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^{18}F-Sodium Fluoride (NaF) PET/CT in obese patients on LYSO PET/CT system: Patient dosimetry, optimization of injected activity and acquisition time

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Abstract

Purpose: ^{18}F-Sodium fluoride (NaF) PET/CT has a rapid single-pass extraction and fast clearance from soft tissues resulting in a better target to background ratio. This study aims to establish the optimum acquisition time and dosimetry of ^{18}F-NaF PET/CT to evaluate bone metastases in obese patients. The secondary objective was to evaluate the impact of acquisition time on image quality, lesion detection rate, noise level, and radiation burden in this patient group. **Material and Methods**: A total of sixty patients were included in the study (20 patients with body mass index (BMI) 30-35 kg/m^2, 20 patients with BMI 35-40 kg/m^2, and 20 patients with BMI >40 kg/m^2). Images were acquired after intravenous (IV) injection of 0.06 mCi/kg (2.2 MBq/kg) ^{18}F-NaF. Data was acquired in list mode using ordered subset expectation maximization (OSEM) reconstruction. The raw data could be re-binned to simulate scans with acquisition times of 2, 2.5, and 3-minutes per bed position. Scans were visually analyzed by two observers and scored by rank against a panel of parameters (overall image quality [IQ], noise level, background soft tissue, and lesion detectability), and the contrast-to-noise ratio (CNR) was calculated. **Results**: Mean CNR for OSEM with 2min/bed is 20.19 (±8.39), 2.5min/bed 21.03 (±8.35) and for 3.0min/bed 22.16 (±8.37). There were no statistically significant differences in CNR between different OSEM acquisitions durations (P>0.05). Lesion delineation was excellent and independent of the duration of acquisition. All relevant lesions could be identified with three acquisition settings tested in this study. Patients were injected a mean activity of 215.4±31.3 MBq with estimated mean effective absorbed doses of 4.09±0.59mSv for ^{18}F-NaF PET and 7.88±1.66 mSv for CT alone. **Conclusions:** ^{18}F-NaF PET/CT can be beneficial in obese patients due to its better pharmacokinetics. Optimal osseous staging can be achieved with relatively low doses and radiation burden. Lesion delineation

was excellent regardless of the various acquisition times assessed. However, it is recommended to do 3min per bed position acquisition in patients with BMI >40.

Introduction

Morbid obesity causes many serious health problems, and its prevalence is increasing worldwide. Doubling since 1980, the condition is predicted to affect more than one billion people by the year 2020 (*1,2*). The American Society of Clinical Oncology recently noted that obesity is overtaking tobacco use as the most significant preventable lifestyle risk factor for cancer mortality (*3*). Overweight/obesity contributes to as many as 1 in 5 cancer-related deaths. Historically, imaging for the evaluation of skeletal metastases has mostly been accomplished by using scintigraphy with ^{99m}Tc-MDP. However, the conventional bone scan has certain limitations due to the low quality of obese patients' images secondary to high background soft tissue activity. In bone scintigraphy, image quality is often limited by soft-tissue attenuation and photon scatter caused by overlying fatty tissue. A large amount of fat tissue can entirely obscure the underlying imaged bone (*4*). ^{18}F-NaF PET/CT is superior to conventional planar imaging, especially in obese patients due to its favorable pharmacokinetics, particularly in this group of patients. ^{18}F-NaF PET/CT is less susceptible to artifacts induced by body habitus and retains its image quality and diagnostic confidence. We have previously reported on the advantages and superior diagnostic accuracy of ^{18}F-NaF PET/CT in obese patients to detect bone metastases (*5*). We believe that ^{18}F-NaF PET/CT should be the imaging modality of choice for skeletal staging in obese patients. This study aims to evaluate the impact of acquisition time for ^{18}F-NaF imaging in obese patients to detect bone metastases and optimize protocols, possibly leading to reduced radiation burden.

Material and Methods

Patients

Consecutive obese patients referred for skeletal staging with ^{18}F-NaF PET/CT between April 2018 and October 2019 were included. ^{18}F-NaF PET/CT was performed for (a) routine primary staging/restaging, or (b) when clinical suspicion of bone metastases prompted new imaging workup (e.g., bone pain, elevated tumor marker, suspicious lesions on conventional radiological modality). Cases with missing demographics and scan specific data were excluded from the study. The institutional review board (IRB) approved this retrospective study and the requirement to obtain informed consent was waived.

Body Mass Index (BMI)

Patient height and weight were measured and recorded at the scan time. Based on this information, BMI was calculated as the body weight in kilograms divided by the height in square meters (kg/m^2). Several classifications and definitions for grading obesity are accepted. The WHO criteria for appropriate BMI classification for an Asian population specifies class I obesity (BMI, 30.0 to 34.9 kg/m^2), class II obesity (BMI, 35.0 to 39.9 kg/m^2), and class III or extreme obesity (BMI >40 kg/m^2) (*6*).

^{18}F-NaF PET/CT

Images were acquired after intravenous (IV) injection of 0.06 mCi/kg (2.2 MBq/kg) of ^{18}F-NaF and after a 60 to 90-minute uptake period (*7*). PET emission images were obtained in a three-dimensional mode (3D) time of flight GE Discovery 710 PET/CT system (GE Healthcare) at 3 minutes per bed position from vertex to toes. PET images were reconstructed using ordered subset expectation maximization (OSEM) with point spread function (PSF) modelling protocol algorithm. The standard PET reconstruction algorithm used at our center is time-of-flight (ToF)

OSEM PSF protocol (3 iterations, 32 subsets, 6.4 mm filter). Data were acquired in list mode so that the raw data could be re-binned to simulate scans acquired with 2, 2.5, and 3 minutes per bed position. A non-contrast-enhanced CT was performed using an auto tube current of 50-120 mA determined by an automated algorithm based on the planar scout view in order to achieve a noise index of 20 with a tube voltage of 120 kVp and table pitch of 1.3. Axial CT images were reconstructed in a 512×512 matrix, with a thickness of 2.5 mm. PET, CT, and fusion images were reviewed on a workstation integrated with a PACS on Hermes (Stockholm, Sweden) Hybrid viewer version 2.2.

Image Interpretation and Data Analysis

Qualitative analysis

Visual analyses of the PET images comprising of three reconstructions per case, were performed by two nuclear medicine consultants (designated Scorer 1 and 2 respectively) with experience of more than 8 years. Images were viewed on a Hermes Hybrid viewer version 2.2 Workstation (Stockholm, Sweden). The reconstructions were labeled A to C in a randomized order, with the CT component available for image fusion. Cases were reviewed sequentially and the image quality (IQ) was scored (from 1=excellent to 5=unacceptable) considering: overall IQ, background soft tissue IQ, noise level, and lesion detectability. Scorers also indicated their most and least preferred reconstruction for each case. Inter-rater agreement on ranking within each IQ parameter was assessed using Cohen's kappa statistic.

Quantitative analysis

Contrast-to-noise ratio (CNR) was calculated using the methodology described in the paper by Beijst et al. (*8*). The contrast-to-noise ratio (CNR) is defined as:

$$CNR = \frac{C_H - C_B}{\sigma_B}$$

Where C_H is the mean count or standard uptake value (SUV) value in the target volume of interest (VOI), C_B is the mean count or SUV value in the background VOI, and σ_B is the standard deviation (SD) in the background VOI. The target VOI was a sphere with a diameter of 2 cm (volume 4.2 cm^3) centered in the L3 vertebra. Background spherical VOIs of the same diameter were centered on the right or left psoas muscle at the L3 level.

Lesion analysis

Each site of abnormal radiotracer uptake was graded using a five-point scale (1=definitely benign; 2=possibly benign; 3= equivocal; 4= possibly malignant; and 5=definitely malignant) based on the intensity of uptake, its anatomical location, and morphological features on CT using a standardized reporting system [5]. A score of 1 to 3 was considered negative, and scores 4 and 5 were positive for metastatic disease. Patients were followed every 3-6 months for a minimum of one year after the initial ^{18}F-NaF PET/CT imaging. The composite of follow-up data consisting of clinical examination, tumor markers, and serial radiological follow-up (including ^{18}F-NaF PET/CT, bone scan, ^{18}F-FDG PET/CT and, or CT and MRI studies) was considered as the reference standard.

Patient radiation dosimetry

The effective dose imparted by ^{18}F-NaF (internal exposure) was calculated using coefficient 0.089 mrem/mCi (0.024 mSv/MBq) according to ICRP publication 106 (*9*). The volume CT Dose Index (CTDIvol) (mGy]) and Dose length Product (mGy.cm) were directly obtained from the display screen of the CT workstation to estimate the effective dose from whole-body CT scan (external exposure). The estimated effective dose was calculated by multiplying DLP (mGy.cm) with ICRP conversion coefficient "k" 0.015 [mSv/(mGy.cm)] (*10*).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (Chicago, IL, USA). Results were presented as mean ± standard deviation (SD). Analysis of variance (ANOVA) was used to test the significance of the differences between the reconstructions. Post-hoc testing was done by Tukey HSD to determine whether there is a difference between the mean of all possible pairs using a studentized range distribution. P values less than 0.05 were considered to be significant. Cohen's weighted kappa coefficient was used to calculate agreement between reviewers. The possible range of weighted kappa values is from −1 (complete disagreement) to +1 (perfect agreement) and is corrected to eliminate agreement expected by chance alone. Kappa was classified as follows (*11*): 0, chance agreement; <0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; 0.81–1.00, very good agreement. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for ^{18}F-NaF PET/CT based on the true positive and true negative findings together with exact 95% confidence intervals (CI).

Results

A total of sixty patients were included in the study (20 patients with BMI 30-35 kg/m^2 [Class I], 20 patients with BMI 35-40 kg/m^2 [Class II] and 20 patients with BMI >40 kg/m^2 [Class III]). Relevant clinical data are summarized in Table 1.

In all patients, ^{18}F-NaF PET/CT images showed high tracer extraction with low soft tissue and background activity across the range of imaged BMI categories and none of the scans were categorized as suboptimal for diagnostic reading. In the majority of cases (63% and 57% by Scorers 1 and 2 respectively), both scorers chose OSEM 3.0 min as their most preferred reconstruction. In Inter-rater agreement are mentioned in Table 2.

The results of the qualitative analysis of image quality (IQ) with different OSEM reconstructions is described in Table 3. The study did not reveal statistically significant differences in overall image quality (IQ) and individual IQ parameters (noise level, background soft tissue, and lesion detectability) among the group I (BMI 30-35) and group II (BMI 35-40) (Figure 1 and Figure 2). In Group III (BMI > 40), a statistically significant difference in noise level scores was observed ($P<0.001$), with lower noise for the OSEM 3.0 min acquisition, while other individual IQ parameters (background soft tissue and lesion detectability) showed similar scores (Figure 3). The lesion delineation was excellent regardless of the acquisition time. All relevant lesions could be identified at all three acquisition times.

The mean CNR for OSEM 2 min was (20.19±8.39), OSEM 2.5 min (21.03±8.35), and for OSEM 3.0 min (22.16±8.37). There was no statistically significant difference in CNR between the different OSEM reconstructions ($P=0.4$) for any BMI groups, as summarized in Table 4.

^{18}F-NaF PET/CT was graded as definitely benign in 21, possibly benign in 8; equivocal in 2; possibly malignant in 4 and malignant in 25 patients. The diagnostic test characteristics of ^{18}F-NaF PET/CT were as follows: sensitivity 96.6% (95% CI 82.2 – 99.9%), specificity 96.8% (95% CI 83.3 – 99.9%), PPV 96.6% (95% CI 80.3 – 99.5%), NPV 96.8% (95% CI 81.4 – 99.5%) and accuracy 96.7% (95% CI 88.5 – 99.6%).

Patients were administered a mean activity of 215.4±31.3 MBq resulting in an estimated mean effective absorbed dose of 4.09±0.59mSv for ^{18}F-NaF PET and 7.88±1.66 mSv for CT alone. The mean cumulative effective dose of ^{18}F-NaF PET/CT scan was 11.9±2.08 mSv. The average activity and effective dose of ^{18}F-NaF PET among the different BMI subgroups are mentioned in Figure 4.

Discussion

Many studies in the literature demonstrate that the patient's BMI can alter image quality (*12*). In obese patients, image noise is increased because fewer photons are collected, and the increased attenuation correction factors amplify noise. Radiological and nuclear medicine investigations in patients with high BMI can therefore be challenging. Some authors suggest that a higher administered activity per kilogram should be used for a better quality image. The detectability of low-contrast features in PET scans depends on count statistics, which rely on various factors, including the efficiency of the scanner, administered activity, uptake time, acquisition time, and patient size. Increasing the administered activity is less effective at improving image quality than the same proportional increase in acquisition time (*13*). Advances in PET hardware and software in the last two decades have led to a significant increase in the sensitivity of PET scanner systems (*14*), and optimal quality images can be acquired with lower injected activities. The impact of reducing acquisition time on image quality or lesion detectability can be investigated by acquiring data in list mode so that the raw data can be re-binned to simulate scans acquired with reduced acquisition times (*15,16*).

^{18}F-NaF PET/CT has proved to be an excellent bone-seeking agent. Due to high bone uptake, minimal binding to serum proteins, rapid single-pass extraction, and fast clearance from the soft tissues, (*17,18*) allows a shorter time interval between injection and imaging (*19*). The improved bone-to-background ratio and the higher spatial and contrast resolution of ^{18}F-NaF PET/CT lead to better delineation of bone lesions. Ohnona et al. (*20*) suggested that the dose of ^{18}F-NaF may be lowered up to the half of the recommended dose without significant untoward effect on image quality; with such reduction of injected activity, the effective dose of ^{18}F-NaF would be equal to or less than that of ^{99m}Tc-MDP.

The current study aims to evaluate the overall impact of varying acquisition times of ^{18}F-NaF PET by using modern 3-dimensional and ToF function to provide optimum acquisition parameters in obese patients and, in turn, the impact of acquisition time on image quality, lesion detection rate, noise level and soft-tissue uptake of ^{18}F-NaF in this patient group. Patient data was investigated using list-mode acquisition to obtain comparable 2, 2.5, and 3-min frames. Qualitative and quantitative analysis showed that image quality was excellent regardless of the various acquisition times assessed. All relevant lesions could be identified on all three acquisition times. There was no difference in contrast to noise ratio among shorter and longest acquisition time, and acquisition time did not seem to significantly influence lesion detection rates. Most importantly, the current study results demonstrate that it is clinically feasible to reduce acquisition times from 3 to 2 min per bed position in Class I and Class II obese patients. Our study shows that, OSEM reconstruction using 3 min/bed has a relatively higher CNR but this was not statistically significant in BMI >40 (P=0.20), indicating that image quality was only slightly adversely affected by the shorter acquisition time in extremely obese patients. There was however significant improvement on visual assessment of image noise when using the 3 min/bed acquisitions in this group (P=0.001). Perhaps a higher acquisition time (3 minutes) should therefore be preferable in this group (Figure 3).

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines (*21*) suggest a fixed activity of 5-10mCi of ^{18}F-NaF for adults. The European Association of Nuclear Medicine (EANM) (*7*) guidelines suggest 1.5–3.7MBq / kg in adults with a maximum recommended dose of 10 mCi for obese. Our center has adapted a low injected activity protocol for ^{18}F-NaF PET by injecting 2.2 MBq/kg (0.06mCi/kg) of ^{18}F-NaF for patients in all BMI groups, which is relatively low compared to the usual injected activity of 5-10mCi. Recently published

data from our group showed that a good quality adult scan could be achieved with as low as 0.06mCi/kg of ^{18}F-NaF (*22*). The current findings suggest that ^{18}F-NaF activity can potentially be lowered further in prospective trials reducing the radiation burden even below that of ^{99m}Tc-MDP dose levels.

In our study, the mean effective absorbed ^{18}F-NaF PET was calculated at 4.09±0.59 mSv, comparable with ^{99m}Tc-MDP bone imaging. The typical value for an effective dose of an1110 MBq ^{99m}Tc-MDP bone scintigraphy in an obese adult is around 6.32 mSv. Similarly, Lim et al. (*23*) reported that the radiation dosimetry for ^{18}F-NaF PET is similar to ^{99m}Tc-MDP imaging. The diagnostic quality ^{18}F-NaF imaging can be effectively performed using overall less administered activity than ^{99m}Tc-MDP (*7*).

Our clinical experience shows that ^{18}F-NaF PET/CT is less susceptible to artifacts induced by body habitus and retains its image quality even in patients with high BMI. In our study ^{18}F-NaF PET/CT had excellent diagnostic test characteristics for the detection of bone metastases, with similar results were reported by Jambor I. et al. (*23*). ^{18}F-NaF PET/CT is a sensitive tool for detecting skeletal metastases and is more sensitive and specific in evaluating osteoblastic metastases and has less equivocal findings (*24*).

Our study has some limitations; scans were performed on a highly sensitive LYSO PET/CT system using TOF which may not be ubiquitously available. The high-resolution reconstruction protocol used includes point spread function modelling, which generated relatively smoother images with low noise characteristics. Also, the OSEM reconstruction settings were not changed for the simulated acquisition times per bed position. Further work needs to be repeated with different scanner technology types and other reconstruction protocols in obese populations to further validate these results.

Conclusions

^{18}F-NaF PET/CT facilitates high-quality imaging in obese patients. Healthcare institutions should consider ^{18}F-NaF as an imaging agent of choice for detecting metastasis in this patient group. ^{18}F-NaF PET/CT retains its image quality in patients with a high BMI even with a lower injected activity 2.2 MBq/kg (0.06mCi/kg) and reasonable acquisition time (2-3 min/bed). ^{18}F-NaF PET/CT is less susceptible to artifacts secondary to obesity, and dedicated protocols are not required for morbidly obese patients. Moreover, our results suggest that further reductions in administered activities are possible with the current generation of PET/CT devices.

Disclosures

No potential conflict of interest relevant to this article was reported.

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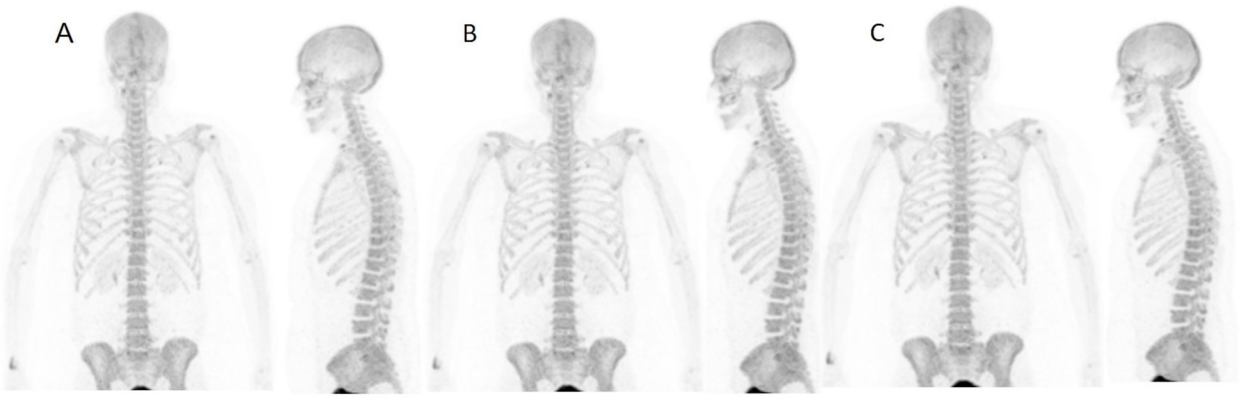

FIGURE 1. 44-years old female, class I obesity with BMI of 32.4kg/m^2. Anterior and lateral MIP ^{18}F-NaF PET images with reconstructions using a different acquisition time per bed. a) OSEM 2 min b) OSEM 2.5 min c) OSEM 3 min. On visual analysis, there is no difference in image quality among different image acquisition times.

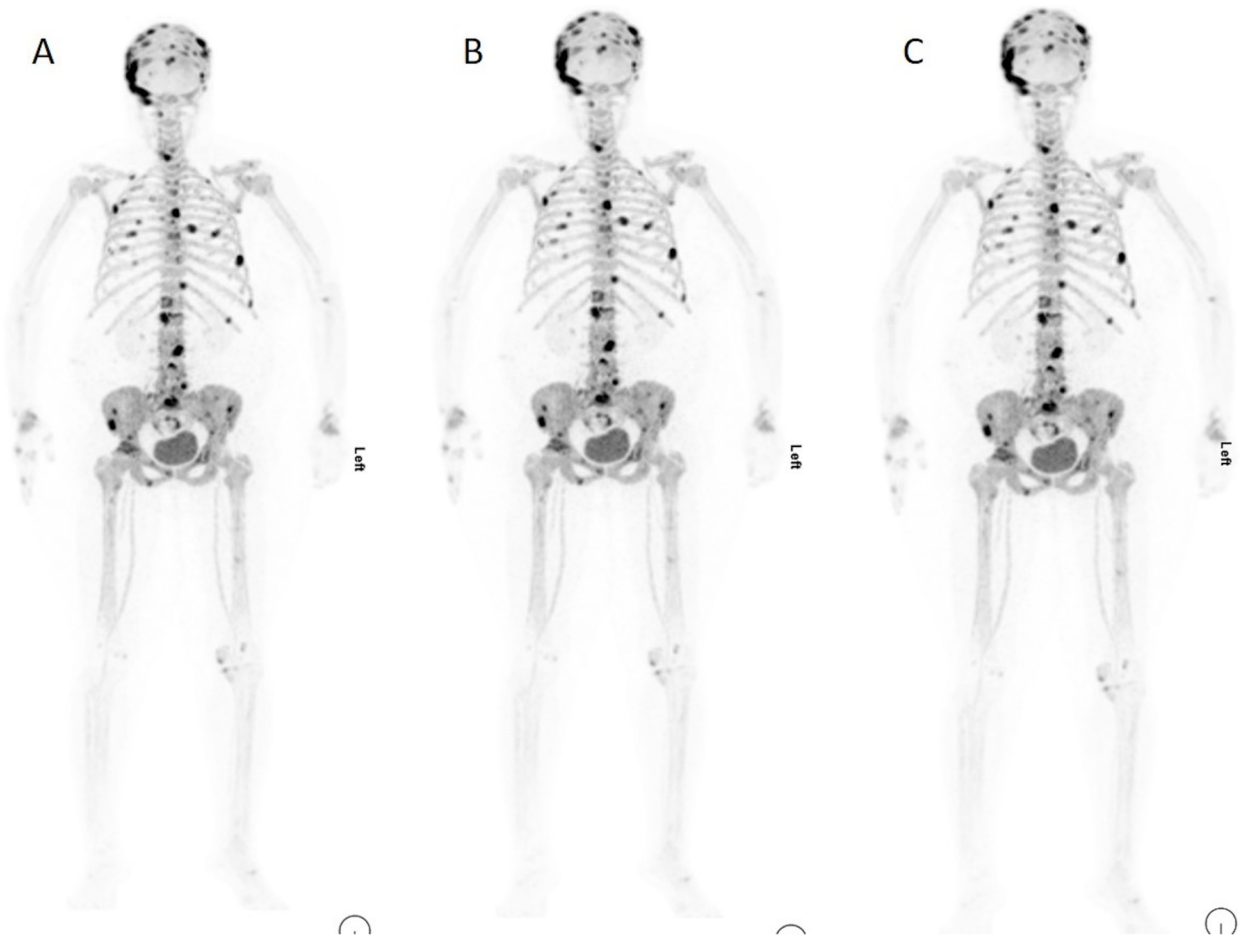

FIGURE 2. 60-years old female, class II obesity with BMI of 38.6 kg/m^2. Anterior MIP ^{18}F-NaF PET images with different time per bed reconstructions. a) OSEM 2 min b) OSEM 2.5 min c) OSEM 3 min. There is no difference on visual analysis in overall image quality and lesion detection, among the different time acquisition.

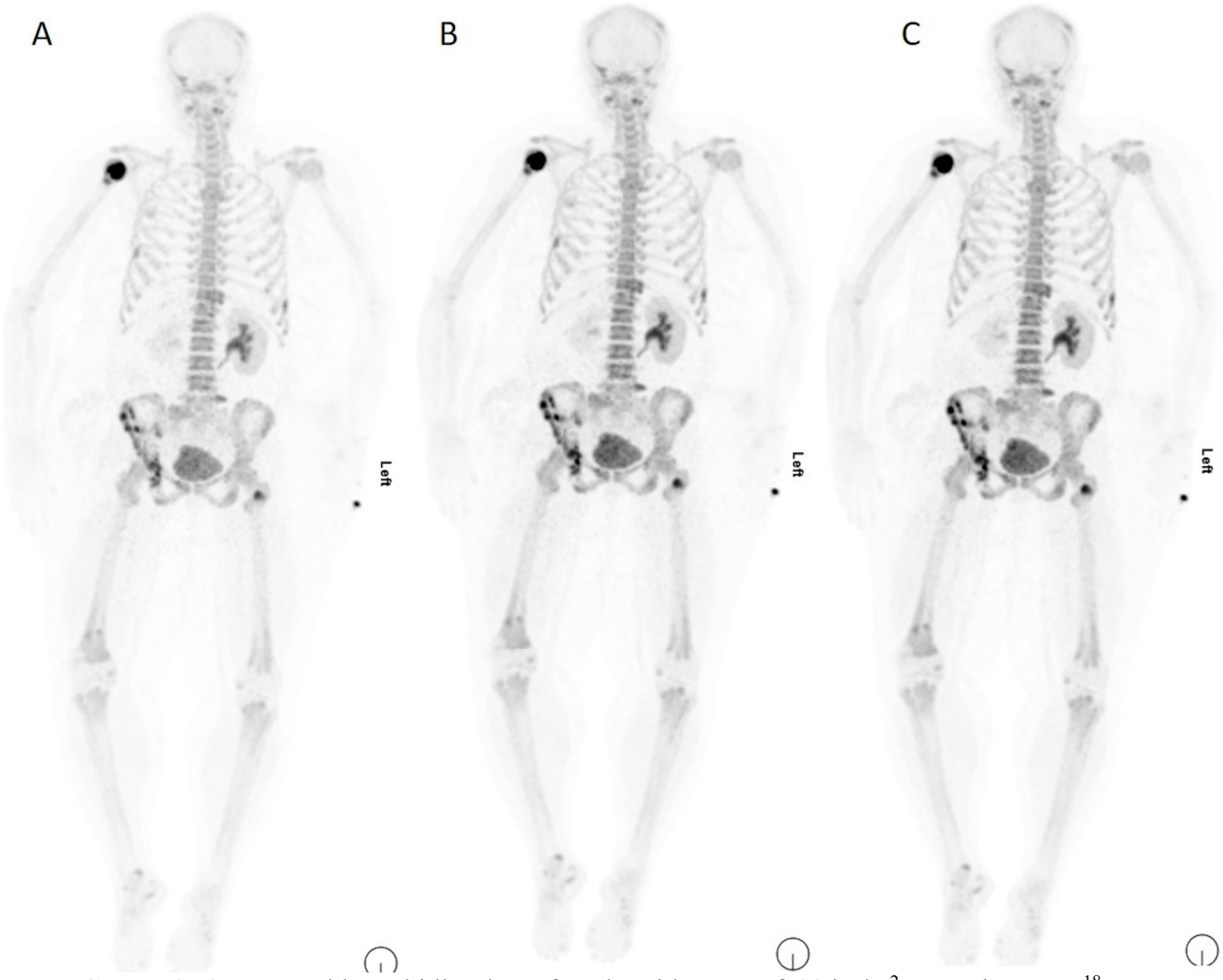

FIGURE 3. 45-years old morbidly obese female with BMI of 44 kg/m^2. Anterior MIP ^{18}F-NaF PET images with different time per bed reconstructions. a) OSEM 2 min b) OSEM 2.5 min c) OSEM 3 min. The visual analysis shows a noise gradient decrease from images (a-c). The readers considered image reconstruction (c) to have the best clinical information and quality at the lowest noise level.

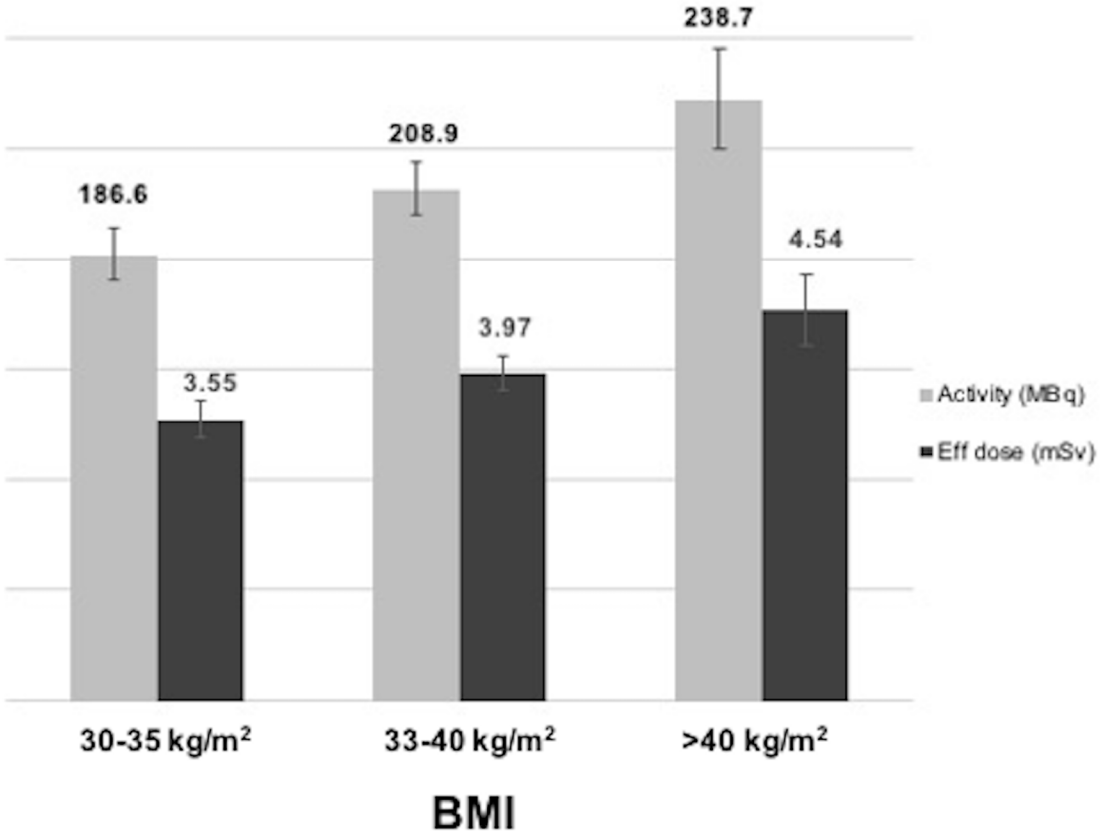

FIGURE 4. Average dose and effective dose of ^{18}F-NaF among the different BMI subgroups.

Table 1: Patient characteristics.

	Mean (SD) / Frequency
Mean Age	58.5±10
Injected activity (MBq)	215.4±31.3
Female:Male	53:7
Weight (kg)	97.8±15.2
BMI (kg/m^2)	39.33±5.84
Uptake time	62.16±12.1 min
Dose length product (DLP)	525.4±111.2 (mGy.cm)
Effective Dose	
^{18}F-NaF	4.09±0.59
Computed tomography	7.88±1.66
Cumulative Dose	11.9±2.08
Primary Tumor	
Breast Cancer	51
Prostate Cancer	7
Others	2

Table 2: Inter-rater agreement of IQ parameters with different OSEM reconstructions.

Parameter	Highest Rank reconstruction		Agreement	Kappa	P value
	Scorer 1	Scorer 2			
Overall IQ	OSEM 3.0 (63%)	OSEM 3.0 (57%)	moderate	0.644	<0.001
Background soft tissue	OSEM 2.5 (57%)	OSEM 3.0 (50%)	poor	0.200	0.118
Noise level	OSEM 3.0 (80%)	OSEM 3.0 (87%)	moderate	0.762	<0.001
Lesion detectability	OSEM 3.0 (50%)	OSEM 3.0 (52%)	moderate	0.749	<0.001

Table 3: Qualitative analysis of image quality (IQ) parameter with different OSEM reconstructions. The IQ parameter was scored (from 1=excellent to 5=unacceptable).

	Sum score Overall IQ				**Sum score Background**				**Sum score Noise level**				**Sum score Lesion detectability**			
OSEM	**2.0**	**2.5**	**3.0**	**P value**	**2.0**	**2.5**	**3.0**	**P value**	**2.0**	**2.5**	**3.0**	**P value**	**2.0**	**2.5**	**3.0**	**P value**
BMI 30-35	23	20	20	0.07	22	20	20	0.18	30	21	20	0.87	22	20	20	0.18
BMI 35-40	21	20	20	0.44	26	21	21	0.85	35	23	21	0.65	20	20	21	0.44
BMI >40	30	24	20	0.22	30	23	20	0.39	40	33	22	0.001*	22	20	20	0.18
All BMI	74	64	60	0.41	78	64	61	0.45	105	77	63	0.001*	64	60	61	0.07

*Statistically significant

Table 4: Contrast to noise ratio between the different OSEM reconstructions.

Contrast to noise ratio	**OSEM (2.0min)**	**OSEM (2.5min)**	**OSEM (3.0min)**	**P value**
BMI 30-35	24.62±9.87	25.13±8.88	25.74±9.07	0.92
BMI 35-40	17.08±7.06	17.53±7.92	18.16±6.98	0.88
BMI >40	18.88±6.21	20.42±6.63	22.58±7.50	0.20
All BMI	20.19±8.39	21.03±8.35	22.16±8.37	0.40

Graphical Abstract