Optimizing 18F-FDG uptake time prior to imaging improves the accuracy of PET/CT in liver lesions

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Abstract:

Introduction: 18F-FDG PET/CT has emerged as one of the fastest growing imaging modalities. A shorter protocol results in lower target-to-background ratio, which can make identification of mildly FDG-avid lesions and differentiation of inflammatory or physiologic from malignant activity more challenging. The purpose of this study was to find the optimal time delay between radiotracer injection and imaging (TI) that would achieve a better target-to-background ratio, while maintaining adequate counting statistics to ensure scan sensitivity. Methods: Patient population-140 patients (66 male, 74 female; age 42-95) with suspicious hepatic lesions evaluated by an 18F-FDG PET scan were studied. SUV = region of interest activity/ (dose/total body weight). Results: The mean injected dose was 16.5 +/-1.8 mCi, with a mean glucose level of 107 +/- 26.6 (standardized to 90) mg/dl. The uptake time before imaging ranged from 61 to 158 minutes, with a mean of 108.8 +/- 24.8 minutes. The p-values of the correlation of SUV to time were 0.004, 0.003, and 0.0001 for malignant lesions, benign lesions, and background liver respectively. Conclusion: An approximate 90-minute window from the time of injection of 18F-FDG to PET imaging would lead to a significant improvement in targetto-background ratio, and thus more clinically valuable quantitation and more accurate visual interpretation. This benefit outweighs the minimal loss in patient throughput.

Key words: target-to-background ratio, liver lesions, 18F-FDG PET scan

Introduction:

Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with computed tomography (18F-FDG PET/CT) has emerged as one of the fastest growing imaging modalities. The recent expansion of coverage from the center for Medicare services has made its utilization even more feasible for community based hospitals and independent imaging centers. In an effort to maximize throughput, many of these centers utilize a 50-60 minute uptake time following 18F-FDG injection while arguing that the counting statistics are improved using this protocol [*1-3*]. However, a shorter protocol results in lower target-to-background ratio, which can make identification of mildly FDG-avid lesions and differentiation of inflammatory or physiologic from malignant activity more challenging [*4-6*].

The purpose of this study was to find the optimal time delay between radiotracer injection and imaging (TI) that would that would achieve a better target-to-background ratio, while maintaining adequate counting statistics to ensure scan sensitivity. Hepatic lesions and background liver were chosen as the test and control tissue of its relatively predictable parabolic uptake pattern of 18F-FDG [7,8]. Additionally, it's heterogeneous or mottled appearance can often produce areas of benign focal uptake or mask uptake within a malignant lesion that present a challenge during image interpretation [6].

Methods:

The study was approved by human investigation committee (HIC) at William Beaumont Hospital with the following HIC number: 2012-226. Patient population: 140 patients (66 male, 74 female; age 42-95) with suspicious hepatic lesions evaluated by an 18F-FDG PET scan were studied. All included patients had a primary malignancy and were either referred for initial staging or were at least 4 weeks removed from the most recent therapy. Any primary tumor type was considered **which** included colorectal, lung, breast, melanoma, lymphoma, squamous cell of the head and neck. All 140 lesions were biopsy proven with 93 being positive, and 47 negative. All are considered metastatic lesions. **The most suspicious and accessible liver lesion got biopsied even when there was more than one lesion. For the purpose of kinetic analysis, only the biopsied lesions were used in the final analysis.** The number of diabetic patients in the study was not tracked.

Image Acquisition: All patients were imaged on mobile 16-slice PET/CT unit (Siemens/CTI ECAT EXACT and Siemens Biograph 40, Knoxville, TN). The patients received between 10-20 mCi (370-740 MBq) of 18F-FDG. Patients with a serum glucose level of greater than 200 mg/dl at the time of injection were not included in the dataset. The typical imaging protocol called for a TI of 60-90 minutes; however there was significant variation caused by dual-time protocols, throughput requirements, and external workflow factors. These patients were imaged from the base of the skull to the middle of the thighs using 6 bed positions. The images were

reconstructed similarly with OSEM algorithm. Concomitant CT data was used for attenuation correction of all PET images from both cameras using 140 kVp, 120-200 mA, 0.8 s per CT rotation, 1.75:1 pitch using 3 mm slice-thickness. All patients received oral contrast. The standardized uptake value (SUV) was calculated with the following formula: SUV = region of interest activity/ (dose/total body weight).

Image Analysis: The max SUV of each suspicious lesion was obtained using a 3-dimensional region of interest over it. The mean of 5 region of interests of 10 mm in diameter over normal liver, measuring average SUV, were used for an SUV value representative of physiologic liver activity. Then all SUV measurements were corrected for the patient's individual serum glucose variation to a 90 mg/dl using the using the method described by Thie, et al [9].

Statistical Analysis-2nd order polynomial regression was used to individually plot the glucose corrected SUVs of malignant lesions, benign lesions, and background liver over time [10] (by restraining the origin to zero). Logarithmic interpolation for each data point using the Patlak method was performed to generate time activity curves with 95% confidence intervals [11]. The P-values of the SUV of each tissue type as a function of time was determined from Pearson's correlation coefficient.

Results:

The mean injected dose was 16.5 +/-1.8 mCi (610 +/- 66.6 MBq), with a mean glucose level of 107 +/- 26.6 (standardized to 90) mg/dl. The uptake time before imaging ranged from 61 to 158 minutes, with a mean of 108.8 +/- 24.8 minutes. The p-values of the correlation of SUV to time were 0.004, 0.003, and 0.0001 for malignant lesions, benign lesions, and background liver respectively. Regression analysis of the cohort patients showed that the SUV of background liver decreased rapidly over time between 60 and 90 minutes TI, reaching its nadir around 110 minutes and staying relatively stable (Figure 1). At 60 minutes TI, the SUVs of malignant and benign lesions had significant overlap and would be difficult to distinguish prior to 90 minutes when the mean SUVs reach divergence by at least a factor of 2. The SUV of the malignant lesions showed a positive correlation with time, while the SUV of benign lesions demonstrated a negative correlation.

The log scaletime activity curves generated using the Patlak model for **each tissue type** (**malignant, benign and background normal hepatic tissue**) are shown in Figure 2. All 3 tissues are increasing in SUV at 60 minutes TI. The SUV of background liver and benign lesions begins to level off around 80-90 minutes, whereas it continues to rapidly increase in malignant lesions until reaching its plateau around 130 minutes. The divergence between malignant and benign lesions occurs later than the divergence with background liver.

Discussion:

The results demonstrate the significant effect that the uptake time between injection and imaging has on radiotracer activity in malignant versus benign or normal tissue. With background liver serving as control tissue, the time activity curve of benign hepatic lesions closely follows normal liver, except that it has a higher starting activity. The SUV of the three tissue types does not begin diverging until 80 minutes TI when benign and background begin to plateau, and the SUV of the malignant lesions continues to increase. The modeled time activity curves also accurately reflects the lower retention index of metabolically active normal tissue (i.e. hepatocytes, inflamed tissue, granulation tissue, etc.) compared to metabolically active tumors [*12*, *13*]. The decreased separation in activity caused by imaging too soon after radiotracer injection would have an impact on quantitative image analysis, particularly in methods that rely on contrast from background liver activity for comparison. On the other hand, prior studies have shown that imaging beyond 2 hours post injection has little benefit, and imaging beyond 3 hours may lead to confounding results [13,14]. **Figure 2 also supports the results of those studies as the SUV in malignant lesions reaches its plateau at around 2 hours.**

Additionally, a short uptake time prior to imaging can cause a noisier image that can be more challenging to interpret [13]. Another finding in our study those metastatic lesions that were masked by high background activity due to a short uptake time that only became apparent on delayed imaging. In contrast, a short uptake time produced heterogeneous activity with an area that appeared more focal. However, on delayed imaging this area washed out and became similar to background liver. This marked change in image target-to-background contrast may lend credence to many dual-time imaging protocols that have been proposed to improve 18F-FDG characterization of liver lesions [15,16].

This study demonstrated that a shorter TI results in higher background liver activity, which has been proven to reduce overall PET sensitivity and accuracy [17]. Any loss of patient throughput by adopting a 90 minute TI could be mitigated by appropriately staggering injection times. Standardization of imaging protocols across different facilities would have many benefits. Comparability of studies and cross-correlation of SUV would be simplified, which becomes very important when patients transfer care to different institutions and their treatment response needs to be established [18]. Additionally, many data collection studies and quantitative image analysis techniques would have greater universal applicability that may help to aid in more rapid advancement of PET applications [19]. A longer uptake time prior to imaging would lead to less misleading SUV measurements and likely less misidentification and equivocation. However, it appears dual-time protocols imaged at 60 minutes and 120 minutes post-injections would be most appropriate to illicit a different retention index between benign and malignant lesions.

Conclusion:

An approximate 90-minute window from the time of injection of 18F-FDG to PET imaging would lead to a significant improvement in target-to-background ratio, and thus more clinically valuable quantitation and more accurate visual interpretation. This benefit outweighs the minimal loss in patient throughput.

Acknowledgment:

Special thanks to Robert Ceruti, CNMT and William Weifeng Wong, Cranbrook Educational Community for their help in the figures.

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Figure 1: Regression plot (by restraining the origin to zero) of the glucose corrected SUVs for each lesion and background liver as function of time.



Figure 2: SUV VS. Time - Interpolated Data over entire time period. Time activity curves for each tissue type based on modeled data showing similar uptake at 60 minutes. SUV in malignant tumors diverges at around 80 minutes.