A survey of PET activity in Germany during 1999

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Abstract. Positron emission tomography (PET) is the most powerful molecular imaging technique currently available for clinical use. The aim of this study was to provide public health information on PET procedures carried out in Germany – a country with a very high number of PET installations. To this end, all facilities that in 1999 were running at least one dedicated PET system were contacted and requested to provide information in a questionnaire on the radiopharmaceuticals applied, the total number and age distribution of patients and volunteers examined, the main diagnostic applications and the range of administered activities. Based on the information provided by 48 of the 60 PET facilities in Germany, an annual frequency of about 0.34 PET procedures per 1,000 inhabitants was estimated, associated with an annual per capita effective dose of about 1.9 µSv. Averaged over all PET procedures, the mean effective dose to patients was 5.6 mSv. The age distribution of patients and volunteers was skewed markedly towards higher ages; only a very small fraction (<3%) of patients were children younger than 15 years while older patients, and especially those in the age group between 41 and 65 years, were overrepresented relative to the general population. In total, 28 different PET radiopharmaceuticals were used, with only half of these having been administered to more than 20 patients each. The most frequently applied radiotracer was the glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), which was utilised in more than 84% of all PET procedures. For this tracer, the median value for activities applied for examinations in the three-dimensional (3D) acquisition mode was only half of that used for two-dimensional (2D) measurements. Based on a statistical analysis of the distribution of mean FDG activities administered to patients in the 48 PET facilities who responded to our inquiry, diagnostic reference levels of 370 and 200 MBq are proposed for the 2D and the 3D mode, respectively.

Keywords: Positron emission tomography – Radiopharmaceuticals – Frequency of application – Radiation exposure – Diagnostic reference levels

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Introduction

Positron emission tomography (PET) is "an analytical imaging technology developed to use compounds labelled with positron-emitting radioisotopes as molecular probes to image and measure biochemical processes of mammalian biology in vivo" [1]. Its broad scope, flexibility and sensitivity make it the most powerful molecular imaging technique currently available for clinical use. On the basis of advanced measurement and evaluation techniques and the large number of available physiological, biochemical, pharmacological or molecular biological probes, PET can be used to image key biomedical functions in vivo both under basal conditions and during diverse pharmacological or physiological stimulations. It is thus an established tool for use in patient-related clinical research and is increasingly used in pharmaceutical research and development.

Moreover, PET has gained increasing clinical acceptance, which is reflected by the presence of an increasing number of PET installations in hospitals and even in private practices. In Germany, the clinical value of PET has been evaluated by different panels of recognised experts within the framework of interdisciplinary consensus conferences. Based on these evaluations, clinical indications for the application of PET in oncology [2, 3, 4, 5], cardiology [6], and neuromedicine [7] have been established.

Although positron-emitting isotopes – including the short-lived isotopes carbon-11, nitrogen-13, oxygen-15 and fluorine-18 – have been incorporated into several hundred potentially useful compounds during the last three decades, only a limited number of PET radiopharmaceuticals are presently considered to be of major interest [8]. The most frequently applied radiotracer in clinical routine is the glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG). This organic compound is a marker for alterations occurring in the glucose metabolism of tumours as well as in various disease-related conditions of the heart and brain. In Germany it has been approved for use in a number of clinical indications by the Federal Institute for Drugs and Medical Devices (BfArM).

It was the aim of this study to gain an overview of PET examinations performed in Germany in the year 1999 and to estimate both the collective and the per capita effective dose to the German population arising from these examinations. Exposures received by medical staff working within a PET centre or by patient's relatives and other ward staff arising from contact with patients following a PET procedure have been reported in previous studies [9, 10].

Materials and methods

In order to characterise the practice of PET in Germany in terms of both the type and the frequency of procedures carried out, along with the associated levels of dose to individual patients, a nationwide survey was conducted by means of a questionnaire soliciting provision of detailed information. To this end, all university and state-run hospitals (n=35) as well as private practices (n=25) in Germany that in 1999 were running at least one dedicated PET system with a circular detector configuration (coincidence-adapted gamma camera systems were explicitly excluded) were requested to provide the following details for each of the PET radiopharmaceuticals used:

- Annual number of applications
- Age and sex distribution of patients and volunteers (patients or healthy persons) examined
- Fraction of procedures performed within the framework of clinical routine and research
- Main diagnostic applications (oncology, cardiology, neurology, others)
- Mean value and range of administered activities
- Fraction of examinations performed in the two-dimensional (2D) acquisition mode (with interslice septa) and in the three-dimensional (3D) acquisition mode (without interslice septa)
- A prognosis as to whether the number of patients examined using the radiopharmaceutical under consideration would increase or decrease in the coming years

All PET facilities that did not respond to our inquiry were contacted by telephone in order to obtain at least confirmation that they had carried out PET examinations in 1999, and, if they had done so, which radiopharmaceuticals had been applied. All data were saved in anonymous form in a worksheet file and analysed using the program package SigmaPlot (Version 7.1; SPSS Science Software, Erkrath, Germany).

For all reported PET radiopharmaceuticals, equivalent doses to the various organs and tissues of the patients were estimated using the dosimetric formalism developed by the Medical Internal Radiation Dose Committee of the United States Society of Nuclear Medicine (MIRD). From these organ doses, the effective dose was calculated using the tissue weighting factors summarised in ICRP Publication 60 [11]. Where these were available, the dose coefficients, i.e. the effective doses per MBq of activity administered, as listed in ICRP Publication 80 [12], were used in this study. For the other radiopharmaceuticals, cumulated activities were estimated on the basis of human or animal data published in the literature and used to calculate organ equivalent doses and effective doses using either the computer program MIRDOSE3 [13] or the S values derived by Cristy and Eckerman [14]. In accordance with ICRP Publication 80, the same dose coefficients were used for both male and female patients. In contrast to this publication, however, we did not perform an age-dependent analysis, because only a very small fraction of the PET examinations were performed on children younger than 15 years of age. Moreover, the higher dose coefficients for children are partly balanced out by the lower activities applied to children as compared with adults.

For FDG – by far the most frequently applied radiopharmaceutical – the significance of differences in the average activity administered in hospitals and private practices was tested by applying the Mann-Whitney rank sum test at a significance level of P=0.05, using the program package SigmaStat (Version 2.03; SPSS Science Software). Since the administered activity depends to a considerable extent on the acquisition mode, the statistical test was performed separately for 2D and 3D measurements.

Results

Of the 60 PET facilities in Germany, 48 responded to our inquiry and filled out the questionnaire. The response rate was 94% for hospitals (33 out of 35) and 60% for private practices (15 out of 25). In total, data on nearly 25,000 PET examinations were reported and used for further evaluation. About 82% of these examinations were performed in clinical routine and about 18% in clinical research.

According to the information provided in the questionnaires, 28 different PET radiopharmaceuticals were applied to patients and volunteers, but only half of them were applied to more than 20 patients each. The relevant data for these 14 radiopharmaceuticals are summarised in Table 1. The three PET radiopharmaceuticals most frequently used in 1999 were [^{18}F]FDG, [^{15}O]water, and [^{13}N]ammonia. The main diagnostic applications of these radiotracers are indicated in Fig. 1.

As summarised in Fig. 2, the annual number of tracer applications varied considerably between the 48 facilities which responded to our inquiry. While in 18 (37%) of these facilities less than 250 procedures were performed, four PET centres (8%) performed more than 1,000 tracer applications per year. In the majority of private practices (73%) less than 250 patients were examined in 1999. Figure 3 reveals that PET examinations were performed only in the 2D mode in 24 facilities (50%) and only in the 3D mode in 11 facilities (23%).

Table 1. Summary of PET procedures conducted in Germany in 1999

Nuclide	Compound	Function	No. of reporting hospitals/ practices	Reported or estimated total number of applications	Average activity (MBq)	Dose coefficient (μSv/MBq)	Estimated collective dose (manSv)
^{11}C	L-Methionine	Amino acid transporter and protein synthesis	5/0	350	659	5.2	1.20
	Acetate	Myocardial oxidative metabolism	2/0	61	769	4.5	0.21
	Flumazenil	Benzodiazepine receptors	2/0	54	743	4.5[a]	0.18
	Raclopride	D2 receptors	2/0	52	393	4.3	0.09
	PK 11195	Marker of activated microglia	1/0	32	300	2.7[a]	0.03
	N-Methyl-4-piperidyl acetate	Cerebral acetylcholinesterase activity	1/0	24	740	5.0[a]	0.09
	Hydroxyephedrine	Re-innervation of transplanted heart	1/0	21	704	22	0.32
^{13}N	Ammonia	Myocardial blood flow	5/0	579	904	2.0	1.05
^{15}O	Water	Regional blood flow	8/0	2,579	2,388	0.93	5.73
	Butanol	Cerebral blood flow	1/0	184	550	0.41	0.04
^{18}F	2-Fluoro-2-deoxy-D-glucose	Glucose transport and phosphorylation	33/ 15	17,411 $\xrightarrow{1.06}$ 18,456[b] 3,013 $\xrightarrow{1.66}$ 5,002[c]	341 263	19 19	119.6 25.0
	L-Dopa	Presynaptic dopaminergic function	5/0	258	211	24	1.31
	Fluoride	Bone metabolism	4/0	113	406	24	1.10
	5-Fluoro-2′-deoxyuridine	Cell proliferation	1/0	25	200	33	0.17
14 other radiopharmaceuticals applied to less than 20 patients each			7/0	<150	–	–	<1.5

[a] This value gives only a rough estimate for the dose coefficient since no detailed data are available on the biodistribution of the radiotracer

[b] A correction factor of 1.06 (35/33) was used to estimate the total number of examinations performed in hospitals (for details see text)

[c] A correction factor of 1.66 (25/15) was used to estimate the total number of examinations performed in practices (for details see text)

Only 13 facilities (27%) took advantage of the possibility of adapting the acquisition mode to the given clinical investigation. Interestingly, compared with hospitals, a far higher fraction of practices acquired projection data exclusively in the 3D mode (9% vs 53%).

The age and sex distribution for patients and volunteers undergoing a PET procedure in the year 1999 is plotted in Fig. 4a. For comparison, the corresponding frequency distributions for the German population [15] are shown in Fig. 4b. Specific demographic differences were observed between the patient population under consideration and the general population. The unimodal age distributions for both male and female patients are skewed towards higher ages. Only a very small fraction

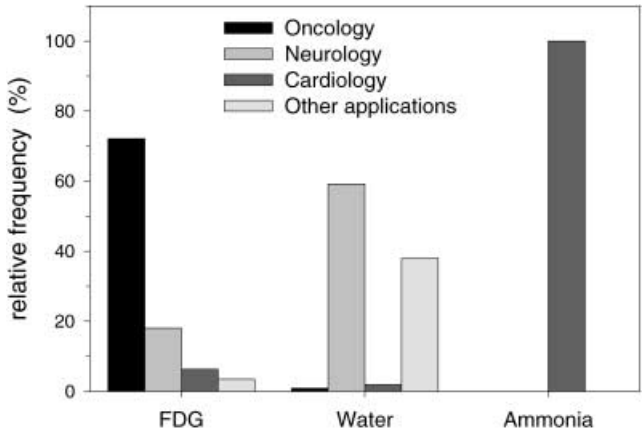

Fig. 1. Main foci of diagnostic applications for the three PET radiopharmaceuticals most frequently administered to patients and volunteers in the year 1999, namely [^{18}F]FDG, [^{15}O]water, and [^{13}N]ammonia (cf. Table 1). In the case of [^{15}O]water, neurofunctional activation studies are in part shown under "other applications"

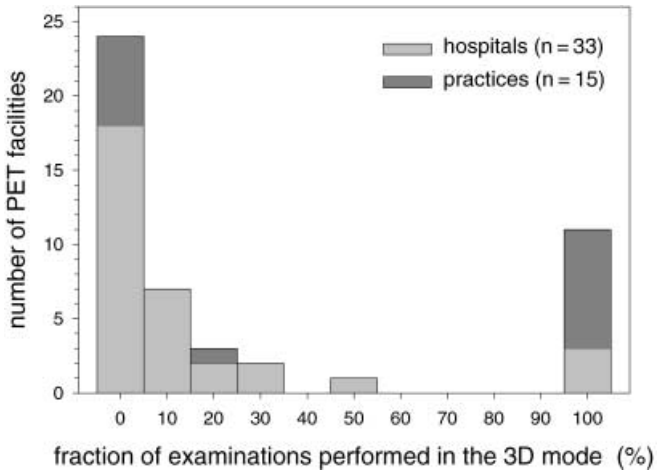

Fig. 3. Distribution of the relative fraction of PET examinations performed in the 3D acquisition mode in 48 PET facilities. While all PET procedures were performed in the 3D mode (without interslice septa) in only 11 facilities, there were 24 facilities in which the measurements were performed only in the conventional 2D mode (with interslice septa)

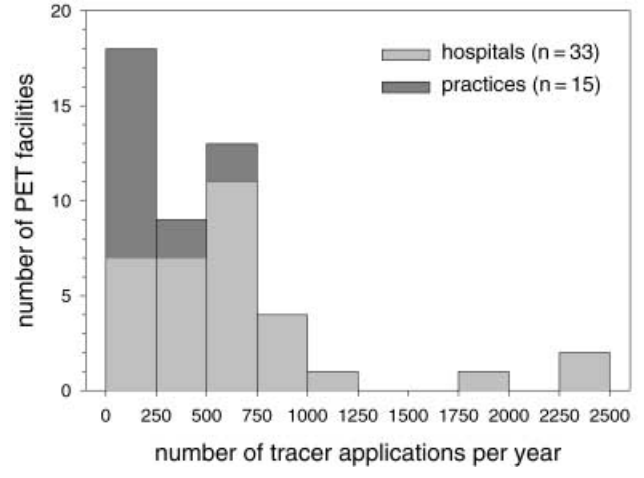

Fig. 2. Distribution of the annual number of radiotracer applications carried out in 48 PET facilities

(<3%) of patients were children younger than 15 years while older patients, and especially those in the age group between 41 and 65 years, were overrepresented relative to the general population.

On the basis of the frequency data summarised in Table 1 for PET procedures conducted in 1999 and the corresponding dose coefficients, the collective effective dose to the German population related to PET examinations in the year 1999 was estimated. To this end, the number of FDG applications indicated in the question-

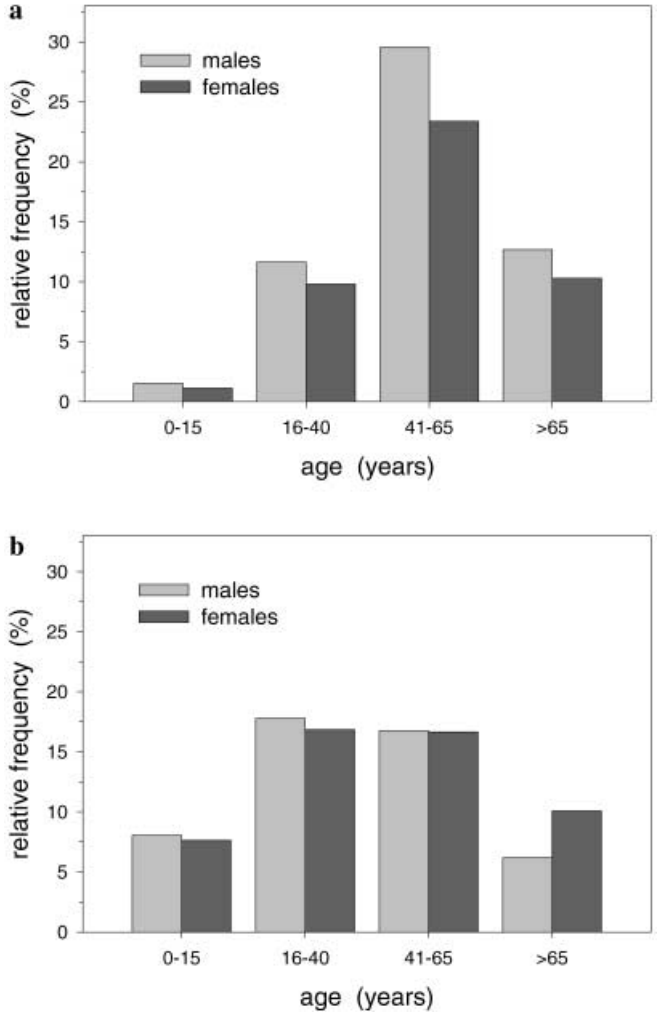

Fig. 4. Age and sex distribution **a** for patients and volunteers undergoing a PET procedure in the year 1999 and **b** for the German population in the same year [15]. The four age groups are defined as in the UNSCEAR report [17]

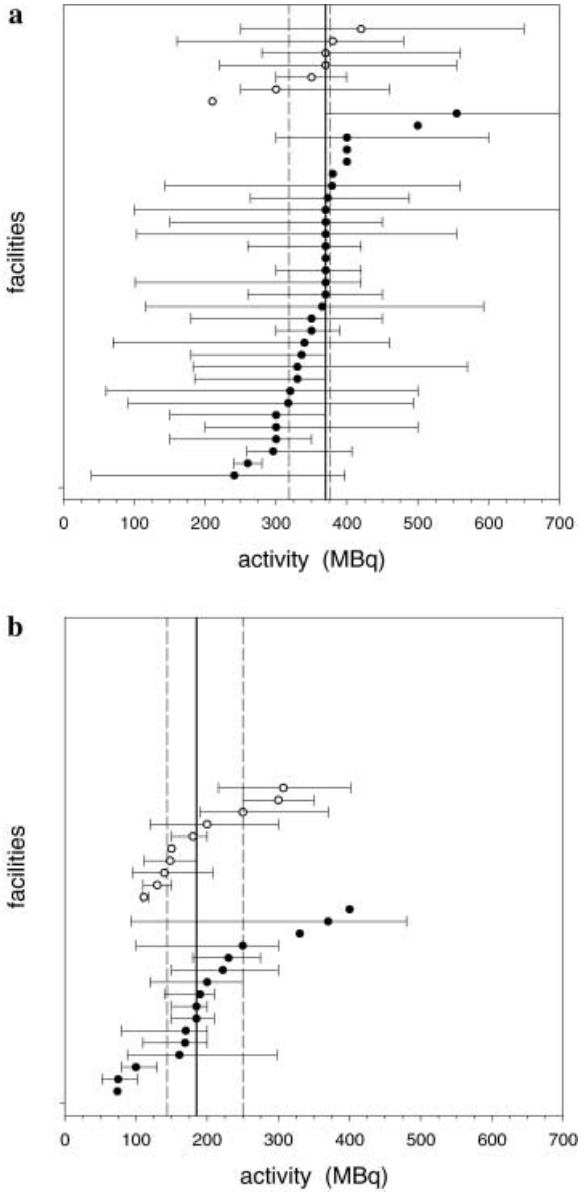

Fig. 5. Mean value and (where indicated in the questionnaire) the range of FDG activities applied in hospitals (●) and private practices (○) for PET examinations of patients and volunteers **a** in the 2D acquisition mode and **b** in the 3D acquisition mode. The *solid and broken vertical lines* represent the median value and the interquartile range, respectively

naires by 33 hospitals and 15 private practices were extrapolated in relation to the total number of 35 hospitals and 25 practices, using correction factors of 1.06 and 1.66, respectively. This is a reasonable approach, since the inquiries made by telephone at the 12 PET facilities that did not respond to our written inquiry yielded the information that in ten of them FDG was applied exclusively while in the other two FDG was used in a large majority of cases (alongside [^{18}F]fluoride and L-[^{18}F]fluoro-dopa). The extrapolation from the sample to the total study group of PET facilities yielded a total number of about 28,000 PET examinations and a collective effective dose of approximately 158 manSv. In relation to the 82.16 million inhabitants of Germany [15], this results in an annual frequency of about 0.34 PET examinations per 1,000 inhabitants, and an annual per capita effective dose of about 1.9 μSv.

Although the relative fraction of FDG applications varied considerably between the different PET facilities (range, 28%–100%), the glucose analogue is by far the most frequently applied radiopharmaceutical and is used in more than 84% of all PET procedures. The range of FDG activities administered and the corresponding mean values for the 48 facilities that responded to our inquiry are plotted in Fig. 5a and b for measurements performed in the 2D and the 3D acquisition mode, respectively. These plots reveal that the activities applied in the sensitive 3D mode (median of mean values, 185 MBq; interquartile range of mean values, 148–250 MBq) are significantly (P<0.001) lower as compared to 2D measurements (median of mean values, 370 MBq; interquartile range of mean values, 320–373 MBq). On the other hand, neither in the 2D nor in the 3D mode were there significant differences between mean activity values administered in hospitals and private practices (P>0.5).

Discussion

This paper provides for the first time a comprehensive overview of the frequency and practice of PET examinations performed in both clinical routine and research in Germany. The results presented for the year 1999 were extracted from questionnaires filled out by 80% of all PET facilities running at least one dedicated PET system with a circular array of detectors. They are thus of a high level of reliability from a statistical point of view.

The evaluation revealed that about 0.34 PET procedures were performed per 1,000 inhabitants in the year 1999, resulting in an annual per capita effective dose to the general public of about 1.9 μSv. This corresponds to 0.8% of all nuclear medicine procedures performed in Germany (about 44 per 1,000 inhabitants) and to 1.7% of the associated total per capita effective dose (0.11 mSv) [16]. Averaged over all PET procedures, the mean effective dose to patients was 5.6 mSv. It should be noted that the total number of patients and volunteers undergoing a PET examination is somewhat lower than the total number of 28,000 tracer administrations, since more than one radiopharmaceutical is sometimes administered (i.e. in multi-tracer studies). As a consequence, radiation exposure to individual patients or volunteers may be higher than the doses estimated for single-tracer examinations on the basis of Table 1.

As unambiguously stated in the UNSCEAR 2000 report [17], both the collective and the per capita effective dose provide "convenient indicators of overall exposure in the assessment of diagnostic practice. They broadly

reflect in a qualitative manner the risks to health of the stochastic (though not deterministic) effects associated with exposure to ionising radiation... allowing a robust comparison of practice between, *inter alia*, types of procedure, countries, and time periods. However,... effective doses should not be used directly for estimating detriment (to individuals or populations) from medical exposures by application, for example, of the nominal fatality probability coefficients given by ICRP. Such assessments would be inappropriate and serve no purpose in view of the uncertainties arising from potential demographic differences (in terms of health status, age, and sex) between particular populations of patients and those general populations for whom the ICRP derived the risk coefficients." The last point is clearly substantiated by our data in a twofold manner: Firstly, the age distribution for patients undergoing a PET procedure differed considerably from that for the general public, as demonstrated by Fig. 4. Secondly, in 1999 more than 60% of all PET examinations were conducted in order to elucidate special aspects of diagnosis, staging and therapy control of tumours, and were thus linked to a high individual benefit for the patients examined. Moreover, a proportion of these examinations were performed on patients with a markedly reduced life expectancy, which may have been shorter than the latency period for the development and still more so for the lethal outcome of radiation-induced cancer. Accordingly, the proportional fraction of the collective effective dose attributed to this group of patients is radiobiologically ineffective [18].

A majority of the facilities which responded to our inquiry expected that the number of PET examinations would increase in the coming years. This, however, need not necessarily result in an increase in the annual collective effective dose. As demonstrated by Fig. 5a and 5b, there is considerable potential for reduction of the activity administered to patients and volunteers, by acquiring projection data not in the conventional 2D but rather in the more sensitive 3D mode. For FDG, for example, the median from the mean activities applied in different PET facilities for 3D measurements (185 MBq) was only half of that applied for 2D measurements (370 MBq). This corresponds well with the results of a previous phantom study [19]. In this investigation, it was demonstrated that PET images reconstructed from 3D data sets were of superior image quality as compared with the corresponding 2D images, although the activity concentrations in the different compartments of the phantom were only half as high as those used for the 2D measurements.

In accordance with the recommendations of ICRP Publication 73 [20], the Council of the European Communities issued, in 1997, the Medical Exposure Directive [21]. Among other things, it requires that the Member States establish and use diagnostic reference levels (DRLs) for frequently applied and high-dose diagnostic examinations in radiology and nuclear medicine. DRLs in nuclear medicine represent "optimum" values for administered activities, which are appropriate for obtaining the relevant diagnostic information for standard groups of patients. These reference or guidance levels can be established nationally, on the basis of the experience of the relevant professional groups (i.e. in the form of an "expert judgement"). Although the establishment of DRLs in nuclear medicine is explicitly not based on the 75th percentile of the activity distribution as measured in various types of hospitals and practices, as in the case of diagnostic radiology, this quantity nevertheless provides – alongside the median value – a valuable parameter in the characterisation of clinical practice.

The data plotted in Fig. 5a for FDG examinations performed in the 2D acquisition mode prove that the median value (370 MBq) is nearly identical with the 75th percentile (373 MBq), so that a DRL of 370 MBq can be straightforwardly defined. For FDG measurements in the 3D mode, on the other hand, establishment of the DRL is somewhat more difficult since the median value (185 MBq) and the 75th percentile (250 MBq) differ considerably (Fig. 5b). However, taking into account the results of the above-mentioned phantom study, an "optimum" value of 200 MBq can be recommended as the DRL for FDG procedures performed in the 3D mode. The DRLs proposed correspond to representative effective doses of 7.0 and 3.8 mSv per examination, respectively. Since more than half of the mean activity values summarised in Fig. 5 for FDG examinations were reported by university hospitals and, moreover, since there were no significant differences ($P<0.001$) between the mean FDG activities administered in hospitals and in private practices, the derived DRLs can serve as the element of "expert judgement" as suggested by the Medical Exposure Directive. It is important to note in this context that these DRLs apply for standard-sized persons (or represent the mean value for groups of patients); they should be reduced for children but on the other hand may be exceeded in larger patients.

In summary, the data presented in this paper characterise the frequency of use and practice of PET procedures in Germany, a country with a very high number of PET installations [17]. The role of PET in patient care will certainly be enhanced in the future through continuing advances in hardware technology and data processing, and especially through the development of new compounds labelled with short-lived positron-emitting radionuclides. According to our survey, a large number of PET radiopharmaceuticals are currently under investigation, creating considerable potential for metabolic tracer imaging and physiological studies in both biomedical research and clinical practice. Conversely, a reduction in radiation exposure to patients and volunteers can be achieved by performing more PET examinations in the sensitive 3D mode and by introducing more rigorous standards for patient protection, for example by the establishment and use of diagnostic reference levels.

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