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Title: Dose optimization in ^{18}F-fluorodeoxyglucose positron emission tomography based on NECR measurement and image quality assessment

Running Title: Dose Optimization in Positron emission tomography

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Abstract

Rationale: The present study aims to optimize injected dose of 18F-FDG in whole body PET/CT scan and assess its effect on Noise Equivalent count rate (NECR) and visual image quality (IQ) assessment. **Methods:** Patients scheduled to undergo 18F-FDG PET/CT were prospectively recruited in the study from January to December 2019, regardless of the indication/underlying disease. Patients were divided into four groups and injected different amounts of 18F-FDG radioactivity/kg body weight (1.85 MBq/kg, 3.7 MBq/kg, 5.5 MBq/kg and 7.4 MBq/kg). All patients underwent 18F-FDG PET/CT studies and $NECR_{local}$ was calculated by noting the trues rate, total prompts and randoms rate for each bed position. Whole body $NECR_{global}$ was calculated as average of NECR for all bed positions. Qualitative IQ assessment was done for each bed-position (IQ_{local}) and for whole-body PET (IQ_{global}) by two readers using 5-point scores based on prevalence of noise, contrast and lesion detectability. Values of NECR and IQ in all four activity groups were compared. Patients were also subdivided into four body mass index (BMI) groups [group I-15-20(kg/m^2), group II-20.1-25 (kg/m^2), group III-25.1-30 (kg/m^2) and group IV-30.1-35 (kg/m^2)] for comparison. A p value <0.05 was considered significant. **Results:** A total of 109 patients underwent 18F-FDG PET/CT studies after injecting different amounts of 18F-FDG radioactivity and a mean uptake time of 62.32 minutes. Mean value of $NECR_{global}$ and IQ_{global} for each group were found to be significantly different from other groups ($p<0.05$), with higher NECR and IQ values in high-activity groups in comparison to low-activity groups. The overall image quality was acceptable in all patients, even in lowest-activity group (1.84 MBq/Kg). The mean values of $NECR_{global}$ and IQ_{global} were found to be significantly different in all the four BMI groups ($p < 0.05$) except between group II and III ($p>0.05$). $NECR_{local}$ and IQ_{local} were moderately correlated ($r=0.64$). **Conclusion:** Optimisation of injected 18F-FDG radioactivity from 7.4

MBq/kg (200 μCi/kg) body weight to 1.85 MBq/kg (50 μCi/kg) body weight resulted in acceptable image quality, despite reduction in NECR.

Keywords: NECR, Image quality, FDG PET, Dose optimisation

INTRODUCTION

The burgeoning demand of Positron Emission Tomography/Computed Tomography (PET/CT) imaging in providing personalised health care has led to continuous evolution of technology to provide the best image quality. This has resulted in incorporation of advancements like Point spread function (PSF) and Time of Flight (TOF) in reconstruction algorithms to improve the spatial resolution of the PET images {*1-4*}. PET/CT scanners incorporated with TOF and PSF aim to get good image quality even with lesser radioactivity injected to patient {*5, 6*}. Decreasing the dose of injected activity is always a welcome step to reduce radiation exposure to the patient. However, despite the use of advanced technology, there is a limit below which the administered radioactivity cannot be reduced without increasing the acquisition time in order to get good image quality. So, the injected dose and acquisition time need to be balanced to achieve diagnostic PET image quality.

Image quality assessment of PET images is an arduous task due to the physics of PET image acquisition. All the counts acquired during PET acquisition are not true coincidence counts, but also include the random and scatter counts. These random and scatter counts do not reflect the true activity distribution in the body and thus, deteriorate the PET image quality. Using signal to noise ratio as a quantifying parameter for image quality assessment is not very promising, since it takes into account all the prompt counts including random and scatter counts. However, noise equivalent count rate (NECR) is the image quality parameter that quantifies the contribution of true counts in total prompts, and thus is better representative of image quality. A higher value of NECR ensures better signal to noise ratio in the patient data {*6, 7*}.

NECR has been used routinely as a parameter for comparing image quality of PET scanners. Its use as a tool for assessing clinical image quality in PET/CT images of the patient has been reported since few years {*6-9*}. There is limited literature on the value of NECR in relation to activity injected per kg body weight and its relation to image quality. The studies computing NECR as image quality parameter are mostly phantom or simulation studies {*10-12*}. Two retrospective studies have measured NECR in patient population and one of these studies have calculated only regional NECR of liver {*8-9*}.

According to European Association of Nuclear Medicine (EANM) guidelines, activity is administered linearly or quadratically with patient weight and acquisition time {*13*}. Keeping a minimum acquisition time of 1 min and for weight ranging between 45-75 kgs, the 18F-FDG dose ranges from 4.07-7.03 MBq (110-190 μCi)/kg body weight. Other studies have also recommended dose ranging from 5.55-7.4 MBq (150-200 μCi)/kg body weight {*9-10,14*}.

The present study aims to optimize injected dose of 18F-FDG in order to reduce effective exposure from whole body PET/CT scan, assess its effect on NECR and visual IQ assessment.

METHODOLOGY

Patient Population

This prospective study included a total of 112 patients who were referred for 18F-FDG PET/CT imaging from January to December 2019, regardless of indication. The study was duly approved by the departmental review board, and written informed consent was obtained from all the patients. Patients with fasting glucose levels higher than 200 mg/dl and those who had not fasted for at least 4 hrs were not included. Patients with partial extravasation of the 18F-FDG activity seen on PET/CT study were excluded as it affects the quantification of image quality. The patients were divided into four groups depending on 18F-FDG radioactivity injected/kg body weight. In the first group of patients (group a), the injected dose of 18F-FDG was 1.85 MBq/kg (50 µCi/kg) body weight, for second (group b), third (group c) and fourth group (group d), the injected dose was 3.7 MBq/kg (100 µCi/kg), 5.5 MBq/kg (150 µCi /kg) and 7.4 MBq/kg (200 µCi /kg); respectively. Further, the study population was divided into four groups based on BMI [group I-15-20(kg/m^2), group II-20.1-25 (kg/m^2), group III-25.1-30 (kg/m^2) and group IV-30.1-35 (kg/m^2)] for comparison of effect of BMI on IQ and NECR.

PET/CT imaging

All patients underwent whole body PET/CT study from base of skull to mid-thigh using 3-D time of flight-based PET/CT scanner (Discovery MIDR, GE Healthcare, USA), at 45-75 mins post administration of radioactivity. A helical CT with tube voltage of 120 kVp, variable tube current (150-350 mA) was acquired cranio-caudally followed by a PET scan in caudocranial direction keeping 90 sec time per bed position for group a and 60 sec time per bed position for remaining three groups. The whole-body PET images were reconstructed in a matrix of 192 x 192 using ordered subset expectation maximisation (24 subsets, 2 iterations) and a Z-axis gaussian filter with FWHM of 5.5 mm. During PET acquisition, counts (true counts, total prompts and randoms) were recorded for each bed position.

Image analysis: The acquired PET images were assessed for image quality using two methods - quantitative and qualitative image analysis. Quantitative image quality was assessed with the measurement of NECR for each bed position ($NECR_{local}$). This was done by taking the ratio of square of true counts to that of sum of true, random and scatter (total prompts). The unit for NECR being kilocounts per second (kcps). NECR for the whole-body scan of patient ($NECR_{global}$) was defined as the mean of $NECR_{local}$ value of all the bed positions for whole body acquisition.

For the clinical and qualitative analysis of image quality, the acquired PET/CT images were transferred to a dedicated review workstation (Advantage Workstation 4.7, GE Healthcare, USA). PET Maximum intensity projection (MIP) and transaxial images were visually assessed and scored for image quality by a Nuclear Medicine Physician (HS) and a Physicist (NR), each having more than 8 years of experience. Image Quality scores were defined to evaluate image quality. The IQ local score was a 5-point scale assigned to each bed position, where 1 means poor, 2 means bad, 3 means acceptabe/average, 4 means good and 5 means excellent Image Quality. The IQ global score (IQ_{global}) was assigned to whole study after assesing all bed positions and MIP image using the same 5-point scale. The readers assessed the PET image quality subjectively based on: prevalence of noise, contrast between different tissues and organs and lesion detectability.

Statistical analysis:

Quantitative parameters with normal distribution were expressed using mean and standard deviation. The mean values of $NECR_{global}$ and IQ_{global} were compared in all four groups using independent t-test for each pair of groups. The mean values of $NECR_{global}$ and IQ_{global} were compared in the four BMI groups using independent t test for each pair of groups. Correlation amongst $NECR_{global}$, IQ_{global}, and BMI as well as amongst $NECR_{local}$, IQ_{local}, and BMI was assessed using Karl's Pearson correlation coefficient. The two-way multivariate analysis (two-way MANOVA) was applied to study if there was interaction between the activity group and BMI group while evaluating $NECR_{global}$ and IQ_{global} values. P-values were considered significant if < 0.05.

RESULTS

A total of 112 patients were recruited, of which 3 were excluded due to partial extravasation of radioactivity. Only 109 patients (38 males, 71 females) in the age group (14-80 years) with mean age of 49.8±16.1 years were included. Descriptive mean values of injected activity, $NECR_{global}$, IQ_{global}, BMI and uptake time in all four groups, group a (n=18), group b (n=18), group c (n=18) and group d (n=18) have been tabulated in Supplement Table 1.

Comparison of $NECR_{global}$ and IQ_{global} in different activity groups

$NECR_{global}$ and IQ_{global} showed a statistically significant difference ($p < 0.05$) amongst all the four activity groups with group d showing highest $NECR_{global}$ and IQ_{global} scores and group a showing lowest $NECR_{global}$ and IQ_{global} scores. The mean IQ_{global} Score in group a was 3 denoting overall acceptable image quality, even in the lowest activity group. No study was reported as bad/poor image quality in any group.

Correlation of image quality scores and BMI

The value of correlation coefficient between $NECR_{global}$ and IQ_{global} was found to be r = 0.47 ($p<0.05$). The correlation of $NECR_{global}$ and IQ_{global} with BMI was found to be negative, r = -0.46 and -0.40 ($p<0.05$); respectively. $NECR_{local}$ and IQ_{local} score values were found to be moderately correlated with each other having correlation coefficient value, r = 0.64 ($p < 0.05$). No significant correlation was found between $NECR_{local}$ value and BMI as well as between IQ_{local} score and BMI (Figure 1).

Comparison of $NECR_{global}$ and IQ_{global} in different BMI groups

Variation in mean value of $NECR_{global}$ and IQ_{global} for different BMI groups [15-20(kg/m^2), 20.1-25 (kg/m^2), 25.1-30 (kg/m^2), 30.1-35 (kg/m^2)] within each activity group has been shown in Supplemental Figure 1. Also, the mean values of $NECR_{global}$ and IQ_{global} were found to be significantly different in all the four BMI groups ($p < 0.05$) except between group II and III ($p >0.05$).

Difference in visual image quality in patients with similar BMI but injected with different amount of radioactivity can be seen in Figure 2 and Figure 3.

Interaction effect between the activity group and BMI group on image quality parameters

The two-way multivariate analysis (two-way MANOVA) showed there was no statistically significant interaction effect between activity group and BMI group on both $NECR_{global}$ and IQ_{global} values, $F (12,190) = 1.631$, $p=0.086$; Wilks' Lambda = 0.822.

DISCUSSION

Dose optimization is a major concern while dealing with any type of nuclear medicine procedure as it aims to minimize the radiation exposure to the patient as well as to the occupational workers who are dealing with patients with administered radioactivity while preserving image quality. To minimize the exposure to the patient, the amount of administered activity to the patient can be reduced according to ALARA principle. However, image quality can get compromised by reducing the administered activity due to insufficient counts for generating good image quality. Increment in administered activity in PET (beyond certain level) also degrades the IQ since random counts also increase with increase in administered activity which further degrades the IQ. Optimization of the administered dose and IQ is essential for 18F-FDG PET/CT studies. The conviction behind the rapid evolution in PET instrumentation and reconstruction algorithms is to minimise the activity injected to patients as much as possible while maintaining diagnostic image quality. Use of improved scintillator crystals like LYSO and incorporation of techniques like TOF and PSF in reconstruction algorithm has made this feasible by improving the spatial resolution, image contrast and decreasing the noise in the image.

NECR has been used as quantitative PET image quality parameter either in phantom studies or in simulation studies {*10-12*}. Only few studies have used it as an analysis parameter in patient studies. Chang *et al* studied the effect of injected dose and BMI on NECR, however they computed NECR only for one bed position with liver {*8*}. Queiroz *et al* also assessed the clinical image quality and compared it with NECR measurements in patient population {*9*}. NECR can be used as an objective measurement of Image quality of a PET system. Higher NECR value is expected to ensure a good signal to noise ratio and lesser noise in the reconstructed images. In the present study, NECR along with visual image quality assessment was used to assess the quality of 18F-FDG PET images acquired using different weight-based doses and assess its effect on IQ.

The mean value of $NECR_{global}$ for all the patients (n=109) in our study was 92.57 kcps. This is lower than mean value of $NECR_{global}$ computed by Queiroz *et al* in their study (n=75, NECR 106.4 kcps). Also mean value of $NECR_{global}$ calculated in patients segregated according to BMI (group I <20 kg/m^2, group II = 20.1 to 25 kg/m^2, group III = 25.1 to 30 kg/m^2 and group IV = 30.1 to 35 kg/m^2) were 91.5, 85.25, 88.5 and 63.22 kcps; respectively in the present study as compared to 133.04, 112.49, 102.34 and 86.79 kcps; respectively in their study. The decreased mean value in the present study can be explained due to inclusion of even lower activity group of 1.85 MBq/kg (50 μCi/kg) in our study. An increasing trend of NECR value with decreasing BMI was observed in our study, except for group II and group III for which there was no statistically significant difference in the mean values. The similar trend was observed in the study by Queiroz *et al* {*9*}. The value of NECR calculated in the present study cannot be compared with that which was computed in study by Chang *et al* as they calculated the NECR value only for one bed position of liver, unlike the present study for which NECR value was calculated for each bed position and then averaged {*8*}.

Though many studies have compared NECR with visual assessment, no study has compared the value of NECR and visual assessment in patients group injected with different amount of activities per kg body weight. The quantitative and qualitative analysis of image quality in our study showed a significant difference in patient groups injected with different activities. The mean value of $NECR_{global}$ and IQ_{global} was highest for group injected with 7.4 MBq/kg (200 µCi/kg) body weight and lowest for patients injected with 1.85 MBq/kg (50 µCi/kg) body weight as shown in Supplement Table 1. However in a similar study, Chang *et al* compared the local NECR for liver, and found there was no statistically significant change in values of NECR when the injected activity was increased from 296–444 MBq (8-12 mCi) to 555–740 MBq (15-20 mCi) {*8*}. The difference in findings in two studies can be explained due to use of higher range of activities compared to that used in the present study [89.91-463.24 MBq (2.43-12.52 mCi)].

Queiroz *et al* in their study showed that patient NECR and their respective IQ was strongly correlated with each other and negatively with BMI {*9*}. They also found that there was significant and positive correlation between IQ_{local} and $NECR_{local.}$ A similar, moderate and significant correlation between IQ_{local} and $NECR_{local}$ was observed in the present study. $NECR_{global}$ calculated for all patients was also correlated with IQ_{global} and both these parameters had a negative correlation with BMI, however the correlation was weak. One possible explanation for a weak correlation of IQ_{global} with BMI and $NECR_{global}$ can be use of discrete score in our study, unlike continuous score used by Marcelo *et al* {*9*}.

A number of studies have been done to optimize 18F-FDG activity, to achieve good image quality. In a study by Geismar *et al,* authors concluded that an optimal 18F-FDG dose of 4 MBq/kg body weight can be used only in patients with BMI ≤ 22 kg/m^2, otherwise a dose of 5 MBq/kg body weight was needed to obtain good image quality in patients with BMI >22 kg/m^2 {*15*}.

Another similar study by Everaert *et al* determined the 18F-FDG activity ≥8MBq/kg (200µCi/kg) body weight as an optimized dose with 2-3min per bed position, for obtaining good IQ in case of LSO PET/CT scanner {*14*}. However, in the present study, in the second lowest activity group i.e. for 3.7 MBq/kg body weight as well as for highest BMI patient (35.28 kg/m^2) and with 1 minute per bed position acquisition time, diagnostic image quality was maintained. A comparable figure of optimized dose as 3.8 MBq/kg body weight has been given by Queiroz *et al*, however their study was a retrospective study and was not supported by any patient's images {*9*}. Feasibility of reducing the injected activity to 1.85 MBq/kg (50 µCi/kg) was done in a group of 18 patients, by increasing the acquisition time to 90 sec per bed position from 60 sec per bed position. It was observed that though the NECR value was comparatively reduced, acceptable diagnostic image quality could be achieved in this group as well, even for patients having BMI as high as 34.64kg/m^2.

For all the 109 patients in the present study with administered activity from 1.85 MBq/kg to 7.4 MBq/kg body in different groups, IQ score was more than or equal to 3. This implies that the image quality obtained ranged from acceptable to excellent quality in patients with different BMI. In the present study, 18F-FDG activity ≥1.85 MBq/kg body weight was considered as an optimized dose for obtaining acceptable IQ in patients undergoing whole body 18F-FDG PET/CT using 60-90 second imaging time/bed position depending on administered activity. In the future, PET scanners with even faster crystals, coupled with silicon based photomultiplier tubes aiming to enhanced system sensitivity and spatial resolution, can pave the way for usage of even lesser administered radioactivity.

CONCLUSION

Optimisation of injected 18F-FDG radioactivity from 7.4 MBq/kg (200 μCi/kg) body weight to 1.85 MBq/kg (50 μCi/kg) body weight resulted in excellent to acceptable image quality in all patients. Administration of low radiotracer activity (1.85 MBq/kg) can achieve acceptable PET image quality with reduction in radiation exposure to the patients.

DISCLOSURE

No financial disclosure.

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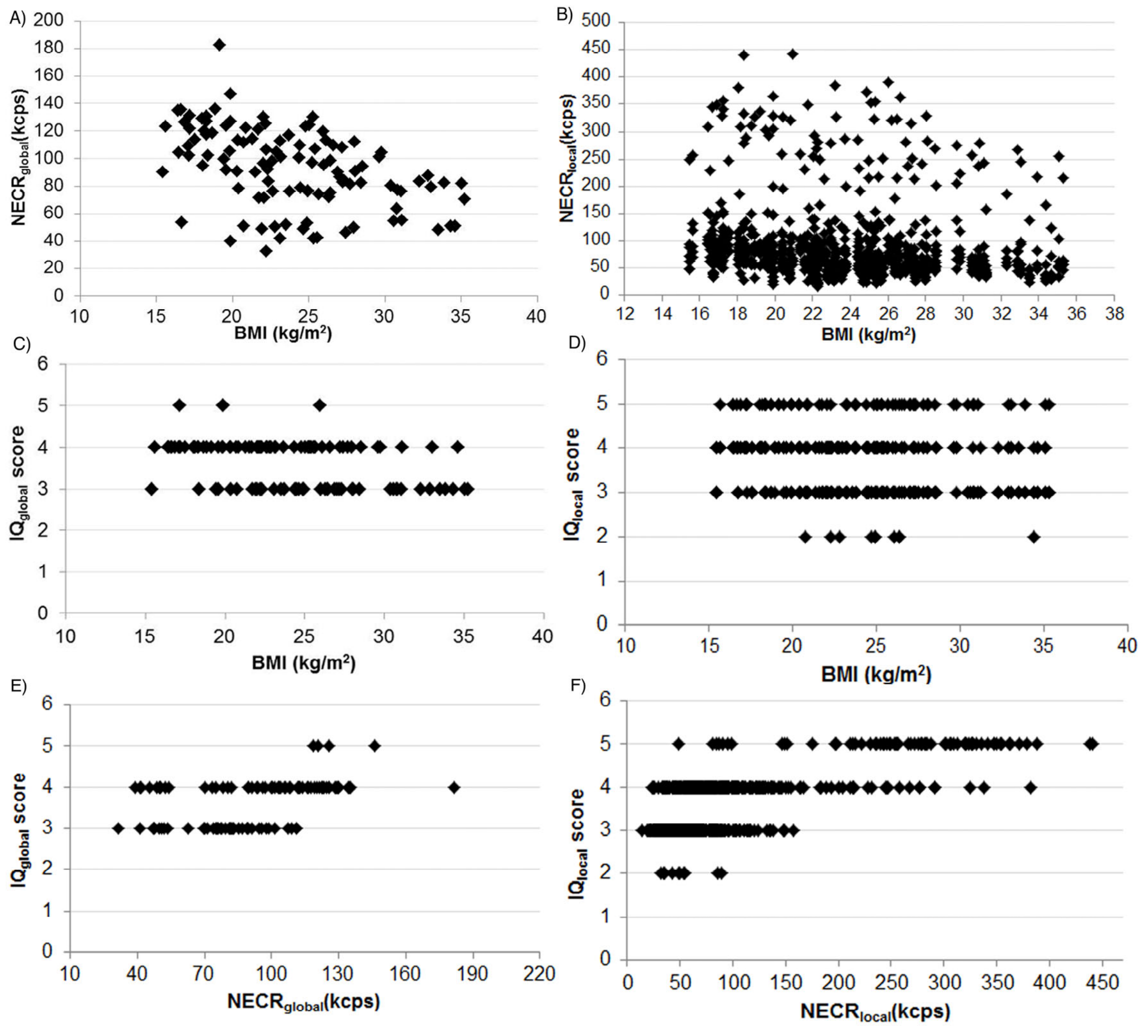


Figure 1: Variation in value of A) $NECR_{global}$ with BMI B) $NECR_{local}$ with BMI C) IQ_{global} score with BMI D) IQ_{local} score with BMI E) IQ_{global} score with $NECR_{global}$ F) IQ_{local} score with $NECR_{local}$

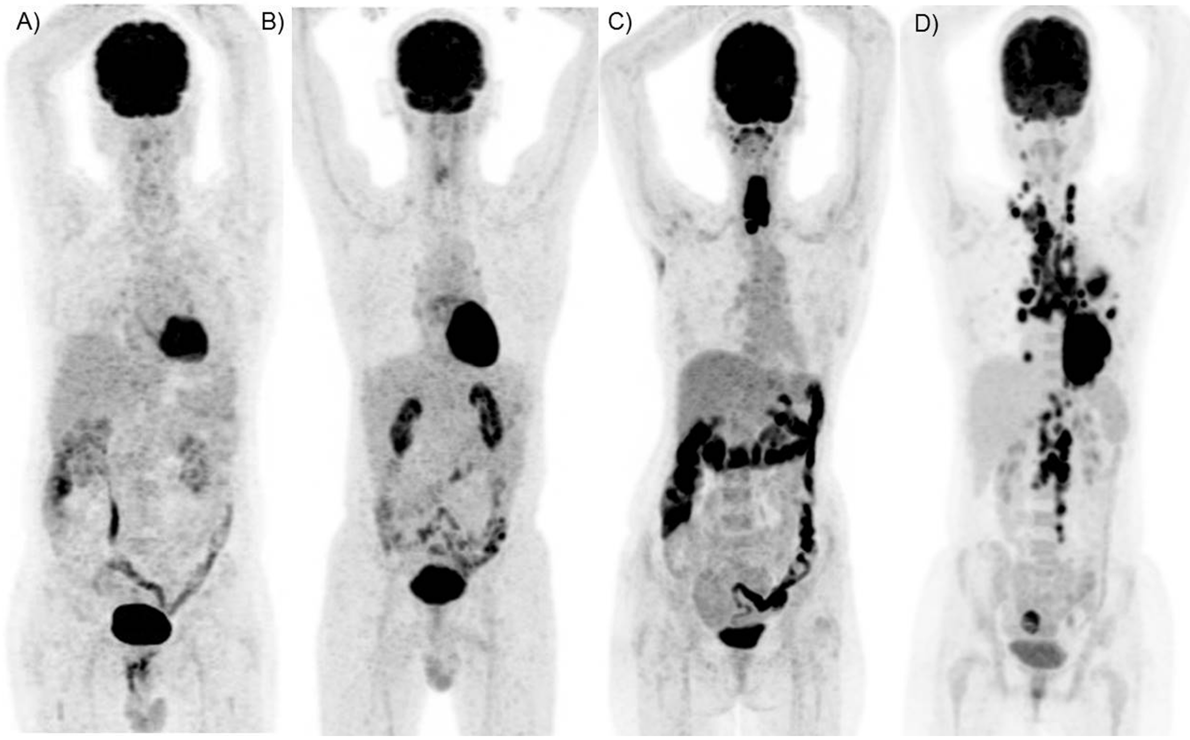


Figure 2: 18F-FDG PET MIP images of four different patients having approximately same BMI (20.00 kg/m^2) A) having administered activity: 1.85 MBq/kg (50μCi/kg) body weight, $NECR_{global}$: 50.55 kcps, IQ_{global} score: 3 B) having administered activity: 3.7 MBq/kg (100 μCi/kg) body weight, $NECR_{global}$: 77.78 kcps, IQ_{global} score: 4 (C) having administered activity: 5.5 MBq/kg (150 μCi/kg) body weight, $NECR_{global}$: 90.23 kcps, IQ_{global} score: 4 D) having administered activity: 7.4 MBq/kg (200 μCi/kg) body weight, $NECR_{global}$: 146.30 kcps, IQ_{global} score: 5

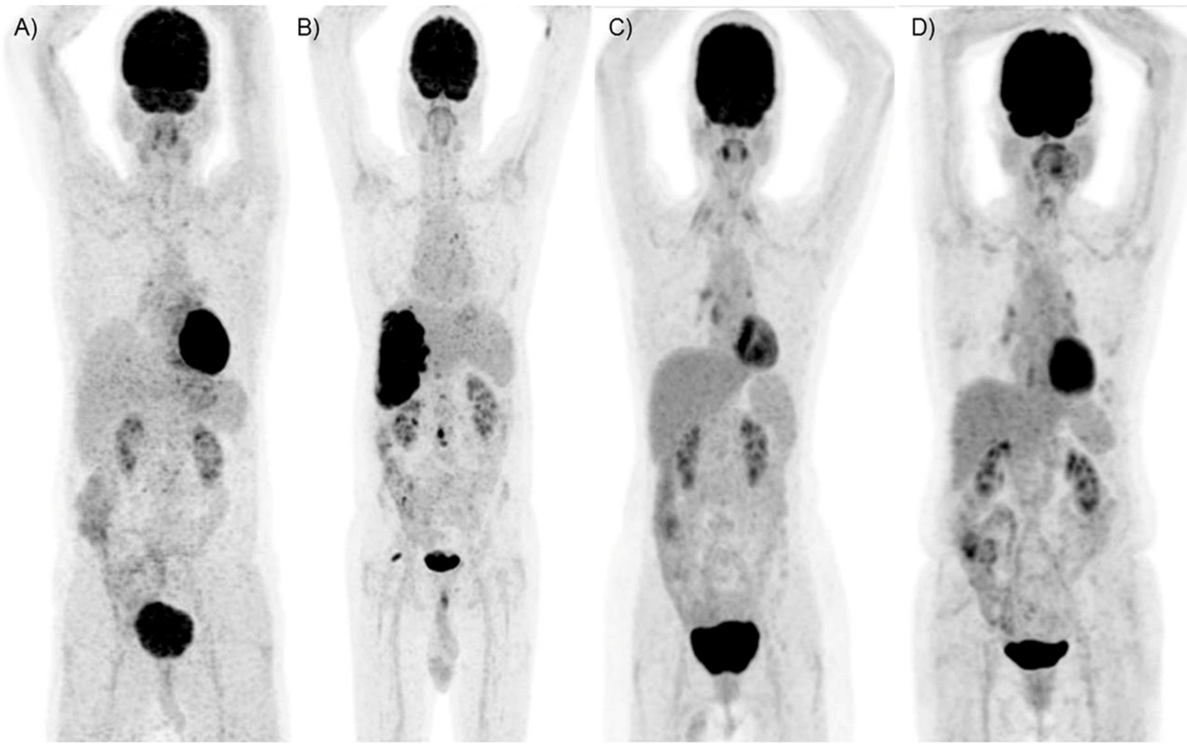
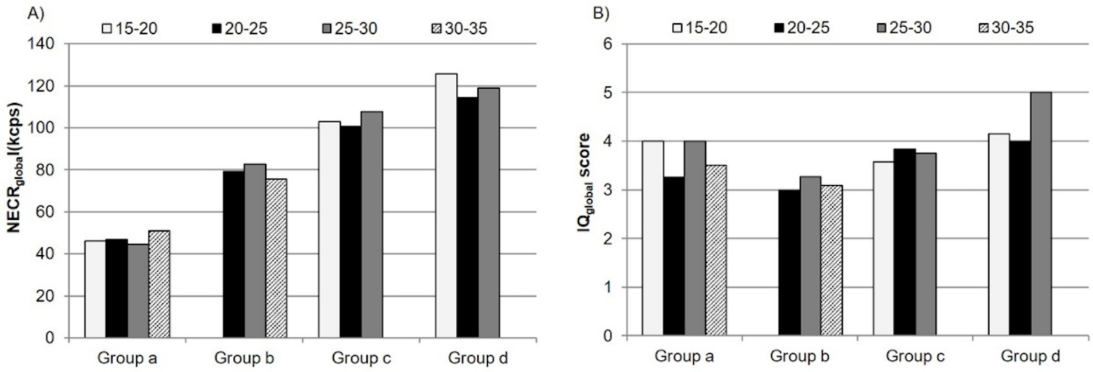


Figure 3: 18F-FDG PET MIP images of four different patients having approximately same BMI (25.00 kg/m^2) A) having administered activity: 1.85 MBq/kg (50 µCi/kg) body weight, $NECR_{global}$: 48.25 kcps, IQ_{global} score: 3 B) having administered activity: 3.7 MBq/kg (100 µCi/kg) body weight, $NECR_{global}$: 75.72 kcps, IQ_{global} score: 3 C) having administered activity: 5.5 MBq/kg (150 µCi/kg) body weight, $NECR_{global}$: 129.54 kcps, IQ_{global} score: 4 D) having administered activity: 7.4 MBq/kg (200 µCi/kg) body weight, $NECR_{global}$: 122.94 kcps, IQ_{global} score: 4



Supplemental Figure 1

Variation in mean value of A) NECRglobal and B) IQglobal for different BMI groups [15-20(kg/m2), 20.1-25 (kg/m2), 25.1-30 (kg/m2), 30.1-35 (kg/m2)] within each activity group.

	18F-FDG(μCi/kg)			Uptake Time (minutes)			BMI (kg/m^2)			IQ_{global} Score			$NECR_{global}$(kcps)		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
Group a (n=18)	53.0	42.5	61.7	70.0	49.0	75.0	25.6	16.7	34.6	3.5	3.0	4.0	47.2	32.2	54.4
Group b (n=30)	102.4	91.7	109.0	58.9	50.0	70.0	27.9	15.6	35.3	3.1	3.0	4.0	79.6	53.8	96.1
Group c (n=32)	150.6	141.0	168.0	61.2	50.0	70.0	23.0	15.5	29.8	3.8	3.0	4.0	103.7	70.9	130.0
Group d (n=29)	199.4	191.0	210.0	59.2	50.0	70.0	19.6	20.4	26.0	4.1	3.0	5.0	120.0	75.5	146.0

Table 1: Mean 18F-FDG injected activity, Uptake time, BMI, IQ_{global} Score and $NECR_{global}$ corresponding to each activity group (Min.: Minimum; Max.: Maximum, FDG: Fluorodeoxyglucose, kg/m^2:kilogram/square meter, BMI: Body Mass Index, IQ: Image Quality, NECR: Noise Equivalent count rate)