applying correction formula, the maximum SUV for the liver lesion was 13.7.
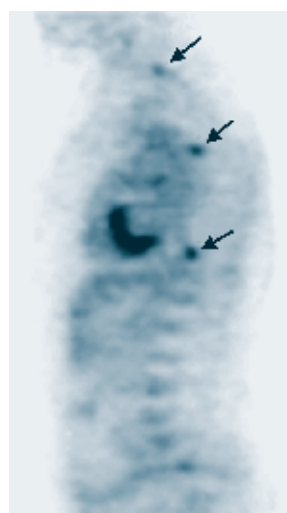


**Figure 5.** Sagittal slice of ^{18}F-FDG PET image. Foci of increased ^{18}F-FDG uptake is visualized in the lower cervical, mid thoracic and lower thoracic vertebrae. The maximum SUV for the lesions were 4.7, 6.9 and 6.0. The mean background SUV was 0.8 for the cervical lesion, 1.4 for thoracic lesions. The sizes of the lesions were 0.7cm, 1cm and 1.2cm, respectively. The recovery coefficients for the lesions were 0.2, 0.3 and 0.5. The corrected maximum SUV for the lesions were 17.3, 19.7 and 12.6, respectively.

cantly greater than those of lung lesions (P<0.05) and mediastinal-hilar lesions (P<0.05).

The most significant correction in the SUVmax values occurred for small sized lesions in all four groups. For example, a 1.2cm lung lesion with SUVmax of 4.5 increased up to SUVmax of 11, after correction. Another 1.4cm mediastinal lesion with SUVmax of 5.1, increased up to SUVmax of 12.

## Discussion

One of the challenges encountered with quantification using ^{18}F-FDG-PET imaging is the partial volume effect. This effect is mainly observed for small objects because of the limits of spatial resolution of PET. Each PET camera has an intrinsic point spread function (PSF), which is a profile of how much a point source when imaged in air, spreads out onto the reconstructed image. The width of this PSF, which is characterized by measuring the full-width-half-maximum (FWHM), is used as a measure of spatial resolution. As long as objects of interest are greater than 2 times the FWHM, the PSF is to a great extent contained within the reconstructed object. However, if the object of interest is less than 2 times the FWHM, then a significant fraction of radioactive counts will spill out of the reconstructed object into the surrounding tissue [9]. The metabolic activities measured for these small sized lesions are not accurate, and will generally underestimate the true metabolic activities of these lesions. This may account for some of the variability in results reported in the literature related to the prognosis and survival in patients with cancer, for which measurements of lesional ^{18}F-FDG uptake were performed and reported without correcting for the partial volume effect. For example, there are several publications in the literature that report the prognostic outcomes of lung cancer patients based on uncorrected SUV measurements of the primary and/or metastatic lesions [2, 16-18].

Use of partial volume correction will reduce the measurement error related to the underestimation of lesional ^{18}F-FDG uptake, particularly for the small sized lesions, and will therefore accentuate subtle differences in lesion metabolism that may be present. For this reason, we have applied a partial volume correction technique to measurements of SUV among lung cancer lesions found in different anatomical sites of the body to accurately assess for the differences in lesional ^{18}F-FDG uptake and therefore tumor metabolism among these sites.

In this study, we decided to use maximum ^{18}F-FDG uptake values (rather than mean values) of lesions to calculate corrected SUV. Compared to SUVmean, SUVmax is generally less operator dependent and more reproducible to obtain. We observed that the average partial volume corrected SUVmax of lung cancer lesions was variable based on disease site, with lesions increasing in metabolic activity on average when moving from the lungs to the nodes, solid organs, and bone marrow, although we were only able to demonstrate a statistically significant difference between the average partial volume corrected SUVmax of bone marrow lesions and those of the lungs and lymph nodes. This may be related to the rela-

tively small number of subjects in our study population and the associated relatively small number of malignant lesions that were assessed.

There were no lesions smaller than 1cm in the four Groups studied. The most significant correction in the SUVmax values occurred for small sized lesions in all four Groups.

Other limitations of this study include its retrospective nature, a lack of histopathological correlation with ^{18}F-FDG-PET imaging findings, and measurement errors related to the model used for partial volume correction, which assumes that lesions are spherical in shape. Perhaps some lesions assessed on ^{18}F-FDG-PET imaging may have changed in size from those measured on CT, given the range of time intervals between the dates of acquisition of these two imaging studies, although these intervals were minimized as much as possible.

Our observation on ^{18}F-FDG-PET imaging that there is variability in lung cancer lesion metabolism depending on the site of disease may have implications regarding the assessment of tumor metabolism, the study of the relationship between tumor metabolism and the tumor microenvironment, and for the optimization of local and systemic therapeutic interventions for individual patients. These findings will require further validation through future prospective studies to determine the relationships between partial volume corrected measures of lesional ^{18}F-FDG uptake with measures of patient outcome, treatment response prediction, and treatment monitoring.

*In conclusion,* we have shown in this study, that the average partial volume corrected SUVmax of metastatic lesions, as measured from ^{18}F-FDG-PET imaging in subjects with lung cancer, is variable between different anatomical sites in the body, with highest level of metabolism noted in lesions that involve the bone marrow. To our knowledge, this has not been previously described in the literature. These findings may have implications for understanding tumor biology the relationship between tumor and tumor microenvironment, resistance or susceptibility of metastatic lesions to treatment and treatment monitoring through ^{18}F-FDG-PET.

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