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VARIABILITY OF [^{18}F]FDG ADMINISTERED ACTIVITIES AMONG PATIENTS UNDERGOING PET EXAMINATIONS: AN INTERNATIONAL MULTICENTER SURVEY

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Given the large number of [^{18}F]fluorodeoxyglucose (FDG) PET examinations performed annually throughout the world, reduction of the administered activity without compromise of the clinical information being sought is encouraged. Guidelines issued by the SNMMI and European Association of Nuclear Medicine (EANM) differ greatly on the choice of the activity that should be administered to patients: the EANM suggests a personalised activity based on the patient's body weight, whereas the SNMMI recommends the administration of fixed activities. The authors analysed a database of 24 716 [^{18}F]FDG administrations performed worldwide in 15 PET centres to assess the degree of heterogeneity, in relation to available technology, operational protocols and reference guidelines. Median activities based on the patients' body weight were 43 % lower than fixed-activity administrations ($p < 0.001$). When TOF scanners are available, the median activity is lowered, but when comparing centres with the same technology or those that use the same operational protocols, weight-based activities are still significantly lower than fixed activities.

INTRODUCTION

Positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG) is an important diagnostic tool used for staging, prognosis, treatment monitoring and follow-up of several oncological diseases(1), as well as the assessment of infectious and inflammatory diseases(2).

As with any diagnostic test that exposes patients to ionising radiation, the operational protocols of PET represent a compromise between opposing needs, which is image quality versus limitation of the effective dose to patients and operators. Accurate PET diagnostic results can be obtained either with the administration of high [^{18}F]FDG activity, high radiation exposure and short scanning time or with the administration of low [^{18}F]FDG activity, low radiation exposure and long scanning time, with increased risk of motion artefacts. In clinical settings, one must therefore balance the effective radiation dose to the patient and the scanner workflow, as well as the capacity of the patients to lay on the scanner bed for the duration of the examination.

Since the large number of PET examinations performed annually worldwide significantly contributes to the progressive increase of the radiation dose to the patients and to the operators, any action to reduce the administered radioactivity should be actively sought. This is particularly important considering that often PET examinations are conducted on patients suffering from curable diseases, in whom the monitoring of the disease after treatment requires further diagnostic imaging procedures that entail the exposure to ionising radiation.

In nuclear medicine, diagnostic reference limits (DRLs) guide clinicians as to the appropriate administered activities to achieve diagnostically reliable images under most conditions and for most patients; administered activities deviating from the relevant DRLs therefore warrant justifications(3). Member States of the European Commission have defined the DRLs related to some diagnostic tests with radiopharmaceuticals, but, at this time, no DRL for [^{18}F]FDG PET has been defined; to this end, some authors have conducted surveys of local practices as a basis for proposing DRL for PET(4).

In clinical practice, the information on [^{18}F]FDG uptake is most frequently expressed as Standardized Uptake Value (SUV), a variable that provides an index of metabolic function derived from the concentration of the radiopharmaceutical in a region or voxel of interest, normalised to the injected activity. The simplicity and versatility of the SUV make it suitable for clinical practice, as it does not require any arterial blood sampling, which is required instead when quantification of glucose metabolism is sought(5). The net activity administered may be obtained by measuring, with a dose calibrator, the activity of the syringe containing the radiopharmaceutical before and after the administration to the patient. However, this procedure results in a greater exposure of the personnel involved, in addition to the risk of environmental contamination and accidents during handling of syringes with exposed needles.

Current guidelines of the EANM for [^{18}F]FDG PET in oncology and in inflammatory disease[6, 7] recommend the administration of radiopharmaceutical activity that is linearly related to the weight of the patients and in accordance with the physical characteristics of the scanner used. According to these guidelines, PET examinations can be performed after the administration of as little as 185 MBq of [^{18}F]FDG, which is associated with an effective dose of 3–4 mSv[8]. Unlike the administration of a fixed amount of radiopharmaceutical, the personalisation of a radiopharmaceutical activity proportional to the patient's body weight helps to obtain comparable concentrations of the radiopharmaceutical in tissues and substantially similar quality of the images among different patients, under the same scanning conditions and for the scanner type. Some authors have found, however, that, at least in the paediatric population, a linear relationship between administered activity and body weight can lead to insufficient counting statistics[9]. More recently, other authors have shown that the use of a quadratic relationship further improves the counting statistics in obese patients and results in greater consistency in the signal-to-noise ratio regardless of the patient weight[10]. On the other hand, other guidelines, such as those of the SNMMI, do not explicitly suggest the need of a personalised administered activity based on individual patient characteristics but indicate rather a generic range of activities to be administered[6, 11], chosen according to the performance characteristics of the scanner, apparently prioritising counting statistics and image quality in relation to the scanner used without explicit concern for the patient's radiation exposure.

The aim of this work was to assess the degree of heterogeneity in the administered activity when performing [^{18}F]FDG PET examinations performed in Europe, Australia and the USA and analyse it in relation to the available technology, operational protocols and reference guidelines in the different participating centres and to provide an estimate of exposure of the dose received by the patients and to evaluate whether the administration of a weight-based activity of [^{18}F]FDG is associated with a different radiation exposure in comparison with a fixed-activity protocol.

MATERIALS AND METHODS

A database of 24 716 [^{18}F]FDG injections performed in 15 centres was collected. Participating PET sites included large institutional hospitals and outpatient clinics in the USA (no. 8), Europe (no. 4) and Australia (no. 3), where an MEDRAD® Intego system (Bayer Medical Care, Inc., Indianola, PA, USA) was available. This device allows injection of the prescribed amount of radiopharmaceutical with an error of only 0.77 % with a residual activity remaining in the system corresponding to 0.07 % of the activity delivered[12]. This system has an option, called weight-based dose (WBD), which enables the calculation of the activity to be administered as a function of the body weight of the patient, using a linear factor that can be set by the user. When this option is enabled, the user enters only the weight of the patient, which is recorded in the database. The system records also the prescribed activity and the activity measured by the system just before its injection into the patient (delivered activity). The delivered activity was used in this analysis.

The effective doses received by the patients when performing a PET scan were estimated using the [^{18}F]FDG dose conversion factors proposed by the ICRP[13].

Data were provided by Bayer Medical Care in anonymous form. Through a questionnaire, each centre provided information on the available scanners, the time interval between administration and image acquisition (uptake time), the duration of the acquisition (time per bed position and axial anatomical scan coverage of the standard examination) and guidelines followed in the choice of the activity to be administered.

Univariate statistics and comparison of populations were performed using non-parametric tests, given the non-Gaussian distribution of administrations, using the statistical software R (R Foundation for Statistical Computing, Vienna, Austria).

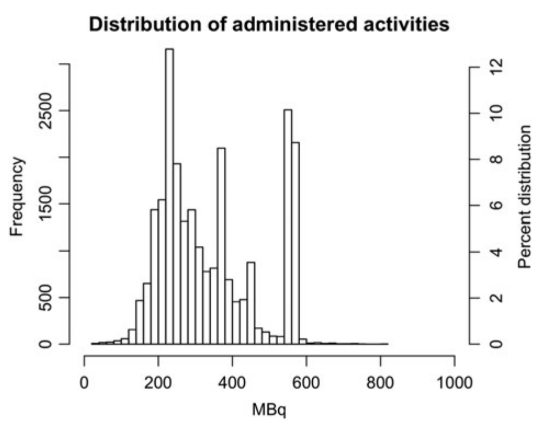

Figure 1. Frequency distribution of [^{18}F]FDG administered activities in 24 716 PET examinations. Each bar represents the number of injections within a 20 MBq range.

RESULTS

The average activity of [^{18}F]FDG administered to patients during the execution of 24 716 PET examinations was 340.3 $\pm$ 133.9 MBq (mean $\pm$ SD) (Figure 1). The distribution of the administered activity differs from the normal distribution (Kolmogorov–Smirnov test, $p < 0.001$); therefore, the data are described by measuring median and quartiles (Q1 is lower quartile, and Q3 is upper quartile). The median of the administered activities was 300.7 MBq (Q1 = 230 MBq, Q3 = 439.2 MBq, range 36.2–814.0 MBq).

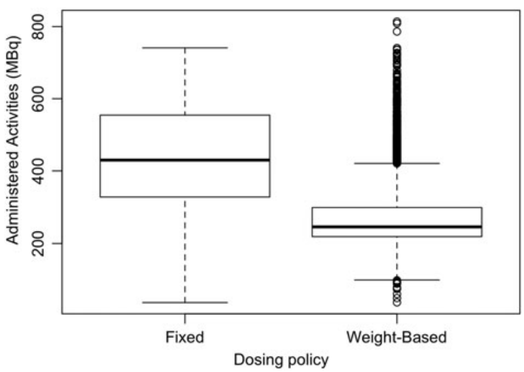

Figure 2. Box-and-Whisker plots of [^{18}F]FDG administered activities in fixed regimen and in weight-based regimen. The dark line inside the box represents the median; top and bottom of the box represent upper and lower quartiles, respectively. Dashed lines extending outside the box represent variability outside the upper and lower quartiles. Circles represent outliers. On the left is the plot of the distribution of 11 893 fixed administrations; on the right is the distribution of 12 823 injections based on the weight of each patient.

When the MEDRAD® Intego system was used in the WBD mode, the 12 823 recorded administrations had a median of 246.1 MBq (Q1 = 219.0 MBq, Q3 = 299.7 MBq, range 36.7–814 MBq), compared with a median of 429.8 MBq (Q1 = 328.9, Q3 = 554.5 MBq, range 36.2–741.0 MBq) of 11 893 injections performed with the equipment in the fixed-activity mode (Figure 2). The difference of the medians is statistically significant (Mann–Whitney test, $p < 0.001$). The distribution of delivered activities (Figure 3) based on the patients' body weight is unimodal (as is the distribution of the weight in the population); in contrast, on the histogram of the distribution in the fixed-activity regimen, some peaks of frequent activities are detectable coinciding with activities of ~555 MBq (no. 1483 administrations, 6.0 % of the total, with administered activity equal to 555 MBq, and 4615 administrations, 39 % of the total, in the range 550–580 MBq) and 370 MBq (no. 1144 administrations, 4.6 % of the total with administered activity equal to 370 MBq, and 1816, 15.3 % of the total, in the range 360–380 MBq).

The different operating protocols adopted in the participating centres resulted in widely varying uptake times, between the administration of [^{18}F]FDG and the start of the PET acquisition. Uptake times ranged between a minimum of 50 min and a maximum of 90 min. For the analysis, the authors considered uptake times up to 60 min as standard (21 468 administrations)

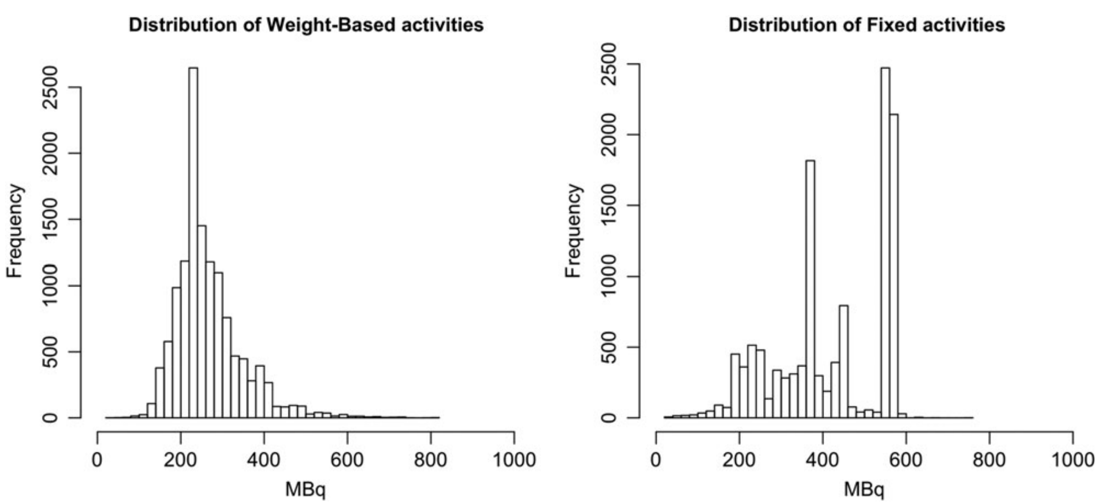

Figure 3. Frequency distribution of administered activities. Left: distribution of doses in 12 823 injections, performed on the basis of each patient's body weight. Right: distribution of 11 839 injections in the fixed regimen. Peaks are clearly seen, ~555 and 370 MBq, which are activities typically used in the fixed regimen. Other injections are distributed in a range between 37 and 700 MBq.

and long uptake times those >60 min (3248 administrations). The median of the administered activity was 279.7 MBq (Q1 = 228.9 MBq, Q3 = 369.4 MBq, range 36.2–814.0 MBq) in the centres with standard uptake time and 569.3 MBq (Q1 = 445.0 MBq, Q3 = 572.7 MBq; range 50.5–590.2 MBq) in the centres where a longer uptake time was used (difference on the medians + 103 %, $p < 0.001$, Figure 4).

Based on the characteristics of the scanners, the duration of each position of the bed varied between 1 and 4 min. The data were grouped into two categories: short (<2.5 min, 13 054 injections) or long acquisition time (≥2.5 min, 11 662 injections). The median of administered activity with short acquisition time was 247.0 MBq (Q1 = 217.8 MBq, Q3 = 332.1 MBq, range 36.2–554.5 MBq), compared with 441.8 MBq (Q1 = 291.7, Q3 = 555.0 MBq, range 46.8–814.0 MBq) in the centres with long acquisition time (+79 %, $p < 0.001$).

According to the available technology, the data were divided between injections in patients who had a PET examination with a Time-of-Flight (TOF) or a conventional (non-TOF) scanner. As a centre had both a TOF and a non-TOF scanner available and from the database it was not possible to differentiate the administrations depending on the equipment used, the data from this centre (3154 administrations) were excluded from this part of analysis. The median of administered [^{18}F]FDG activities in 7785 patients in whom the examination was performed with a non-TOF scanner was 552.1 MBq (Q1 = 370.4, Q3 = 567.0, range 46.8–736.4 MBq), compared with 243.8 MBq (Q1 = 213.0 MBq, Q3 = 309.7 MBq, range 36.2–814.0 MBq) in 13 777 patients who had the examination in a TOF scanner (difference 126 %, $p < 0.001$, Figure 5). The authors did not detect any correlation between the administered activity and the age of the available scanner (Figure 6).

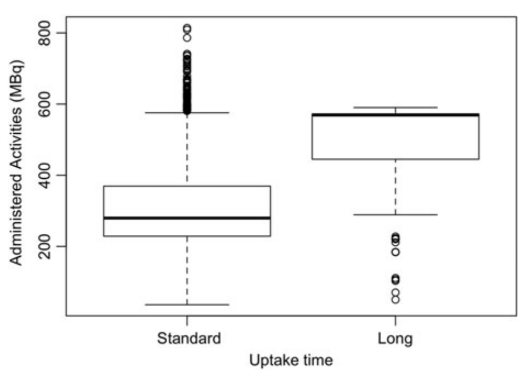

Figure 4. Box-and-Whisker plot of administered [^{18}F]FDG activities stratified by uptake time. Left: standard uptake time (up to 60 min). Right: uptake time longer than 60 min.

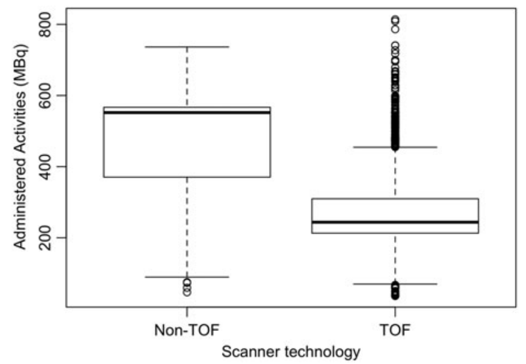

Figure 5. Box-and-Whisker plot of the distribution of [^{18}F]FDG administered activities in relation to scanner technology. The use of TOF scanner is associated with lower doses.

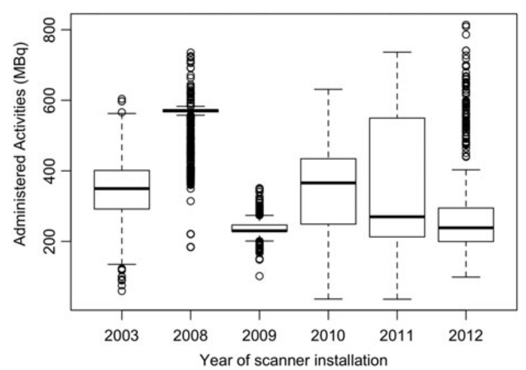

Figure 6. Box-and-Whisker plot of the distribution of [^{18}F]FDG administered activities in relation of scanner age. No correlation was found between the activities and then scanner obsolescence.

The authors also compared the effective doses received by the patients when performing a PET scan with the injection of a fixed or a weight-based activity in comparable conditions of available scanner technology and operational procedure. Regardless of the available technology, when the administrations are personalised based on the weight of the patient, the effective dose is lower in comparison with a fixed-activity regimen. The reduction ranges between 18 and 46 %, in relation to the characteristics of the scanner and duration of the scan. The difference is statistically significant (Table 1).

DISCUSSION

In this study, the authors analysed the records of the administration of [^{18}F]FDG of nearly 25 000 examinations performed in 15 centres on 3 continents, using an automatic injector allowing the fractionation and injection of individual patients activities from a

Table 1. Median of administered activities in patients as function of scanner technology and duration of PET exam. *p*: result of Mann–Whitney test.

Technology	Acquisition time per bed position	Fixed regimen			Weight-based regimen			*P*
		No.	Delivered activity (MBq)	Effective dose (mSv)	No.	Delivered activity (MBq)	Effective dose (mSv)	
Non-TOF	Long (>2 min)	5016	556	11.1	1271	378	7.6	<0.001
	Short (≤2 min)	1498	368	7.4	0			n.a.
TOF	Long (>2 min)	1020	442	8.8	1201	238	4.8	<0.001
	Short (≤2 min)	4353	281	5.6	7203	230	4.6	<0.001

single vial containing up to 27.75 GBq of radiopharmaceutical. Each PET centre decides the administration regimen according to the characteristics of the PET scanner available and the operational procedure used (time of uptake, duration and axial extent of the scan, reference guidelines). The SNMMI and the EANM have issued procedural guidelines for the use of PET in oncology and in inflammatory and infectious diseases. These guidelines differ greatly on the choice of the activity to be administered to the patient. In particular, whereas the SNMMI suggests a range of activities(6, 11), the EANM recommends dosing based on the weight of the subject(6, 7). In accordance with these guidelines, differences among PET centres following different guidelines can be expected and were previously reported(14). However, the limited number of participating centres in the present analysis does not allow making inferences about practices at the continental level.

In addition to the reference guidelines, other factors underlie the wide variability in the choice of administered activity. The different sensitivity of the scanners available in participating centres is associated with acquisition times that vary between 1 and 4 min for each bed position. State-of-the-art TOF scanners allow completion of a total body examination (from the head to the root of the lower limbs) in <10 min compared with ~30 min generally required when less-sensitive equipment is used. On the other hand, shorter acquisition times can be performed even with less-sensitive scanners, if it is decided to increase the activity administered to the patient. In fact, the authors found that some centres perform fast scans with non-TOF scanners, and the effective dose received by the patients is 31 % higher than the dose received by patients that perform the examination on a TOF scanner.

The authors found that in 13 % of the authors' sample, a long delay between the administration of [^{18}F]FDG and the acquisition was applied. This can be used to differentiate between malignancy and inflammatory or infectious diseases and to enhance the specificity of [^{18}F]FDG PET imaging in oncology(15). In this case, images are acquired later than the standard 60-min uptake time, and this justifies the administration of higher activities of ^{18}F. Theoretically, the administered activity should be increased by 17 %, when the images are acquired after 90 min in comparison with a standard uptake time of 60 min, to achieve the same counting density. The authors observed that the median of administered activities in the centres applying uptake times up to 90 min was 103 % higher than the median administered activities in the centres with standard uptake time; thus, the higher administered activity is not due only to the correction for the decay of the isotope.

In this work, the authors have also shown that, regardless of the available technology and acquisition time, the choice of personalising the injections with the body weight of the patient is associated with the administration of significantly lower activities. The advantages of customising the activity are several: first, it ensures constant signal-to-noise ratio in all patients, regardless of individual characteristics; this is particularly important in the case of cancer patients who are often subjected to repeated PET scans at different stages of the disease when, with the progression of the disease, body mass can vary considerably. Furthermore, the administration according to the weight ensures less radiation exposure on an individual basis for patients and in the effective dose received by the operators. From the data obtained in this study, the effective dose per patient varies between 4.6 and >11 mSv, depending on the available technology and the policy chosen for the determination of the activity to be administered. In addition, the European directives require the optimisation on an individual basis of diagnostic procedures that expose patients to radiation and recording of activity administered individually(16).

It should however be noted that even when the injections were performed with the WBD mode disabled, besides the sharp peaks related to the administration of some standard fixed activity, the distribution of administered activities presents a continuum, which is the expression of the fact that the operator has adapted a generally fixed activity to some individual characteristics of the patient that cannot be deduced from the available data. Moreover, the administration of higher activities is associated with higher quality images, but the analysis of the images or the results of the examinations was not among the aims of this work.

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