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Liver SUL_{mean} at FDG PET/CT: Effect of FDG uptake time

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Abstract

Objective—To establish the magnitude change and inter-reader reliability of Liver SUL_{mean} in dual time point imaging at 1 and 2 hours and 1 and 4 hours.

Methods—Early and Delayed FDG PET/CT scans were included for 28 patients (13 males and 15 females) who had normal liver by CT or US. The average uptake time between the early and delayed scans were 55 minutes (range 44-69) for pancreatic adenocarcinoma patients (n = 19) and 184 minutes (range 140-197) for neurofibromatosis (NF) patients (n = 9). 30-mm- diameter spherical VOI was placed within the right lobe of the liver above, below, and at the level of the main portal vein by two independent readers. Correlation coefficients, Analysis of variance, intraclass correlation coefficient (ICC), and Bland-Altman analysis were performed.

Results—The mean liver SUL_{mean} was between 1.39 and 1.42 and between 1.28 and 1.3 in early and delayed images, respectively (p = 0.001). There is time dependent reduction in the mean Liver SUL_{mean} at 2 hour (7-8%) and four hour uptake time (15-21%), compared to one hour. The correlation coefficient between delayed uptake time and Liver SUL_{mean} reduction is 0.39 to 0.41 at the upper aspect of liver. The ICC for two readers varied between 0.997 and 0.998 and between 0.995 and 0.999 in early and delayed images, respectively (p=0.001).

Conclusion—There is time dependent reduction of mean Liver SUL_{mean}, about 7-8% within the clinically relevant FDG uptake time, in the same patient with excellent inter-reader agreement in early and delayed images within the right lobe of the liver. Therefore Liver SUL_{mean} could represent a useful reference parameter in quantitative analysis of dual-phase FDG PET/CT in malignancy or atypical infection/inflammatory disease. Furthermore, it may be suitable as normalization factor in currently available formulae quantifying therapy response on PET imaging.

Keywords

FDG PET/CT; SUL_{mean}; inter reader agreement; dual time imaging

Introduction

The FDG activity in the liver has been used both qualitatively and quantitatively as a standard in PET/CT imaging in oncology[1]. The liver mean Standardized Uptake Value (SUV_{mean}) normalized to lean body mass (SUL_{mean}) has been proposed as a quality measure for FDG PET/CT and was used in the PET response criteria in solid tumors (PERCIST) 1.0 [2]. SUL_{mean} of the liver is usually measured by placing a spherical volume of interest (VOI) in the right lobe of liver. Liver SUV_{mean} has also been utilized as normalization factor in PET derived quantitative therapy response formulations, which were further adapted to assess residual disease in colorectal malignancy [3,4]. In our previous work[5], we demonstrated that Liver SUL_{mean} has almost perfect inter-reader reliability, regardless of whether the volume of interest (VOI) is placed at the upper, lower, or portal vein level of the right lobe of the liver and the inter reader variability is least in the upper aspect of the right lobe of the liver.

FDG PET/CT is a valuable imaging study in the management of many human solid tumors [6-11]. Dual time point and delayed FDG-PET imaging may allow for distinction between malignant and benign processes, as the pattern and rate of FDG uptake over time may vary considerably between these two processes [12-16]. In patients with head and neck malignant tumors [17], pulmonary nodules [15, 18], breast cancer [19], pancreatic tumors [20], and skeletal tumor [21], several authors have reported significant improvement in the diagnostic accuracy of FDG PET with dual-time-point scans. The time from tracer injection to the time of PET scanning (uptake period) has been shown to have an effect on lesion SUV [22, 23]. The FDG uptake time can vary due to workflow issues in a clinical practice.

The magnitude change of Liver SUL_{mean} due to variable uptake time in the same patient has not been established. The reader reliability of measuring liver SUL_{mean} on delayed scans is also not known. Hence, the objectives of this study are to establish the magnitude change of Liver SUL_{mean} in dual time point imaging at 1 and 2 hours and 1 and 4 hours and to establish inter reader reliability of dual or delayed uptake time on liver SUL_{mean} .

Materials and methods

Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act-compliant retrospective review of FDG PET/CT images and patient records. Informed consent requirements were waived. Patients who previously underwent clinical studies with early and delayed FDG PET/CT scan at our institution were identified, between February 2010 and June 2012. Patients who had undergone previous systemic or local therapy or who had any structural hepatic lesions, including hepatic cysts or fatty infiltration seen in Computed Tomography (CT) or Ultra Sound (US), within 3 months of baseline PET/CT were excluded to establish a cohort of patients with normal livers.

A total of 28 patients (13 men and 15 women) with biochemical and morphological normal liver were found eligible and included in the study. Of these, 19 were pancreatic adenocarcinoma patients with 1-hour and 2-hour delayed PET/CT scans as well as 9 represented neurofibromatosis type-1 patients with 1-hour and 4-hour delayed PET/CT

imaging. In pancreatic patients the average post injection time was 64 minutes ($\pm$ 5; range 56-73) on early scans and 118 minutes ($\pm$ 6; range 109-129) on the delayed scans, with an average time between the scans of 55 minutes ($\pm$ 8; range 44-69). For the neurofibromatosis patients the average post injection time was 68 minutes ($\pm$ 8; range 57-79) on the early scans and 253 minutes ($\pm$ 21; range 225-286) on the delayed scans, with an average time between the scans of 184 minutes ($\pm$ 18; range 140-197).

PET/CT protocol

All patients fasted for at least 4-hours before FDG dosing, with a serum glucose level below 215 mg/dl, mean of 116 mg/dl (range 86-193). [18F] 2-fluoro-2-deoxy-D-glucose (FDG) was administered according to a weight based formula 9.62 MBq/Kg (0.26mCi/Kg). The mean amount of administered FDG was 579.8 ± 132.1 MBq, range 384.8 – 891.7 MBq (15.7 ± 3.6 mCi, range 10.4-24.1 mCi). For the early PET/CT imaging, a whole body protocol was utilized, extending from the base of skull to the mid-thighs. After the initial PET/CT imaging study was completed, the patients remained in the Nuclear Medicine Department for the second acquisition. For the pancreatic tumors the delayed scans were performed from the dome of the liver to the lower level of the kidneys. In the neurofibromatosis patients, a delayed whole body scan was completed at approximately 4-hours after FDG injection.

Twenty eight patients were scanned on a GE Discovery VCT (General Electric Medical Systems, Waukesha, WI) 64-slice PET/CT scanner. Both early and delayed images were performed in 3D acquisition mode with 4.25 minutes per bed position. The images were reconstructed using OSEM algorithm (ordered subset expectation maximization), with 128 $\times$ 128 matrix, 2 iterations, 21 subsets, 3mm post reconstruction gaussian filter, standard Z filter, 4.7 mm pixel and 3.27 mm slice thickness.

All PET data were reconstructed with and without CT-based attenuation correction. Non-contrast CT scan was used for attenuation correction of PET images and for morphologic co-registration. CT parameters were 50cm axial field of view (FOV), 512 $\times$ 512 matrix, weight-based amperage (20–200 automated mA), 120 kVp, 3.75mm reconstructed slice thickness, pitch of 0.984 and 0.5sec gantry rotation speed.

Liver SUL_{mean} measurements

All FDG PET/CT scans were independently interpreted on a MIMvista workstation (software version 5.2; MIM Software Inc. Cleveland, OH) by two readers, who are both board certified Nuclear Medicine physicians. PET, CT, and fused PET/CT images were reviewed in the axial, coronal, and sagittal planes. Liver SUL_{mean} values were measured in the following three separate areas within the right lobe of the liver: (a) the right lobe above the portal vein (segments VII and VIII), (b) below the level of the portal vein in the right lower lobe (segments V and VI), and (c) at the level of the right portal vein (straddling segments V through VIII) (Figure 1). Spherical 30 mm diameter VOI's were placed at these three locations based on the CT and cross-referenced with the PET to assure that the VOI's were within the metabolic boundaries of the right liver. The right lobe of the liver was used because it is easier to draw the ROI at different levels, giving its larger size and it is the most common site used in clinical practice [16, 20, 24, 25].

Statistical Analysis

In-between group analysis for two groups was performed with an independent 't' test with a significance level of 0.05. For repeated-measures analyses, adjustment for multiple hypothesis testing comparing the three locations within the right lobe of the liver was performed with an analysis of variance (ANOVA) with repeated measures, using general linear model, polynomial contrast, and Bonferroni post-hoc analysis between all pairs, with adjustments (Confidence interval [CI], 95%; significance level, 0.05). We present our summary statistics as means $\pm$ standard deviations for continuous variables or as frequencies and percentages for categorical variables. Variability of the liver SUL_{mean} measurement for the study population was determined with the coefficient of variation at different levels of the right lobe of the liver. Reliability of liver SUL_{mean} measurements between the readers and between the dual time point PET images was tested using the intraclass correlation coefficient generated by a two-way random-effects model with an absolute agreement definition (type A), reported as a point estimate with a 95% CI. The independent variable was patient and the dependent variable was readers liver SUL_{mean} measurement. The placement of the VOI (within the right lobe of the liver) was considered fixed. The absolute agreement definition considers systematic differences between the two readers relevant in estimating the ICC. The ICC ranges between 0 and 1.00, with values closer to 1.00 representing better reproducibility. ICC is interpreted as follows: An ICC of 0.00–0.20 indicates slight reproducibility; an ICC of 0.21–0.40, fair reproducibility; an ICC of 0.41–0.60, moderate reproducibility; an ICC of 0.61–0.80, substantial reproducibility; and an ICC of greater than 0.80, almost perfect reproducibility [15]. The agreement between readers' measurements was evaluated with Bland-Altman analysis reporting the bias (average of all the differences between pairs of measurements), standard deviation (SD) and the 95% limits of agreement (average measurement $\pm$ 1.96 $\times$ SD). Precision was calculated as 95% CI width divided by two and was expressed as percentage multiplying by 100. The agreement was evaluated between readers at each level (the upper, lower, and portal vein levels of the right lobe of the liver). Pearson's correlation coefficients between the elapsed time (early and delayed scans) and the percentage reduction (baseline – delayed / baseline $\times$ 100%) of liver SUL_{mean} was established. We used the Prism 5 (GraphPad Software, San Diego, Calif) and SPSS 20 (SPSS, Chicago, Ill) statistical packages for all analyses.

Results

Patient Demographics

A total of 28 patients were included in the study; 13 men (46.5%) (mean age, 58.7 years $\pm$ 16.8; range, 28–78 years) and 15 women (53.5%) (mean age, 50.2 years $\pm$ 20.3; range, 19–72 years). The baseline FDG PET/CT scans were performed for staging of pancreatic cancer (n = 19, mean age 66 years, range 48–78) and neurofibromatosis (n = 9, mean age 39 years, range 19–73).

Impact of duration of delay and Liver SUL_{mean}

For the pancreatic oncologic patients (average uptake time between early and delayed scans of 55 minutes), the average SUL_{mean} change was between 7–8%, while for the NF1 patients (average time between early and delayed scans of 184 minutes) the average SUL_{mean} change

was between 15-21% (Table 1 and Figure 2). The correlation coefficients between the uptake time and liver SUL_{mean} at the upper aspect of the right lobe of the liver are $r^2=0.3991$ for reader 1 and $r^2=0.4186$ for reader 2 (Figure 3). The absolute change from early to delayed scans of upper level Liver SUL_{mean} in the pancreatic oncologic patients was 0.10 (SD ± 0.06 , range -0.01 to + 0.19) for reader 1 and 0.10 (SD ± 0.06 , range 0.01 to + 0.23) for reader 2 at an uptake time about two hours. For the NF patients the absolute change in the same upper level was 0.22 (SD ± 0.09 , range 0.10 to + 0.36) for reader 1 and 0.23 (SD ± 0.11 , range 0.07 to + 0.45) for reader 2.

Inter-reader agreement and variability for Liver SUL_{mean} and placement of VOI: Effect of early and delayed scans

We investigated the reliability of the liver SUL_{mean} as measured by two independent readers at three levels within the right lobe of the liver in both early and delayed scans. The average measurements made by the two readers are summarized in Table 2. There was excellent agreement between readers for each one of the three levels in both early and delayed images with the ICC (Table 3). These results suggest that the inter reader reliability is almost perfect for measuring liver SUL_{mean} in early as well as delayed FDG PET/CT.

On Bland-Altman analysis, bias were -0.001 (SD ± 0.03), -0.013 (SD ± 0.03) and -0.012 (SD ± 0.03) at the upper, lower and portal vein level for early images (Figure 4). On delayed images bias were 0.004 (SD ± 0.04), -0.001 (SD ± 0.03) and -0.022 (SD ± 0.05) at upper, lower and portal vein level, respectively (Figure 4 and 5). These results suggest the variability is minimal between the readers in both early and delayed images.

Discussion

The purpose of our study was to establish the magnitude of change in Liver SUL_{mean} due to dual time imaging or delayed imaging and also to investigate the agreement and variability in measuring liver SUL_{mean} on early and delayed images in dual point FDG PET/CT. In this study, we have demonstrated that liver SUL_{mean} values reduces in a time dependent manner between 7-8% at about two hours and 15-21% at about four hours compared to Liver SUL_{mean} value at about one hour uptake time. Similar to our prior study of early scans (uptake time about an hour), we have demonstrated excellent inter-reader agreement in delayed scans, regardless of the site of VOI placement within the right lobe of the liver. The significance of these results is that there is very small variability or change in liver SUL_{mean} between one and two hour uptake time which are the most relevant uptake time for clinical studies as most of the studies would be performed in this time interval.

Since we use Liver SUL_{mean} for quality control as well as, sometimes, for deciding threshold for including index lesions for therapy assessment or measuring metabolic tumor volume or total lesion glycolysis of tumors, the magnitude of liver SUL_{mean} reduction is important, especially with prolonged uptake time greater than 50-70min. In some studies with dual point FDG PET/CT, liver SUV was used as control and the VOI was marked in the right lobe of liver [16, 20, 24, 25]. Koyama et al. suggested stable or slightly decreased ratio of FDG uptake in the hepatic parenchyma to other soft tissues from early to delayed scans [26]. However, independent hepatic parenchyma activity was not evaluated. Kubota et al.

[14] showed that the SUV_{max} changes in normal liver were significantly decreased from early to delayed images. Similar results were seen in the study by Nishiyama et al [16]. Both these studies investigated the changes in liver SUV_{max} between early and delayed images. Nishiyama et al in their later studies [24, 25] have shown that SUV_{mean} tends to be significantly lower in delayed scans compared to the early scans ($P < 0.0001$). However, recent studies by Kubota et al [27] and Chin et al [28] showed that there is no significant variability of the liver SUV_{mean} between early and delayed images in two different and independent set of patients. However, these authors did not perform direct comparison of the early and the delayed image of the same patients, unlike in our study.

Our previous study [5] has shown that liver SUL_{mean} values measured at three different levels of the right lobe of the liver in early images have almost perfect inter-reader agreement with the highest precision in the upper aspect of the right lobe of the liver. The results in this study indicate that there is excellent inter reader agreement in liver SUL_{mean} both in early as well as delayed images. Other studies also have shown that SUV measurements have excellent inter-reader reproducibility [29]. The reliability and variability of the liver SUL_{mean} are consistent [30-32] with other studies.

Our study results need to be interpreted in the context of our study design. We used two sets of patients, pancreatic cancer and neurofibromatosis patients for whom we routinely do two-hour and four-hour delayed imaging in our clinical practice. Our study population is moderate size for early and delayed imaging studies and small at four hour delayed imaging. However the advantage of this study population is both early and delayed images were done in the same patients, minimizing the impact of co-variates. For the inter-reader component of the study, we used one software, MimVista software, and we need to test the inter reader agreement and variability using multiple vendor software systems for quantitative imaging.

In conclusion, there is a very small change about 7-8% in Liver SUL_{mean} for most uptake times relevant to clinical FDG PET/CT scans. Therefore Liver SUL_{mean} could represent a useful reference parameter in quantitative analysis of dual-phase FDG PET/CT in malignancy or atypical infection/inflammatory disease. There is very good inter reader agreement when liver SUL_{mean} is measured at three different levels of the right lobe of the liver in delayed scans with uptake time greater than one hour. Hence, liver SUL_{mean} is a reliable parameter for quality control and threshold setting for background FDG uptake and tumor volume segmentations in FDG PET/CT scans in clinical practice. Furthermore, it may be suitable as normalization factor in currently available formulae quantifying therapy response on PET imaging.

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Figure 1. Placement of 30mm diameter spherical VOI within the right lobe of the liver: upper (red contour), portal vein (blue contour) and lower (yellow contour) levels demonstrated in PET and corresponding CT images.

Figure 2.

Early and delayed Liver SUL_{mean} measured by reader 1 at the upper aspect of right lobe of liver. There is a very small time dependent decrease in liver SUL_{mean} during clinically relevant FDG uptake time between one and two hours. (A) Uptake time and liver SUL_{mean}. (B) Individual patient early and delayed SUL_{mean} with line diagram.

Figure 3. Correlation plot between liver SUL_{mean} decrease from early to delayed scans and the uptake time elapsed between the scans measured by reader 2 at upper aspect of right lobe of liver

Figure 4.

Bland Altman analysis between reader 1 and reader 2 in the early images. X axis: mean of the two readings and Y axis: difference between the two readings from the mean.

Figure 5.

Bland Altman analysis between reader 1 and reader 2 in the delayed images. X axis: mean of the two readings and Y axis: difference between the two readings from the mean.

Table 1
Average Liver SUL_{mean} measurements at different liver levels, in early and delayed scans, for both readers

	Early scan			Delayed scan		
	Upper level	Portal level	Lower level	Upper level	Portal level	Lower level
Reader 1						
Mean ± SD (95% CI)	1.39 ±0.34 (1.27 - 1.52)	1.39 ±0.35 (1.26 - 1.52)	1.41 ±0.36 (1.27 - 1.54)	1.28 ±0.40 (1.13 - 1.43)	1.28 ±0.39 (1.13 - 1.42)	1.29 ±0.39 (1.15 - 1.44)
Reader 2						
Mean ± SD (95% CI)	1.39 ±0.32 (1.27 - 1.51)	1.40 ±0.36 (1.27 - 1.54)	1.42 ±0.36 (1.28 - 1.56)	1.28 ±0.40 (1.13 - 1.42)	1.29 ±0.40 (1.15 - 1.45)	1.30 ±0.40 (1.15 - 1.44)

Table 2
Percent change (reduction) in liver SUL_{mean} for the pancreatic oncologic (mean delay 58min) and Neurofibromatosis patients (mean delay 178min) at the upper aspect of the right lobe of the liver

	Reader 1			Reader 2		
	Upper	Portal	Lower	Upper	Portal	Lower
Pancreatic patients	7% (-1% to 15%)	8% (-1% to 14%)	7% (1% to 15%)	7% (0% to 17%)	7% (3% to 14%)	8% (3% to 13%)
NF patients	20% (8% to 39%)	18% (9% to 30%)	15% (-3% to 23%)	21% (6% to 44%)	18% (12% to 23%)	17% (11% to 24%)

Table 3
Inter-reader agreement for Liver SUL_{mean} measurements at different liver levels, in early and delayed scans

	Early scan			Delayed scan		
	Upper level	Portal level	Lower level	Upper level	Portal level	Lower level
ICC (95% CI)	0.997 (0.995 -0.999)	0.998 (0.995 -0.999)	0.997 (0.994 -0.999)	0.998 (0.995 -0.99)	0.995 (0.989 -0.998)	0.999 (0.997 -0.999)
Precision	0.2%	0.2%	0.25%	0.2%	0.45%	0.1%