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Two-Time-Point FDG PET/CT: Liver SUL_{mean} Repeatability

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Abstract

OBJECTIVE—The purpose of this study was to evaluate the repeatability of liver mean standardized uptake value normalized to lean body mass (SUL_{mean}) in the same patients at different time points within the right lobe of the liver at ^{18}F-FDG PET/CT, in a clinical setting.

MATERIALS AND METHODS—Two PET/CT studies performed on two different dates from each of 130 patients who had normal livers according to structural imaging were included in this reader study. The mean (± SD) length of time between the studies was 235 ± 192 days. SUL_{mean} was measured with a 30-mm diameter spherical volume of interest (VOI) placed within the right lobe of the liver (above, below, and at the level of the main portal vein) by two expert readers. ANOVA, intraclass correlation coefficient (ICC), and Bland-Altman analysis were performed.

RESULTS—The ICC for the first and second set of studies varied between 0.487 and 0.535 for reader 1 and between 0.472 and 0.545 for reader 2. The mean percentage variation for SUL_{mean} between the two time scans for the VOIs placed above, below, and at the level of the main portal vein were 3.55% ± 23.19%, 4.65% ± 23.87%, and 4.30% ± 23.03%, respectively, for reader 1 and 4.49% ± 23.23%, 4.33% ± 23.74%, and 4.48% ± 23.01%, respectively, for reader 2. Using 95% CI, the reference range for intrapatient variations between the studies in liver SUL_{mean} was −0.5 to 0.60.

CONCLUSION—There is only fair repeatability of liver SUL_{mean} measured between two time points in the same patient in a clinical setting. Scan-to-scan intrapatient variation in absolute liver SUL_{mean} was −0.5 to 0.60.

Keywords

liver mean standardized uptake value (SUV) normalized to lean body mass (SUL_{mean}); PET/CT; repeatability; therapy assessment

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PET/CT of cancer with combined PET and CT scanners has become a standard component of diagnosis and staging in oncology [1–5]. When evaluating PET/CT for response to therapy, changes may not be visually evident and quantification therefore is important. The most common parameter used to measure tracer accumulation in PET studies is the maximum standardized uptake value (SUV). However, this index is subject to some variability [6–8]. It has been proposed that ^{18}FFDG accumulation in a malignant lesion be compared with the background uptake in the liver parenchyma [9–11].

The liver mean SUV normalized to lean body mass (SUL_{mean}) has also been proposed as a quality measure for FDG PET/CT and is used in the PET Response Evaluation Criteria in Solid Tumors (PERCIST) 1.0 [12]. PERCIST defines a 3-cm spherical ROI in the right hepatic lobe as a quality assurance tool to assess the applicability of quantitative comparisons [12]. Liver SUL_{mean} has almost perfect inter- and intrareader agreement at a single time point [13, 14]. The repeatability and variability of the liver SUL_{mean} in the same patient at different time points and reader reliability of these repeatable measurements have not been established [9, 14–20]. The objective of this study was to evaluate the repeatability and variability of liver SUL_{mean} in the same patient performed at different dates measured by different readers and at different locations in the right lobe of the liver.

Materials and Methods

Institutional review board approval was obtained for this HIPAA-compliant retrospective review of PET/CT images and patient records. Informed consent requirements were waived. Two PET/CT studies from each of 130 patients (83 men and 47 women) performed at two different dates in patients who had normal livers according to structural imaging were included in the study. We excluded patients who underwent chemotherapy or radiation therapy involving the abdomen to minimize the impact on the FDG uptake in the liver between the two-time-point PET/CT studies. We reviewed the imaging reports of contrast-enhanced abdominal CT or sonography in the patient records to exclude patients with any liver abnormalities. SUL_{mean} was measured with a 30-mm-diameter spherical volume of interest (VOI) manually placed within the right lobe of the liver above, below, and at the level of the main portal vein [13].

PET/CT Protocol

All patients fasted for at least 4 hours before scanning. Serum glucose, FDG dose, patient weight, patient height, and injection-to-scanning time for first and second sets of scans are summarized in Table 1. Patients were scanned either on a Discovery ST or a Discovery LS PET/CT scanner (GE Healthcare). Studies on the first system were performed in 3D acquisition mode with 4.15 minutes per bed position. The images were reconstructed using ordered subset expectation maximization algorithms with 128 × 128 matrix, 21 subsets, two iterations, 3-mm postreconstruction gaussian filter, standard Z filter, 4.7-mm pixel, and 3.27-mm slice thickness. The 2D implementation on the Discovery LS used two iterations, 28 subsets, a 5.5-mm postreconstruction gaussian filter, and 3.9-mm pixels. All PET data were reconstructed with and without CT-based attenuation correction. Unenhanced CT was used for attenuation correction of PET images and for morphologic coregistration. CT parameters

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included 16-MDCT with 50-cm axial dynamic FOV, weight-based amperage (20–200 mA automated tube current), 120–140 kVp, 3.75-mm reconstructed slice thickness, pitch of 0.984, 0.5-second gantry rotation speed, and 512 × 512 matrix.

Liver SUL_{mean} Measurements

All PET/CT studies were retrieved from the electronic archival system and were then reviewed at a MimVista workstation, version 5.2 (MIM Software). Measurements of SUL_{mean} were conducted independently by two board-certified nuclear medicine physicians. Reader 1 completed a 3-year nuclear medicine residency, was board certified in nuclear medicine, and was a T32 research fellow in nuclear medicine. Reader 2 completed a 3-year nuclear medicine residency, a 2-year clinical PET/CT fellowship, and was board certified in nuclear medicine. 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: the right lobe above the portal vein (segments VII and VIII), below the level of the portal vein in the right lower lobe (segments V and VI), and at the level of the right portal vein (straddling segments V through VIII) (Fig. 1). Both readers independently placed the VOI in these three locations of the liver for the PET/CT studies of all study patients. The VOI was a sphere with a diameter of 30 mm. The right lobe of the liver was used because of its relatively large size and homogeneity. It is the most common site used in clinical practice as a background standard [21–23]. The analyses were done in a random order of scans (between the first set of scans and second set of scans) in multiple reading sessions over a period of 3 months.

Statistical Analysis

We present central tendencies as mean ± SD. Between-group analysis for two groups was performed with an independent Student *t* test with a significance level of 0.05. For repeated-measures analyses, adjustment for multiple hypothesis testing in comparing the three locations within the right lobe of the liver was performed with ANOVA with repeated measures, using general linear model, polynomial contrast, and Bonferroni posthoc analysis between all pairs. Reliability of liver SUL_{mean} between the readers and between the dual-time-point PET images was measured using the intraclass correlation coefficient (ICC) generated by a two-way random-effects model with an absolute agreement definition and is reported as a point estimate with a 95% CI. The readers are assumed to be randomly selected from a large pool of experts. In this model, the ICC is a measure of absolute agreement and considers systematic differences between the two readers [13]. Results of Bland-Altman analysis with bias and SD of the differences were reported for variability between the readers at each level (the upper, lower, and portal vein levels of the right lobe of the liver). We used MedCalc, version 12.3 (MedCalc Software) and SPSS, version 20 (IBM) statistical packages for all analyses.

Results

Patient Demographics

A total of 130 patients (83 men and 47 women) were included in this study. The length of time between the two studies for each patient averaged 235 ± 192 days. The variation in

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patient weight between the two studies was 0.62 ± 5.14 kg. The plasma glucose concentrations were within the reference range; the mean difference in plasma glucose concentration was −48 ± 15.7 mg/dL. The mean difference between FDG uptake times was −0.23 ± 16.58 minutes. Patient and scanning characteristics are summarized in Table 1.

Liver SUL_{mean} Agreement and Variability: Single-Time-Point Scans

For reader 1, on earlier scans, liver SUL_{mean} was 1.53 ± 0.26 for the upper level, 1.51 ± 0.26 for the portal vein level, and 1.54 ± 0.26 for the lower level. On later scans liver SUL_{mean} was 1.55 ± 0.26, 1.54 ± 0.25, and 1.57 ± 0.25 for the upper, portal vein, and lower levels, respectively. For reader 2, on earlier scans, mean liver SUL_{mean} was 1.52 ± 0.26 for the upper level, 1.52 ± 0.26 for the portal vein level, and 1.53 ± 0.26 for the lower level. On later scans liver SUL_{mean} was 1.55 ± 0.26, 1.54 ± 0.25, and 1.56 ± 0.26 for the upper, portal vein, and lower levels, respectively, for reader 2. These results are summarized in Table 2.

There was high agreement between the two readers for each of the three right liver lobe levels in both first and second scans. In earlier images, interreader ICC for the SUL_{mean}, controlling for location, was 0.990 (95% CI, 0.985–0.993) for the upper level, 0.987 (0.981–0.991) for the portal vein level, and 0.986 (0.981–0.990) for the lower level. In later images, interreader ICCs for the SUL_{mean} were 0.990 (0.986–0.993) for the upper level, 0.991 (0.987–0.994) for the portal vein level, and 0.989 (0.984–0.992) for the lower level. Figure 2 shows Bland-Altman plots of interreader agreement of the liver SUL_{mean} controlling for time point and liver location.

Liver SUL_{mean} Agreement and Variability: Two-Time-Point Scans and Same VOI Location

ICCs for the SUL_{mean} controlling for reader and location were 0.345 (0.071–0.538) for the upper level, 0.366 (0.101–0.552) for the portal vein level, and 0.383 (0.125–0.564) for the lower level for reader 1. ICCs for the liver SUL_{mean} measured by reader 2 controlling for location were 0.412 (0.166–0.585) for the upper level, 0.377 (0.117–0.560) for the portal vein level, and 0.438 (0.204–0.604) for the lower level. These results are summarized in Table 3. Figure 3 shows Bland-Altman plots of intrareader agreement of liver SUL_{mean} between two-time-point scans.

Mean absolute variation in liver SUL_{mean} at the two-time-point scans was 0.018 ± 0.322, 0.032 ± 0.315, and 0.030 ± 0.316 between the first and second scans for reader 1 at the upper, portal, and lower levels, respectively, and 0.033 ± 0.313, 0.028 ± 0.318, and 0.033 ± 0.314, respectively, for reader 2 (Fig. 3). The mean percentage bias for SUL_{mean} between the two-time-point scans was 3.55% ± 23.19%, 4.65% ± 23.87%, and 4.30% ± 23.03% between the first and second scans for reader 1 at the upper, portal, and lower levels, respectively, and 4.49% ± 23.23%, 4.33% ± 23.74%, and 4.48% ± 23.01%, respectively, for reader 2.

Variability of Liver SUL_{mean}: Influence of Scanners

Of the 130 patients, 58 and 72 PET/CT studies were performed on the Discovery LS and Discovery ST systems, respectively, for the first time point. For the second time point, 55 and 75 were performed on the Discovery LS and Discovery ST systems, respectively. A total

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of 48 patients underwent PET/CT on the Discovery LS scanner at both time points, 31 were performed on the Discovery ST, and 51 were mixed (done on the Discovery LS at one time point and the Discovery ST at the other time point).

We performed an ANOVA to look for the influence of scanner change on the bias between the two-time-point liver SUL_{mean} values, fixing reader and location. No statistically significant results were found between the Discovery LS–Discovery LS, Discovery ST–Discovery ST, and mixed scanner groups. These results are summarized in Table 4.

Variability of Liver SUL_{mean}: Influence of Time Interval

We also performed an independent Student *t* test to investigate the influence of the time elapsed between the two PET/CT studies on the change of liver SUL_{mean}. We used a cut-point of 6 months to separate the patients who underwent PET/CT within 6 months ($n = 65$) and patients who underwent PET/CT at greater than 6 months ($n = 65$). No statistically significant difference was noted between the two groups, and the results are included in Table 4.

Discussion

The purpose of our study was to evaluate the agreement and variability in measuring liver SUL_{mean} between PET/CT performed at two time points in the same patient when the parameter was measured by different readers at three different locations within the right lobe of the liver in a clinical setting. In this study, we have shown that liver SUL_{mean} has excellent interreader agreement for same-time scanning regardless of the site of VOI placement within the right lobe of the liver, similar to our prior study [13]. However, there was only weak agreement between the liver SUL_{mean} between the studies performed at two different time points in the same patient. The significance of our results for response monitoring PET/CT is the determination of the expected normal variation of liver SUL_{mean}. Differences in normal liver SUL_{mean} up to 1.1 between baseline and follow-up studies are to be expected in the healthy population. A difference greater than these limits can indicate technical error and preclude quantitative comparison of the studies in a clinical setting. When the difference is greater than this range, interpreting clinicians need to investigate and be vigilant about any technical errors contributing to the effects and may need to take this account in the interpretation of the PET/CT study.

The previous study by Paquet et al. [9] investigated the intrapatient variability of FDG uptake in normal tissue in 70 patients who underwent two FDG PET studies. The studies were performed 271 ± 118 days apart. The ROI differed from ours in that it was defined in a single slice in the middle of the right lobe of the liver with a mean size of 19.2 cm^3. The authors cite an absolute difference of 0.05 ± 0.2 between the two studies for liver SUL_{mean} and an ICC of 0.57. This is indicative of a moderate degree of agreement at best and is similar to our results. The authors further concluded that SUVs measured in the liver of patients who were cancer free were stable over time. In our study, we found an average absolute difference of 0.03 ± 0.27.

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In terms of absolute variation in liver SUL_{mean}, using 95th percentiles, the reference range in our patient population for intrapatient variation was −0.5 to 0.6. This is in comparison with intrapatient variation of −0.9 to 1.1 for liver SUV in the recent study by Boktor et al. [24]. The likely explanation for the smaller variation in liver SUL_{mean} in our patient population is that we selected patients who had normal liver by structural imaging and we excluded patients who underwent systemic chemotherapy or radiation therapy involving the abdomen between the two studies. The study by Boktor et al. did not exclude such patients, which may explain the differences between the studies.

The determination of SUV is susceptible to many technical confounders in addition to intrapatient physiologic variability [25]. We used two different PET/CT machines during the period when our studies were performed. As shown in the Results section, no statistically significant difference in the bias in the liver SUL_{mean} was noted among the two-time-point scans, whether the same scanner was used or the scanner was switched between the pair of studies. There was also no statistically significant difference in the bias between studies performed at an interval of l6 months or less and those performed at greater than 6 months. Hence, the variation in repeatability of liver SUL_{mean} observed in this study is applicable in a clinical setting as the normal reference range of SUL_{mean} in the same patient.

There are several limitations to our study. This is a repeatability study performed in a clinical context with wide variation between scanning times, with the longest interval of 1105 days. However, this simulates the PET/CT studies performed in real-world clinical practice and has the highest applicability. We did not investigate the change in liver SUL_{mean} because of systemic therapy response because our intention was to establish the normal variability. Because this was a retrospective study, we did not strictly control the FDG dose or uptake time, which may have contributed to some of the variability. In addition other factors, such as the patients' underlying conditions and medications, may have affected the liver FDG uptake between the two time points.

Conclusion

Liver SUL_{mean} on FDG PET/CT has excellent interreader agreement, with similar values and variance whether measured at the upper, lower, or portal vein levels on the same scan. However, there was only a fair intraclass correlation between liver SUL_{mean} measured at two different time points in the same patient. Scan-to-scan intrapatient variation in absolute liver SUL_{mean} was −0.5 to 0.60. A difference greater than these limits may indicate technical error and could preclude quantitative comparison of the studies.

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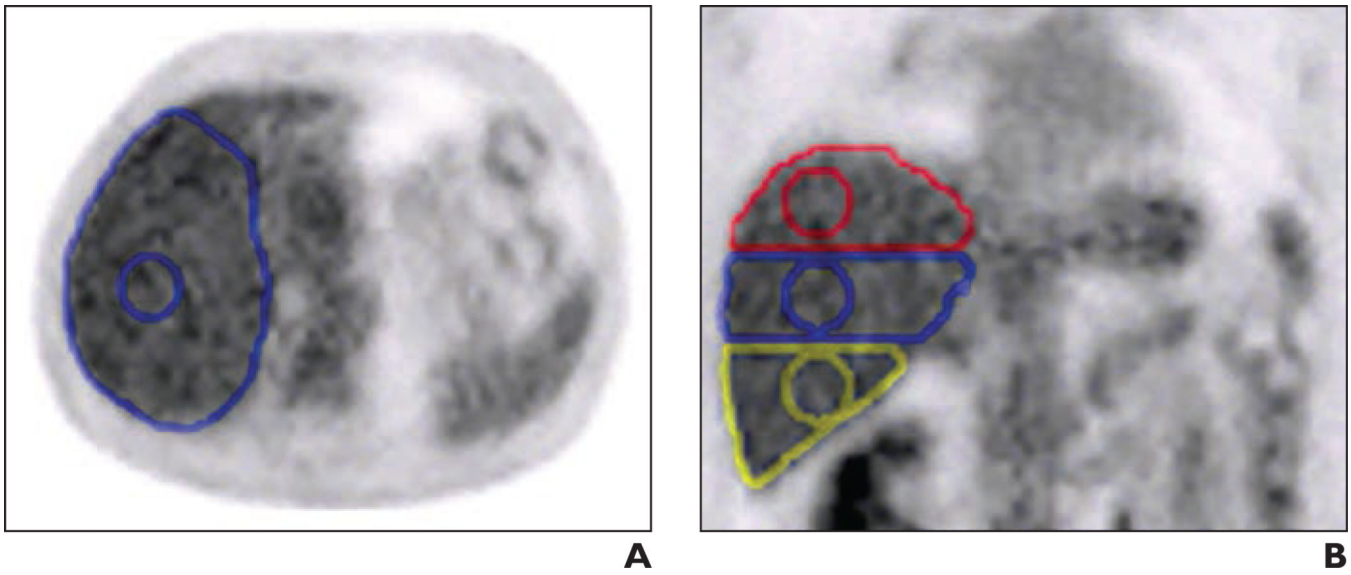

Fig. 1.

Placement of volume of interest (VOI). **A** and **B,** Axial (**A**) and coronal (**B**) PET images show placement of 30-mm-diameter spherical VOIs within right lobe of liver: upper (*red*), portal vein (*blue*), and lower (*yellow*).

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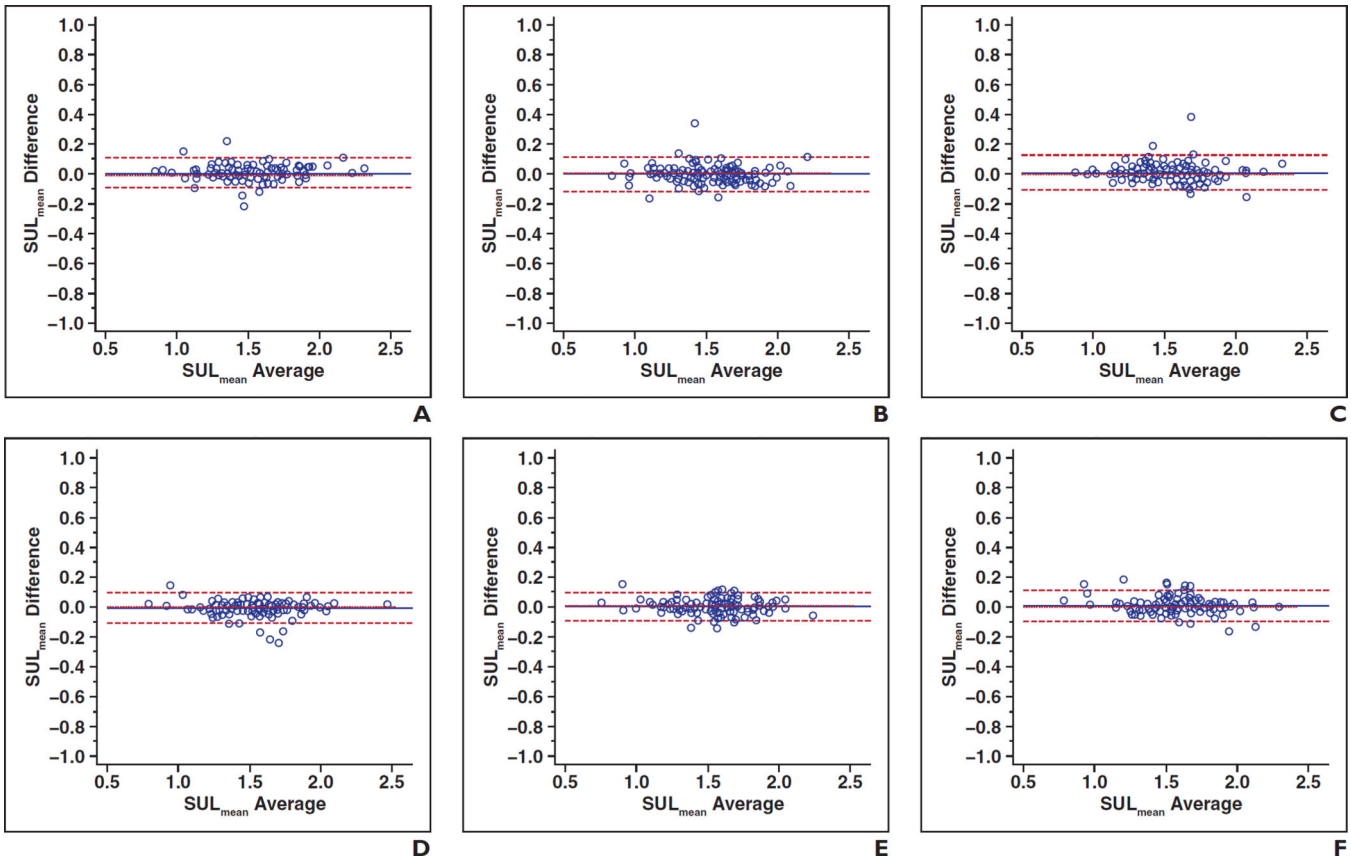

Fig. 2.

Bland-Altman plots show interreader agreement of liver mean standardized uptake value normalized to lean body mass (SUL_{mean}) controlling for time point and liver location.

A–C, Plots show first time point: upper liver (**A**) (intraclass coefficient [ICC] = 0.990), portal vein (**B**) (ICC = 0.987), and lower liver (**C**) (ICC = 0.986).

D–F, Plots show second time point: upper liver (**D**) (ICC = 0.990), portal vein (**E**) (ICC = 0.991), and lower liver (**F**) (ICC = 0.989).

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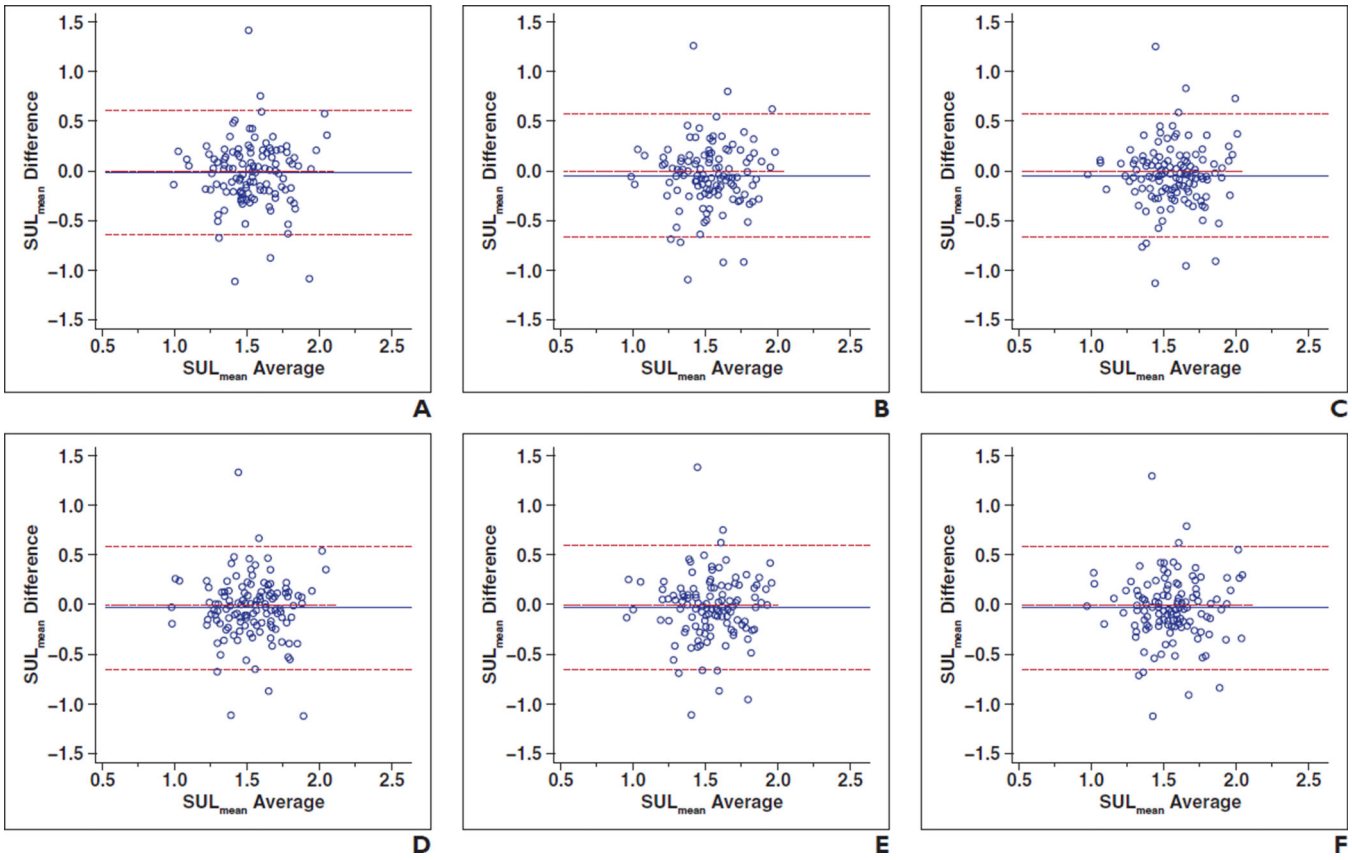

Fig. 3.

Bland-Altman plots show intrareader agreement of liver mean standardized uptake value normalized to lean body mass (SUL_{mean}) between two-time-point scans controlling for reader and location.

A–C, Plots for reader 1: upper liver (**A**) (intraclass coefficient [ICC] = 0.345), portal vein (**B**) (ICC = 0.366), and lower liver (**C**) (ICC = 0.383).

D–F, Plots for reader 2: upper liver (**D**) (ICC = 0.412), portal vein (ICC = 0.377) (**E**), and lower liver (**F**) (ICC = 0.438).

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TABLE 1

Patient and Scanning Characteristics for First- and Second-Time-Point PET/CT for Each Patient

Characteristic	Value
Total no.	130
Sex	
Men	83
Women	47
Age (y)	58.6 ± 13.3 (19–86)
Plasma glucose (mg/dL)	
First scan	100.7 ± 15.8 (63–158)
Second scan	98.9 ± 16.4 (62–154)
FDG dose (mBq)	
First scan	606.8 ± 155.4 (321.9–939.8)
Second scan	595.7 ± 148.0 (284.9–943.5)
Weight (kg)	
First scan	74.2 ± 19.7 (41–159)
Second scan	74.9 ± 19.1 (32–159)
Height (cm)	172.1 ± 11.4 (134–198)
Uptake time	
First scan	65.7 ± 15.9 (51–182)
Second scan	65.5 ± 13.5 (39–125)
Elapsed time between scanning (d)	235.4 ± 192.1 (33–1105)
Patients scanned on Discovery LS[a]	48 (37)
Patients scanned on Discovery ST[a]	31 (24)
Patients scanned once on each scanner[a]	51 (39)

Note—Except where indicated otherwise, data are mean ± SD with range in parentheses. Discovery LS and Discovery ST are manufactured by GE Healthcare.

[a]Data are number with percentage in parentheses.

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TABLE 2

Summary of Mean Liver Standardized Uptake Value Normalized to Lean Body Mass at Different Levels of Liver as Measured by Readers 1 and 2 on Two-Time-Point PET/CT

Value	Upper Liver Level	Portal Vein Level	Lower Liver Level
Reader 1			
First scan	1.53 ± 0.26	1.51 ± 0.26	1.54 ± 0.26
Second scan	1.55 ± 0.26	1.54 ± 0.25	1.57 ± 0.25
Reader 2			
First scan	1.52 ± 0.26	1.52 ± 0.26	1.53 ± 0.26
Second scan	1.55 ± 0.26	1.54 ± 0.25	1.56 ± 0.26

Note—Data are mean ± SD.

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TABLE 3

Absolute Change and Intraclass Coefficient (ICC) for Mean Liver Standardized Uptake Value Normalized to Lean Body Mass (SUL_{mean}) at Two-Time-Point PET/CT Controlling for Reader and Location

Value	Upper Liver Level	Portal Vein Level	Lower Liver Level
Reader 1			
Change in SUL_{mean}	−0.02 (−0.65 to 0.61)	−0.02 (−0.65 to 0.59)	−0.02 (−0.65 to 0.59)
ICC	0.345 (0.071–0.538)	0.366 (0.101–0.552)	0.383 (0.125–0.564)
Reader 2			
Change in SUL_{mean}	−0.02 (−0.65 to 0.58)	−0.02 (−0.65 to 0.60)	−0.02 (−0.65 to 0.58)
ICC	0.412 (0.166–0.585)	0.377 (0.117–0.560)	0.438 (0.204–0.604)

Note—Data in parentheses are 95% CI.

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TABLE 4

Influence of Scanner Change on Bias Between Two-Time-Point Liver Standardized Uptake Value Normalized to Lean Body Mass Values for Each Reader and Location

Value	Discovery LS (*n* = 48)	Discovery ST (*n* = 31)	Mixed (*n* = 51)	*p*	Interscan Time > 6 Mo (*n* = 65)	Interscan Time < 6 Mo (*n* = 65)	*p*
Reader 1							
Upper liver	0.01	−0.01	0.04	0.8	0.04	0.00	0.5
Portal vein	0.02	−0.02	0.08	0.4	0.05	0.01	0.5
Lower liver	0.04	−0.04	0.07	0.3	0.04	0.01	0.6
Reader 2							
Upper liver	0.03	0.00	0.06	0.7	0.05	0.02	0.5
Portal vein	0.03	−0.03	0.06	0.5	0.05	0.01	0.5
Lower liver	0.05	−0.04	0.07	0.3	0.05	0.01	0.5

Note—The bias differences were statistically insignificant. Both early and later PET/CT studies were performed on Discovery LS scanner, both studies were performed on Discovery ST, and one mixed study was performed using Discovery LS and one was performed using Discovery ST. Both scanners manufactured by GE Healthcare.