

RESEARCH ARTICLE

Increasing Uptake Time in FDG-PET: Standardized Uptake Values in Normal Tissues at 1 versus 3 h

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Abstract

Objective: Positron emission tomography (PET) imaging at more than 1 h after 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG) administration may result in less blood pool activity and possibly decreased normal FDG uptake in tissues such as liver. Lower normal background activity could be an important component of improved image contrast on delayed imaging. Increasing FDG uptake in normal organs, however, may mitigate the beneficial effects of blood pool clearance. The purpose of this study is to determine the normal tissue and blood pool FDG uptake at 1 and 3 h after injection.

Subjects and methods: Ninety-nine patients with known or suspected malignancy referred for FDG-PET-computed tomography (CT) were retrospectively evaluated. PET imaging was performed at either 1 h (60 ± 15 min; $n=50$) or at 3 h (180 ± 15 min; $n=49$) after FDG administration. Normal tissue FDG uptake without involvement by malignancy or influenced by artifact (misregistration, “brown fat,” focal muscle uptake, focal atherosclerotic disease) was confirmed by inspection of both the PET and CT scans. Aortic blood pool, adipose tissue, bone marrow, cerebellum, liver, lungs, muscle, and spleen were quantitatively evaluated by CT-guided region of interest analysis in three contiguous slices. Mean standardized uptake values (SUVs) were analyzed using one-way analysis of variance.

Results: Mean SUVs on the 3- versus 1-h images were significantly lower for aortic blood pool 13% ($p < 0.0001$) and adipose tissue 20% ($p < 0.008$). FDG uptake showed significant increases at 3 h compared to 1-h imaging in the cerebellum 40% ($p < 0.0001$), bone marrow 25% ($p = 0.003$), muscle 21% ($p = 0.0004$), and spleen 13% ($p = 0.01$). The liver and lung showed no significant differences (1%, $p = 0.85$; -2%, $p = 0.62$, respectively).

Conclusions: On FDG imaging at 3 h compared to 1 h, significant changes were apparent, but the magnitude of changes was modest overall. Three-hour delayed imaging demonstrated significantly lower aortic blood pool and adipose tissue activity and significantly higher cerebellum, muscle, spleen, and bone marrow activity. Hepatic and lung activities were not significantly different. These results suggest that previously reported improvements in tumor image contrast with delayed imaging may be primarily due to cumulative FDG uptake within the tumor rather than reduction in normal background activity.

Key words: Positron emission tomography, Delayed imaging, Fluoro-2-deoxy-D-glucose, Normal uptake, Standardized uptake value

Introduction

2-Deoxy-2- ^{18}F fluoro-D-glucose-positron emission tomography (FDG-PET) imaging relies on higher glycolytic activity in tumors compared to normal structures as the basis of image contrast. The time between intravenous FDG administration and imaging, the uptake phase, permits both high accumulation of FDG-6-phosphate within tumors and clearance of background blood pool activity to improve image contrast. An extensive characterization of normal uptake in organs using a typical standard uptake time of approximately 1 h and current PET-computed tomography (CT) techniques has recently been published [1]. Extending the uptake phase can increase trapping of FDG-6-phosphate within tumors and also increase the renal clearance of background blood pool activity. Furthermore, the liver contains high levels of metabolically active enzymes including glucose-6-phosphatase. This enzymatic activity could further reduce normal FDG-6-phosphate trapping and overall normal liver background activity; thus, higher tumor contrast specifically for liver tumors may be possible. While having less activity and therefore fewer counts is in itself not desirable, potentially higher tumor contrast at later imaging times could outweigh this effect, leading to overall better tumor detection and characterization.

To what extent a longer uptake phase contributes to background blood pool clearance and uptake in normal organs has not been determined. If an extended uptake phase effectively reduces normal background activity, further efforts to improve or optimize this result may be warranted. The purpose of this study is to examine the FDG uptake in normal organs at 1 h compared to an extended uptake phase at 3 h.

Subjects and Methods

Patients

The protocol for this retrospective study was submitted to our institutional review board (IRB) and deemed exempt from IRB status. An independent data analyst retrieved the studies and anonymized them prior to blinded interpretation and analysis. At our institution, the uptake phase for FDG-PET-CT clinical studies varies to facilitate a busy clinical schedule. The first scheduled patient of the day has an uptake phase of approximately 1 h; for all others, uptake is typically longer than 1 h, with a target of 2 h, but occasionally over 3 h. This retrospective study selected 99 consecutive patients with known or suspected malignancy referred for FDG-PET-CT who met the following inclusion and exclusion criteria. FDG-PET imaging studies included those referred to the PET center between 2003 and 2005 that were performed at either 1 h (60 ± 15 min; $n=50$) or at 3 h (180 ± 15 min; $n=49$) after FDG administration. Both the PET and CT studies were first examined by an experienced nuclear medicine physician to ensure that the following exclusion criteria for normal tissue FDG uptake were met: (1) absence of tumor involvement by malignancy in the normal area of interest, (2) absence of artifacts (misregistration, "brown fat," focal muscle uptake), (3) absence of dose infiltration (axillary lymph node uptake in the extremity of injection), and (4) absence of abnormally high bone marrow (defined visually as intense

bone marrow uptake higher than the liver) and/or high spleen uptake (defined visually as greater than the liver). Patient age, gender, height, weight, history of diabetes, and serum glucose (mg/dl) prior to injection were recorded and compared between the 1- and 3-h uptake groups.

Imaging

All patients were examined on a dedicated PET-CT system (Discovery ST, General Electric, Milwaukee, WI, USA). Patients received FDG on a sliding scale according to weight (0.18 mCi/kg or 6.7 MBq/kg; minimum dose 10 mCi or 370 MBq; maximum 25 mCi or 925 MBq). PET images were acquired for time based on patient weight (2 min per bed position if <150 lbs; 2.5 min per bed position if 150–199 lbs; 3 min per bed position if 200–250 lbs; 4 min per bed position if >250 lbs). The CT protocol included the following parameters: tube current of 30–300 mA determined by an automated algorithm based on the planar view, 140 kVp, and pitch 1.375. The CT axial images were reconstructed in a 512×512 matrix of 50-cm field of view, with a 3.27-mm center-to-center spacing to match the PET and a thickness of 3.75 mm. The noncontrast CT was utilized for PET attenuation correction, and additional corrections for scatter, random events, and dead time were performed in reconstructing 128×128 matrix images, also covering a 50-cm field of view using the OSEM algorithm.

Data Analysis

Reconstructed images were transferred from the scanner workstation to an offline computer for region of interest (ROI) analysis. CT images were downsampled to a 256×256 matrix, and PET images were subsampled to the same matrix to achieve matching pixels. A single experienced nuclear medicine physician drew large ROIs to include the majority of the organ of interest but clearly within the boundary of the organ. Due to variability in organ size, only these general guidelines were used to determine the size of the ROI. The boundary, however, could always be clearly delineated using CT guidance. This allowed for analysis of relatively large regions to reduce the random effects from noise; additionally, it reduced the potential errors from ROI misplacement in adjacent organs. ROIs were drawn on CT images (cortical cerebellum, aorta, lungs, liver, spleen, muscle, fat, and bone marrow), subsequently superimposed on corresponding coregistered PET images. Three contiguous transaxial slices were used for ROI placement to generate volumes of interest. For the cerebellum, the ROI excluded the three most superior transaxial slices at the edge of the field of view. For the blood pool, the ROI was measured at the root of the aorta with exclusion of the aortic wall. For the bilateral lungs, the ROI was placed at the level of the carina with exclusion of the hilar vessels. For the liver, the ROI was placed at least one slice above the level of the porta hepatis vessels. Hepatic masses present on CT examination were excluded by selecting a level not containing a mass lesion. For the psoas muscle, the ROI was placed at the level of the iliac crests. For fat, the ROI was placed in the gluteal region with areas of focal injection sites excluded. For bone marrow, the ROI was placed in the L5 vertebral body.

Standardized uptake values (SUV) corrected for body weight were calculated for each volume, and both maximum and average SUV values were obtained for the volumes. The values reported are those for SUV mean. Representative regions of interest are shown in Fig. 1.

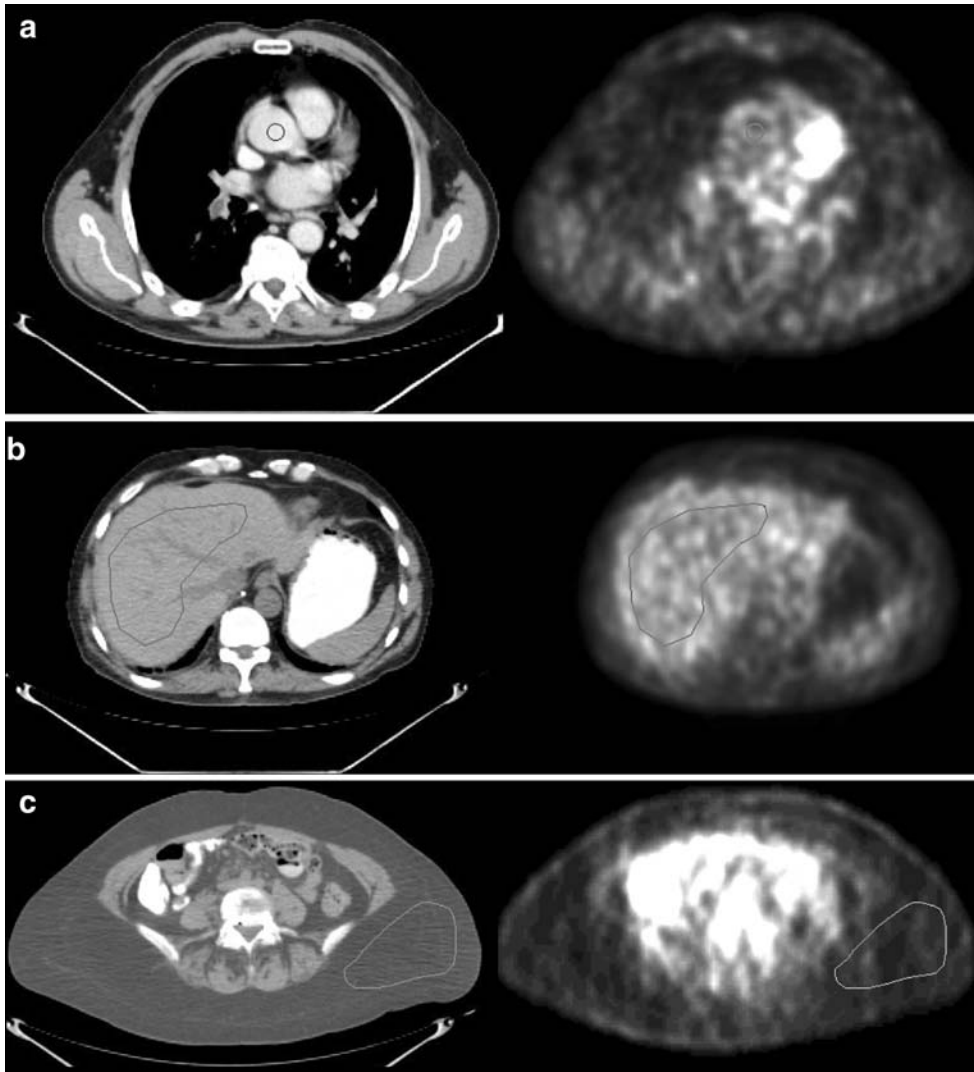


Fig. 1. Representative normal tissues with regions of interest drawn on CT and superimposed on coregistered PET images **a** aortic blood pool, **b** liver, and **c** adipose tissue.

Statistical Analysis

SUV mean values were analyzed using a standard software package (JMP 6.0, SAS Institute, Cary, NC USA). Statistical analysis of continuous variables was performed with one-way analysis of variance, and nominal variables were compared with Fisher's exact test. p values < 0.05 were considered statistically significant.

Results

Patient demographics were similar between groups. Between patients that had 1- versus 3-h uptake phases, respectively, there were no significant differences in patient age (57.9 ± 13.6 versus 60.8 ± 11.3 ; $p = 0.24$), gender (male: $n = 27$ versus $n = 30$; $p = 0.54$), diabetes ($n = 2$ versus $n = 3$; $p = 0.67$), height (172.8 ± 10.6 versus 173.2 ± 10.6 cm; $p = 0.85$), weight (76.6 ± 17.1 versus 81.2 ± 15.6 kg; $p = 0.16$), and serum glucose levels

prior to FDG administration (113.3 ± 41.7 versus 108.5 ± 21.2 mg/dl; $p = 0.47$).

The FDG uptake, however, showed significant differences in mean SUV in several normal regions (Fig. 2). The cerebellum showed the highest mean difference with a significantly higher mean SUV at 3 h compared to 1 h (9.0 ± 1.9 versus 6.5 ± 1.3 ; 40%; $p < 0.001$). The spleen showed a modest but significantly higher mean SUV at 3 h (2.2 ± 0.5 versus 2.0 ± 0.4 ; 13%; $p = 0.01$). Similarly, the bone marrow showed a modestly higher mean SUV at 3-h delayed imaging (1.9 ± 0.7 versus 1.5 ± 0.4 ; 25%; $p = 0.003$). Muscle showed a mild but significantly higher mean SUV at 3 h (0.93 ± 0.29 versus 0.77 ± 0.13 ; 21%; $p = 0.004$).

In contrast, the mean blood pool was modestly lower on 3-h delayed imaging (1.6 ± 0.4 versus 1.9 ± 0.3 ; -13%; $p = 0.001$). Adipose tissue on delayed 3-h imaging was very slightly lower, but this difference was statistically significant

FDG Uptake: 1 Hour versus 3 Hour

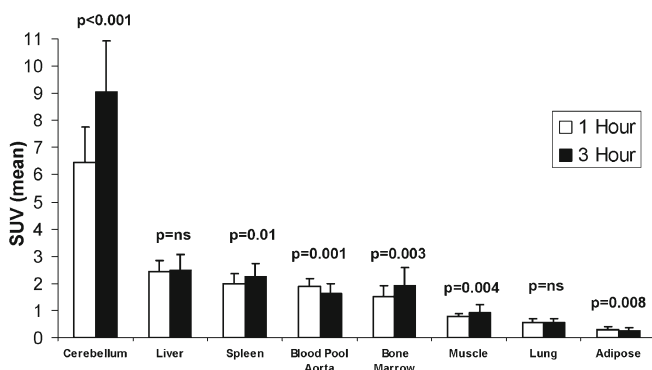


Fig. 2. Standardized uptake values in normal tissues at 1 versus 3 h.

(0.25 ± 0.10 versus 0.31 ± 0.11 ; -20% ; $p=0.008$). Activity in the liver and lung did not show a significant difference on 3-h delayed imaging compared to 1-h imaging (2.5 ± 0.6 versus 2.4 ± 0.4 ; $p=0.85$ and 0.56 ± 0.15 versus 0.57 ± 0.12 ; $p=0.65$, respectively).

Discussion

In FDG-PET imaging, tumor contrast is highly dependent upon not only tumor uptake but also upon the level of normal background. This study investigated the degree to which the latter component was affected by a delayed uptake time by comparing a 3-h delay with a typical delay of 1 h. Detected activity within a volume of tissue, for both tumors and normal tissues, primarily represents the cumulative activity of FDG-6-phosphate trapped within the cells. Although the interstitial and intravascular compartments retain activity, their overall contributions to uptake are considered relatively small after a typical 1-h uptake phase. Since the kidneys continue to clear FDG over time, the vascular component of background activity within normal tissues is expected to decrease. Concordant with these concepts, our data showed a modestly lower blood pool activity on 3-h delayed imaging.

In tumor detection, however, the clinically important background areas of interest are at the sites of tumor occurrence, such as the liver or lung. In these organs, no significant difference in normal background was detected. In the liver, relatively high levels of glucose-6-phosphatase may result in higher levels of FDG-6-phosphate metabolism and a subsequent reduction of intracellular trapping. The lack of a significant difference at 3 h suggests that integrated compartmental influx and efflux are similar at both time points. In the lung, the volume of blood pool is relatively small and, thus, the overall contribution of blood pool clearance is also expected to be small.

In adipose tissue, the mean FDG activity was slightly lower at 3-h delayed imaging. We hypothesized that this is due to blood pool clearance, and a slight theoretical benefit

in contrast may occur when subcutaneous or intra-abdominal tumors are located in the background of adipose tissue. The normal uptake, however, is very low at 1 h and, thus, the benefit attributed to this very small difference is likely to be small.

Sites of slightly higher mean uptake at 3 h occurred in the spleen, bone marrow, and muscle. The spleen and bone marrow contain metabolically active lymphoid and myeloid cells including reticuloendothelial cells, hematopoietic progenitor and stem cells, and lymphocytes. Skeletal muscle has well-established glucose utilization pathways and a relatively small intravascular volume; thus, its higher normal uptake on the delayed imaging is also concordant with expected results. A clinical benefit of delayed imaging with respect to tumor detection, however, may still be possible if a tumor has a rate of FDG uptake that exceeds that of the normal background tissue.

In our study, normal cerebellar brain uptake showed the greatest increase on delayed imaging. Despite this increased activity, a prospective study of CNS gliomas has demonstrated improvements in tumor contrast and lesion detectability on delayed imaging by both visual and quantitative modeling [2]. Because glioma accumulation exceeded that of gray and white matter, higher contrast could still be seen on delayed imaging. Thus, improvement in tumor contrast and detectability may occur for a variety of tumors if their rate of uptake exceeds that of the normal background tissue.

Several groups have evaluated changes in tumor contrast using delayed imaging with a dual-phase imaging protocol. The retention index (RI) is defined as the difference in standardized uptake value between early and late imaging expressed as a percentage of the initial uptake ($RI = (SUV_{\text{delayed}} - SUV_{\text{early}}) / SUV_{\text{early}} \times 100\%$). These reports have generally been favorable showing improvement in detection or contrast for brain [2], breast [3], lung [4], pancreas [5–7], gallbladder [8], hepatocellular [9], cervical [10, 11], intra-abdominal [12], intra-thoracic [13], soft-tissue [14], and other tumors [15, 16]. For nasopharyngeal carcinoma, high sensitivity did not improve with delayed imaging [17]. Most of these studies demonstrate improvement in contrast or tumor detection; however, in some cases, the RI did not provide incremental improvement, and the change in SUV was in many cases close to the reported reproducibility limit of SUV measurements [18, 19].

A dual-imaging protocol has the disadvantage of requiring additional scanning time that may significantly impact clinical workflow and patient scheduling. This logistical issue has probably limited the widespread use of this technique. Because delayed imaging alone may be sufficient to increase tumor contrast, this protocol could be beneficial if the sites of suspected primary tumor, recurrence, or metastases are known or if response to therapy is being evaluated. Whether delayed imaging can result in clinically important differences in outcomes based on improvements in PET interpretations, however, remains unknown. Thus, the value of delayed imaging has not yet been established.

This retrospective study has several limitations. First, direct comparison of regions using paired datasets was not possible. Although in principle a dual-time-point imaging study is preferable, scanning patients a second time with an additional 2 h between scans is logistically very difficult and in many instances clinically impractical. The incremental value of dual-time-point scanning compared to delayed scanning alone has not been conclusively demonstrated, and a single delayed time point may be preferable. In addition, a second CT for attenuation correction would also increase radiation exposure. Second, delayed imaging is disadvantageous due to the reduced rate of true coincidences. SUVs are calculated with a correction for radioactive decay; a region with a similar SUV at 3 h actually has approximately half the true counts of the region at 1 h. However, reduced random events and dead time at lower rates provide some benefit, partially mitigating the true count reduction. Third, in our study, factors that may affect FDG transport, such as diabetes and hyperglycemia, could not be controlled. However, the large sample size and demographic similarity of the two groups improve the power to detect significant differences and reduce outlier effects. Further, the lack of strict demographic exclusion criteria, e. g., diabetes, provides a more inclusive and generalized population that might be more representative of a typical referral population seen in clinical practice. Finally, the possibility of other factors, such as circadian rhythm or actual time of day, may also have contributed to observed differences in FDG uptake. Our analysis method, however, was blinded and did not permit the ability to retrieve this information. Further studies are necessary to test the influence of additional factors that may affect FDG uptake.

Conclusion

A 3-h delayed uptake phase resulted in modest changes in normal background activity that varied depending on location or organ. The previously reported improvements in tumor image contrast with delayed imaging may be primarily due to cumulative FDG uptake within the tumor rather than reduction in normal background activity.

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