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Standardisation Techniques of Independent PET/CT Modalities Utilising PET SUV $_{max}$ as a Potential Conversion Marker

*[1] Hafiz M.H., [2] Noramaliza M.N., [3] Sohel Rana and [1] Fathinul Fikri A.S.
[1] Centre for Diagnostic Nuclear Imaging, UPM, Serdang, Selangor, Malaysia, [2] Department of Imaging, Faculty of Medicine & Health Sciences, UPM, Serdang, Selangor and [3] Institute for Mathematical Research, Faculty of Science, UPM, Serdang, Selangor

Abstract

This study purposed to compare the variation of standardized uptake values, SUV (g/mL) between two independent PET/CT modalities in standardising the PET images quality. Two independent dedicated PET/CT systems were involved in this standardization. The experimental procedure was to analyse technical study of phantom utilising Fluorine -18 Flurodeoxyglucose (^{18}F-FDG) as in vitro markers. The image quality evaluation of patients (n= 21) measured and analysed the mean of SUV $_{max}$ of the lungs (left, right), the brain (left, right) and the liver to ascertain the image quality standard from the 2 independent set of patients undergoing the PET/CT study from two independent imaging centres. Patients were randomised based on the matched fasting blood glucose (FBG) ($p<0.05$) as a reference standard for subject inclusion of the study. The correlations of post variation calibrated SUV with the variation SUV of the patients were analysed using linear regression analysis. Consecutive 21 patients with average age (52.7 ± 13.6 yrs.) were dichotomised to undergo PET/CT studies of two independent PET/CT systems. The transferable calibration constant of the patients of two groups were analysed using phantom SUV $_{max}$ as a gold standard for the calibrated SUV conversion of patients. The ratio of transferable calibration constant of PET/CT was 0.966: 1.035. The linear regression analysis of correlation coefficient (CE) of the post-variation calibrated SUV $_{max}$ for the SUV $_{max}$ variation of the dichotomised patients' lungs (left, right), brain (left, right) and liver were 0.994 ($P<0.001$), 0.995 ($P<0.001$), 0.995 ($P<0.001$), 0.995 ($P<0.001$) and 0.997($P<0.001$) respectively. We concluded that the SUV $_{max}$ was a potential conversion marker to validate the in vivo standardisation techniques for the two independent PET/CT modality systems based on the reference standard of the matched FBG and the in vitro ^{18}F-FDG phantom.

Keywords: FDG, image quality, independent PET, quantification, SUV, standardization.

* Corresponding author: Centre for Diagnostic Nuclear Imaging, UPM, Serdang, and Selangor, Malaysia.

Introduction

The role of Positron Emission Tomography / Computed Tomography (PET/CT) modalities is increasingly vital concomitantly with the increase of cancer cases in Malaysia. As the stated by National Cancer Council Malaysia the cases of cancer increase each year (National Cancer Council Malaysia, 2014). Thus, it is the perfect time to perform the pilot study to standardize the PET/CT image quality in Malaysia since many country had started since 2008. The Netherlands-Protocol has managed to approach the standardisation and quantification PET protocols in 2008 (Ronald Boellaard *et al.*, 2008), the Board of the European Association of Nuclear Medicine (EANM) started take initiative to implement the standardisation of PET/CT imaging in European using the accreditation of (EARL) FDG-PET/CT (Ronald Boellaard *et al.*, 2015). EARL stand for EANM Research Ltd act as an initiative to promote multicentre medicine and research which to unleash the power of molecular imaging and improve practice of nuclear medicine (European Association of Nuclear Medicine Research Ltd, 2017). The Ministry of Health Malaysia (MOH) is seriously taking steps to improve the quality of nuclear services in Malaysia with implementation of Quality Assurance Programme (QAP) for both government and private nuclear medicine centres since 2013. The various requirements of quality control (QC) are performed based on the medical term under Atomic Energy Licensing Act 1984 (The Commissioner of Law Revision Malaysia, 2006, 2010). The implementation is compulsory as the publication of the technical quality control Protocol Handbook of Positron Emission Tomography Computed Tomography (PET/CT) Systems by MOH (Medical Radiation Surveillance Division, 2015). The performance and safety standards of PET/CT systems are assured qualified to perform significant positive standard operating to interpret the PET/CT image quality of standardized uptake value (SUV) in each of stand-alone PET/CT of each centre (Medical Radiation Surveillance Division, 2015). However, the variation of SUV among PET/CT centres still remain unknown without cited research about the comparable multi-centre study in Malaysia. SUV is used extensively as a semi-quantitative index of tumour intake which calculated the radioisotope intake ratio of tumour tissue in comparison with the normal tissue when ^{18}F-FDG was injected into the body has been distributed homogeneously in the whole body. Park Hoon Hee *et al.*, (2011) studied most of cited journals published on 2007 until 2009 (Ronald Boellaard, 2009, Ronald Boellaard *et al.*, 2008, Westerterp *et al.*, 2007) and he conclude the comparison of SUV was made based on experience and qualitative judgement of clinicians (Hee Park *et al.*, 2011). SUV has various quantification such as SUV $_{max}$, SUV $_{peak}$, SUV $_{mean}$ and SUV $_{median}$. However, SUV $_{max}$ is the most commonly used parameter quantification of PET/CT as it convenient to obtain from FDG-PET images (Wilson *et al.*, 2017). Reproducibility of SUV $_{max}$ from 2 independent PET modality are important in ensuring the monitoring studied to analyse SUV uptake for patient for follow-up study. This is because different PET/CT techniques adopt different techniques preparation for the patients which would affect the SUV uptake of a pathological lesions. Even in certain parts of European and Asian country move advanced in standardisation and harmonisation of PET/CT SUV for the past decade but better late than never. Therefore, this pilot study is sought to ascertain the potential of validation of two independent in vivo ^{18}F-FDG PET/CT modalities based on the variation of SUV $_{max}$ as a potential conversion markers based on the derived transferable calibration constant of phantom of an in vitro ^{18}F–FDG uptake.

Materials and Methods

The experimental conceptual of comparison of ^{18}F-FDG standardized uptake values (SUV) of paired PET/CT modalities in Malaysia as given in Fig 1.

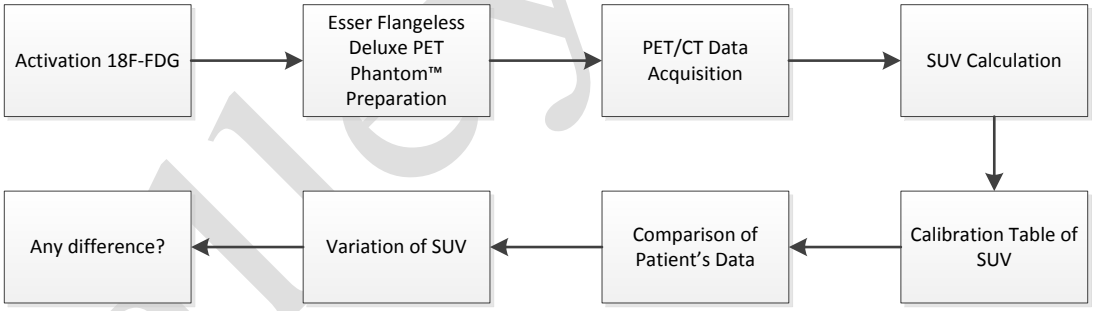

Fig 1: Flow work of whole procedures.

Scanner Modalities

PET/CT modalities of A and B were Siemens Biograph True point 64 and Siemens Biograph 6 respectively. The Siemens Biograph True point 64 PET modality of an LSO crystal detector, 52 rings and 32448 crystal numbers, and the Biograph 6 PET modality of an LSO crystal detector, 39 rings and 24336 crystal numbers. The specifications of PET/CT modality are shown in Table 1.

Quality Control of Dose Calibrators

In order to enhance the accuracy of dose calibrator, both institutions must performed the annually certified dose calibrator by Malaysian Nuclear Agency which approved by Malaysian Ministry of Health (MOH). The MOH is empowered under Section 17 of Act 304 to implement Quality Assurance Programme (QAP). The annually certified dose calibrator imposed under Regulation 53 of Basic Safety Radiation Protection Regulation (The Commissioner of Law Revision Malaysia, 2010). By this certification, the devices secured the reliability of radioactivity which was applied to phantom.

Table 1: Specifications of independent PET/CT modality.

Scanner	Specifications
Siemens Biograph True point 64 	Crystal type: LSO Number of rings: 52 Diameter of ring (cm): 84.2 Number of crystal: 32448 Crystals size (mm^3): 4 x 4 x 20 Coincidence window (ns): 4.5 Acquisition mode: 3D Trans axial FOV (mm): 605 Axial FOV (mm): 216 Slice Thickness (mm): 2 Transmission source: Ge-68
Siemens Biograph 6 	Crystal type: LSO Number of rings: 39 Diameter of ring (cm): 83 Number of crystal: 24336 Crystals size (mm^3): 4 x 4 x 20 Coincidence window (ns): 4.5 Acquisition mode: 3D Trans axial FOV (mm): 585 Axial FOV (mm): 162 Slice Thickness (mm): 2 Transmission source: Ge-68

LSO = lutetium oxyorthosilicate, FOV = field of view

^{18}F-FDG Marker

^{18}F-FDG is a sugar (glucose) molecule analogue with substitution of the oxygen in C-2 position with radiolabelled 18-fluorine (Zukotynski, 2012). Table 2 shows the ^{18}F-FDG radiotracer properties. ^{18}F-FDG has been used for activation phantom in this study.

Table 2: Characteristics of ^{18}F-FDG Radiopharmaceutical

Product	: [18F]-fluorodeoxyglucose (FDG)
Nuclide	: Fluorine-18
Type of radiation	: Positron (e_+, β_+)
Half-life	: 109.8 minutes (110 mins)
Form	: Liquid
Dosage activity	: 17 – 87 MBq

Dilution activation follows PET Phantom Activation of Phantom Dose Chart ACR (American College of Radiology, 2010)

In vitro ^{18}F-FDG Phantom

The ^{18}F-FDG phantom preparation technique was based on the PET Phantom Instructions for the Evaluation of PET Image Quality ACR Nuclear Medicine Accreditation Program PET Module by the American College of Radiology, ACR (American College of Radiology, 2010). The Esser Flangeless Deluxe PET Phantom standardizes the performance measurements of positron emission tomography as shown in Table 3.

Table 3: Specifications of Esser Flangeless Deluxe PET Phantom™. The flangeless phantoms for PET meet the requirements set by the ACR. The flangeless PET phantom provides consistent performance information for any PET system. Multiple performance characteristics of PET modality are evaluated from a single scan of the phantom.

Specifications of Esser Flangeless Deluxe PET Phantom™	
 	Phantom: Cylinder Interior Dimensions: 8" diameter x 7.32" height (20.4 x 18.6 cm) Volume: 6.4 L Cold Rod Insert Height: 3.46" h (8.8 cm) Cold Rod Diameters: 4.8, 6.4, 7.9, 9.5, 11.1 and 12.7 mm Height of Spheres From Base Plate: 5" h (12.7 cm) Solid Sphere Diameters: 9.5, 12.7, 15.9, 19.1, 25.4 and 31.8 mm Phantom Lid: Refillable thin-walled cylinders: 8, 12, 16, 25 (x3) mm Solid cylinder (Teflon¨): 25mm Cylinder height: 1.5 in Lid Closure: Bayonet-Style with Lock Screw

The phantom was filled with the volume of 6400 millilitre (mL) of distilled water. A forty megabecquerel (MBq) radioactivity of ^{18}F-FDG were dispensed to activate the phantom. The dispended ^{18}F-FDG was distributed into the phantom and syringe was flushed

several times to minimize the residual of activity in the syringe and to maximize the activity injected into the phantom. The phantom was shook to homogenize the distribution of ^{18}F-FDG and the distilled water. Left a bubble of air will help to ensure a well-mixed solution in the phantom. After thoroughly mix, a bubble of air can be removed by adding the distilled water. The phantom carefully aligned so it is parallel to the axis of the patient table. The calliper and the laser were using to lay the phantom perfectly (American College of Radiology, 2010, Hee Park *et al.*, 2011, Ronald Boellaard *et al.*, 2014).

Data Acquisition of Modalities

In measuring the SUV, we aligned the phantom parallel to the axis of the table and scanned by 3D whole-body imaging protocol commonly used by the institutions as shown in Table 4.

Table 4: Data acquisition parameters of the independent PET/CT modality of A and B

Parameter / Modality	A	B
Acquisition parameters		
or PET		
Time per bed position	2 min	3 min
Number of bed positions		
Phantom	1 bed	1 bed
Patient	7-8 beds	7 beds
Matrix size	256	128
Zoom	1	1
For CT		
Topogram		
mAs	196	196
kVp	100	100
CT		
mAs	106	106
kVp	120	120
Slice thickness	5 mm	5 mm
Reconstruction Parameters		
Type of reconstruction	True X	OSEM2D
Iterations	3	4
Subsets	21	16
Processing Filter	Gaussian	Gaussian
Setting FWHM	4 mm	5 mm
Slice thickness	5 mm	5 mm

Standardized Uptake Value (SUV)

PET/CT SUV is a semi-quantitative index for measuring the ratio of the actual radioactivity concentration found in a selected part of the body at a certain time point, and the radioactivity concentration in the hypothetical case of an even distribution of the injected radioactivity across the whole body. Park Hoon Hee *et al.*, (2011) mentioned which an SUV is obtained from radioactivity (Bq) which is measured at the ROI with ROI weight (g) and injected radioactivity (Bq) with the weight of solution (g) put into the phantom. An SUV is expressed in an equation as follows:

SUV = [Activity in ROI, mCi/volume (mL)] /Injected activity, mCi/patient weigh (g)]

SUV is evaluated by filling a phantom of or a phantom of the Esser Flangeless Deluxe PET Phantom with 17 - 87 MBq of ^{18}F-FDG diluted with 6400 mL of distilled water to uniform the concentration and were scanned with 1 bed image (American College of Radiology, 2010). Transferable calibration constant of phantom of independent modalities. The calibration constant were obtained from the ratio after-before transferable of SUV mean of scanned phantoms in each independent modalities A and B. The mean of SUV were compared to obtain the transferable-ratio of SUV in each modality. The calculation of calibration constant as Table 5. The calibration constant was used to compare the correlation of standardize the PET/CT image quality (SUV) of the independent modalities.

Table 5: The Calibration constant were obtained from the ratio after-before transferable of SUV scanned phantom (Hee Park *et al.*, 2011)

		After	
		A	B
Before	A	$\frac{\text{SUV mean of A}}{\text{SUV mean of A}}$	$\frac{\text{SUV mean of B}}{\text{SUV mean of A}}$
	B	$\frac{\text{SUV mean of A}}{\text{SUV mean of B}}$	$\frac{\text{SUV mean of B}}{\text{SUV mean of B}}$

In vivo ^{18}F FDG analysis

In order to compare the correlation of standardize the PET/CT image quality (SUV_{max}) of the modalities, 21 patients image data were selected as the patients met the selected criteria for this study. Selected patients need to have an ideal body weight (20 to 25 BMI), fasting blood sugar below 10.0 mmol/L. Out of many patients, only 21 patients met the criteria as many of them were out of ideal body weight (majority were underweight).

Of the patients as Table 6, 11 were male and 10 were female, and their average age was 52.7 ± 13.6 years old with the range between 25 to 77 years old. The average BMI was 22.38 ± 1.76 and the average fasting blood sugar was 4.82 ± 1.71 mmol/L. The patients fasted for minimum 6 hours before PET/CT examination and the fasting blood sugar was below 10.0 mmol/L (180 mg/dL).

Table 6: Patient's details

	PET/CT Modality A	PET/CT Modality B
Number of patients	10	11
Age (years)	51.8 ± 14.9	53.5 ± 13.1
Sex	7 Male:3 Female	4 Male:7 Female
Body Mass Index, BMI (kg/m^2)	21.8 ± 2.0	22.9 ± 1.3
Mean Fasting Blood Glucose (mmol/L)	3.8 ± 1.9 mmol/L	5.7 ± 0.9mmol/L
Uptake time (minutes)	55.00 ± 15.28	52.50 ± 7.91

However in this study, all protocol handled by institution which incorporated the recommended patient preparation of recommendations (Ronald Boellaard *et al.*, 2015, Surasi *et al.*, 2014, Delbeke *et al.*, 2006) were standardised on the preparation techniques with matched mean FBG ($p<0.05$). We only use the appropriate patient data images (Fig 2) that met the qualification as stated as above paragraph.

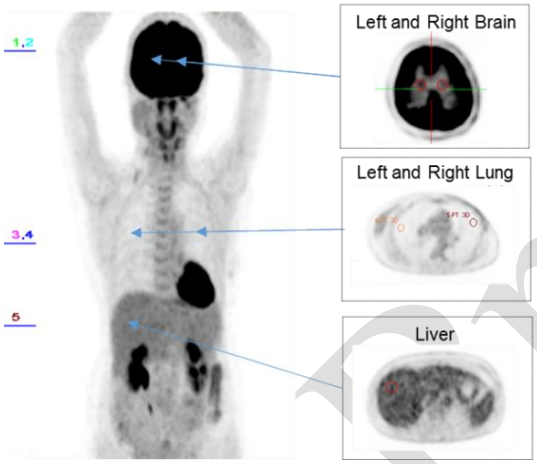

Fig 2: The SUV was obtained for the brain (left, right), lungs (left, right) and liver with the volume ROI of 3 cm^3.

Result

Technical Part (Phantom SUV)
Mean SUV

The phantom was scanned ten times in ten single examination days of PETCT examination for a modality A and B. The means and the standard deviations of the images with delay time of 60 minutes for PET/CT modalities A and B were 0.947 ± 0.020 and 0.980 ± 0.010 respectively. The location of ROI were standardized with 50 cm^3 as Fig 3.

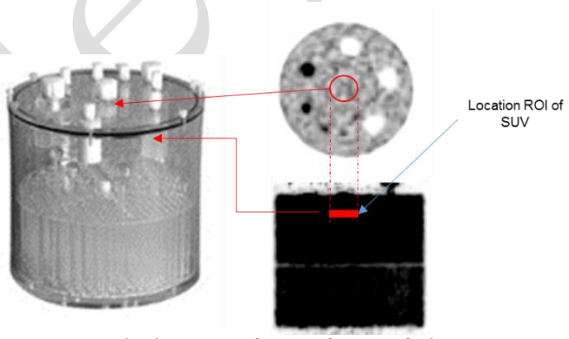

Fig 3: The location of ROI of SUV of phantoms

Percentage Difference of SUV of Independent PET/CT Modalities

Percentage difference of SUV of each PET/CT modality were calculated (Hee Park *et al.*, 2011) using definition as follow,

SUV Difference = (Measured SUV – Expected SUV)/ Expected SUV x 100% (Equation 2)

Which are,

Measured SUV were the image-derived SUV of ROI

Expected SUV was measured on the decay corrected of dose calibrator to scan times. The variation of SUV in each independent PET/CT modality were 4.07% for PET/CT Modality A and 7.69% of PET/CT Modality B (Fig 4).

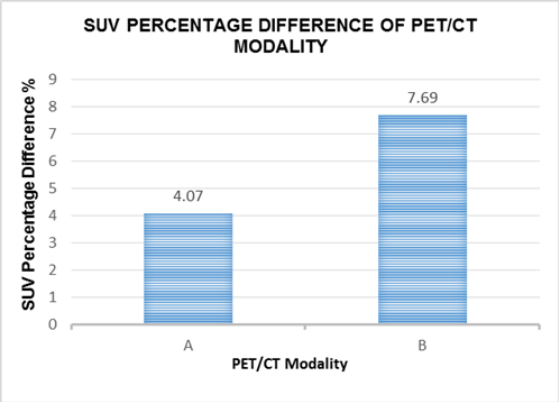

Fig 4: SUV percentage difference of independent PET/CT modality

Transferable Calibration Constant PET/CT Modality Using Phantom

The calibration constant were obtained from the ratio after-before transferable of SUV_{mean} of scanned phantoms in each independent modalities A and B. The mean of SUV were compared to obtain the transferable-ratio of SUV in each modality. The result of transferable calibration constant as Table 7.

Table 7: Result of the transferable calibration constant PET/CT modality of phantoms

After			
		A	B
Before	A	1	1.035
	B	0.966	1

Assessment of in vivo SUV $_{max}$

Patient SUV $_{max}$

For 21 patients who involved in this study, the SUV $_{mean}$ of the selected parts (left and right of brain, left and right of lungs, and liver) were measured (Fig 5). The means and standard deviations of the mean SUV of left lung were 0.577 ± 0.043 and 0.556 ± 0.095. Those for the right lung were 0.560 ± 0.044 and 0.586 ± 0.098. Those for the right brain 6.092 ± 0.584 and 5.841 ± 0.974. Those for the left brain 5.932 ± 0.320 and 5.478 ± 0.915. Those for the liver were 3.164 ± 0.429 and 2.765 ± 0.290 (Table 8).

Table 8: Standardized uptake values (SUV) was measured by the independent PET/CT modality, and SUV was obtained for the left and right of brains, the left and right of lungs and the liver.

Mean of SUV $_{max}$	PET/CT Modality A	PET/CT Modality B
Left brain SUV	5.932 ± 0.320	5.478 ± 0.915
Right brain SUV	6.092 ± 0.584	5.841 ± 0.974
Left lung SUV	0.577 ± 0.043	0.556 ± 0.095
Right lung SUV	0.560 ± 0.044	0.586 ± 0.098
Liver SUV	3.164 ± 0.429	2.765 ± 0.290

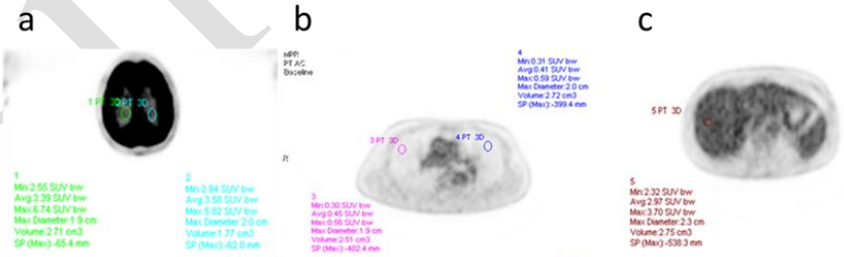

Fig 5: Standardized uptake values (SUV) was measured by the independent PET/CT modality, and SUV was obtained for the left and right of brains (a), the left and right of lungs (b) and the liver (c).

Post-Variation SUV (SUV Calibrated Recovery) Using Transferable Calibration Constant

All of the measured SUVs of selected body-parts were calibrated with the ratio of Transferable Calibration Constant to get the corrected post-variation SUVs of the selected body-parts. By then, all the SUV calibrated recovery were analysed using linear regression analysis to test the correlation quantification between two independent PET/CT modalities. The linear regression analysis of post-variation SUV with the variation SUV of the patients' lungs (left, right), brain (left, right) and liver shown the correlation coefficients were 0.994 (P<0.001), 0.995 (P<0.001), 0.995 (P<0.001), 0.995 (P<0.001) and 0.997(P<0.001) respectively (Fig 6).

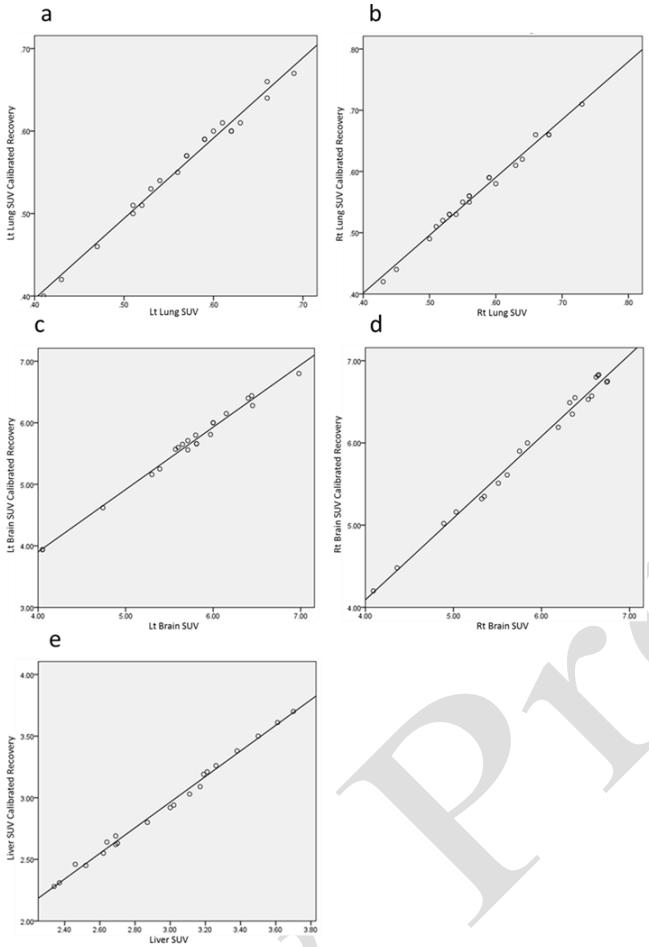

Fig 6: the correlation coefficients of linear regression analysis of post-variation SUV with the variation SUV of the patients' lungs left, right (a, b), brains (left, right) (c, d) and liver (e).

Discussion

All of the PET/CT modalities involved in this study were qualified to test the quantification of SUV_{max} variation for the two independent PET/CT modality systems for which variation were 4.07% and 7.69% for modality A and modality B respectively. This validate the standardisation technique for the two independent PET/CT studies with tolerance limit of the SUV_{max} variations within ±10 %. On 2002, Geworski *et al.* explained clearly in his research about the variation of SUV measured with 23 PET modalities to perform the calibration and cross-calibration among PET scanners. He reported the variation of SUV should be below than ±10% (Geworski *et al.*, 2002). There is no doubt in quality control of PET/CT as the strictly act and regulations implemented by the local authorized organization to improve the quality of nuclear services in this country (Medical Radiation Surveillance Division, 2015). In addition, our phantom used for the in vitro ^{18}F–FDG reference standard was passed the ACR SUV evaluation of background mean which is in range 0.85 – 1.15(American College of Radiology, 2010). SUV_{mean} of phantom scanned by modality A and B were 0.947 and 0.980 respectively. The comparable study of PET image quality of SUVs between phantoms technical study and patient's data clinical study were increasingly investigated by all researchers in past decade. The outputs were towards the standardization and harmonisation of quantification SUV of PET/CT modalities (R. Boellaard, 2011, Ronald Boellaard *et al.*, 2014, Ronald Boellaard, 2009, Ronald Boellaard *et al.*, 2008, 2010, Buckler & Boellaard, 2011, Fukukita *et al.*, 2010, 2014, Hee Park *et al.*, 2011, Hess *et al.*, 2014, Makris *et al.*, 2013). In this particular study, we emphasised that the main influence of the in vivo ^{18}F-FDG uptake should be harmonised based on the FBG standardisation with the matched mean FBG ($p<0.05$) for the dichotomised groups of subjects achieved. The variation in FBG affects the in vivo FDG uptake in the cells facilitated by the glucose 6 phosphatase transport (Fathinul *et al.*, 2013). All other confounding factors i.e. the FDG uptake time, the PET acquisition time per bed positions and the patients related factors to improve the image quality were maintained for the two study protocols. The strength of this study results based on the methods is despite the variation in the physical aspect of the two PET-CT systems in particular the number of the scintillation crystals (Table 1) does not affect the difference in the image quality and therefore standardisation of the two independent PET-CT systems could be validated. The variation of SUV_{max} shown by scanned-phantom were manipulated to establish the transferable calibration constant among the modalities. The result of the transferable calibration constant for Modality PET/CT A and Modality PET/CT B were 0.966 and 1.035 respectively. Linear regression analysis of phantom SUV calibration and utilising the transferable coefficient constant for the in vivo SUV_{max} of the mean of patients' lungs (left, right), brain (left, right) and liver shown the correlation coefficients were 0.994 ($P<0.001$), 0.995 ($P<0.001$), 0.995 ($P<0.001$), 0.995 ($P<0.001$) and 0.997 ($P<0.001$) respectively. These results confirmed that the variation of quantification of SUV was insignificant difference for the subjects undergoing the two independent PET/CT modality by

comparing the technical study and clinical study with the correlation coefficients (CE) ranging from 0.994 to 0.997 ($P<0.001$). However, the finding of result of insignificant difference for two independent PET/CT modality leading to the new inquiry that reliable to be investigated. The result shows the two independent PET/CT modality were produced from same international healthcare manufacturer which is one of the reason the finding was positively correlate. But, is there any significant difference between independent PET/CT modality which is manufactured from vary healthcare manufacturers? Future study should attempt to involve many of institutions to take part in comparison of PET/CT quantification in Malaysia even though there are many obstacles to be achieved. The statement above related to Scholtens *et al.* (2017) which recommend the SUV quantification should become interchangeable between institutions and the research data could be studied into a larger dataset (Scholtens *et al.*, 2017). He also mentioned the significant statistical become better with the involvement of multiple institutions with the large data set. But somehow, it depends on other aspects such as acquisition, reconstruction, protocols measurement and further standardisations (Scholtens *et al.*, 2017). The limitations of this study were the small number of subjects which age variant and unmatched body mass index (BMI). The future research may focus on the factors that affect the PET/CT SUV_{max} such as attenuation coefficient, data acquisition, image reconstruction procedure, ROI setup method, noise, image resolution, radiation dose per unit weight of patient, data acquisition time per bed, overlap between beds and scanning mode in 2D and 3D. For the technical part of phantom, it is notwithstanding that using the various type of PET phantom such as NEMA 1994, NEMA 2002 and NEMA 2012/IEC 200 could also be potentially suitable as the reference in-vitro 18 F-FDG analysis. This study is an imPETus towards the standardisation of PET-CT techniques for this country and therefore the patients has unlimited access to any of the different modality systems which would improve in the quality of the healthcare standard in the year to come.

Conclusion

It is concluded that the variation of quantification of SUV_{max} differences between the subjects undergoing the two independent PET-CT modalities was statistically insignificant difference. This pilot study documented the potential of validation of two independent in vivo ^{18}F-FDG PET/CT modalities based on the variation of SUV_{max} as a conversion markers based on the derived transferable calibration constant of phantom of an in vitro ^{18}F-FDG uptake.

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