

Assessment of Minimum ^{124}I Activity Required in Uptake Measurements Before Radioiodine Therapy for Benign Thyroid Diseases

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This study aimed to assess a hypothetical minimum administered activity of ^{124}I required to achieve comparability between pretherapeutic radioiodine uptake (RAIU) measurements by ^{124}I PET/CT and by ^{131}I RAIU probe, the clinical standard. In addition, the impact of different reconstruction algorithms on ^{124}I RAIU and the evaluation of pixel noise as a parameter for image quality were investigated. **Methods:** Different scan durations were simulated by different reconstruction intervals of 600-s list-mode PET datasets (including 15 intervals up to 600 s and 5 different reconstruction algorithms: filtered-backprojection and 4 iterative techniques) acquired 30 h after administration of 1 MBq of ^{124}I . The Bland–Altman method was used to compare mean ^{124}I RAIU levels versus mean 3-MBq ^{131}I RAIU levels (clinical standard). The data of 37 patients with benign thyroid diseases were assessed. The impact of different reconstruction lengths on pixel noise was investigated for all 5 of the ^{124}I PET reconstruction algorithms. A hypothetical minimum activity was sought by means of a proportion equation, considering that the length of a reconstruction interval equates to a hypothetical activity. **Results:** Mean ^{124}I RAIU and ^{131}I RAIU already showed high levels of agreement for reconstruction intervals of as short as 10 s, corresponding to a hypothetical minimum activity of 0.017 MBq of ^{124}I . The iterative algorithms proved generally superior to the filtered-backprojection algorithm. ^{124}I RAIU showed a trend toward higher levels than ^{131}I RAIU if the influence of retrosternal tissue was not considered, which was proven to be the cause of a slight overestimation by ^{124}I RAIU measurement. A hypothetical minimum activity of 0.5 MBq of ^{124}I obtained with iterative reconstruction appeared sufficient both visually and with regard to pixel noise. **Conclusion:** This study confirms the potential of ^{124}I RAIU measurement as an alternative method for ^{131}I RAIU measurement in benign thyroid disease and suggests that reducing the administered activity is an option. CT information is particularly important in cases of retrosternal expansion. The results are relevant because ^{124}I PET/CT allows additional diagnostic means, that is, the possibility of performing fusion imaging with ultrasound. ^{124}I PET/CT might be an alternative, especially when hybrid ^{123}I SPECT/CT is not available.

Key Words: ^{124}I ; ^{124}I PET; reconstruction parameters; pretherapeutic uptake measurement; benign thyroid disorders

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Radioiodine therapy (RAIT) with ^{131}I is a relevant intervention because of the high prevalence of benign thyroid diseases (1). Although pretherapeutic radioiodine uptake (RAIU) measurement is usually performed with a ^{131}I probe and is considered the clinical standard, a recent study on the correlation between ^{131}I probe RAIU measurement and ^{124}I PET/CT RAIU measurement has shown that application of as little as 1 MBq of ^{124}I provides RAIU results comparable to those obtained with 3 MBq of ^{131}I (2). Thus, ^{124}I PET/CT may become a good alternative for routine evaluations of RAIU in patients with benign thyroid disease, especially because ^{124}I PET/CT may provide additional diagnostic information. Indeed, the functional anatomy shown by ^{124}I PET is superior to that shown by conventional $^{99\text{m}}\text{TcO}_4$ thyroid scintigraphy (3). Also, the ^{124}I RAIU method allows a time-efficient PET-based organ volumetry (4). In addition, there exists the possibility of performing PET/ultrasound image fusion (5–7).

Different activities in one patient can be simulated by obtaining a ^{124}I PET/CT scan in list-mode technique and equating reduction of scan time with reduction of activity. The focus of this study was to assess only the uptake aspect of RAIU. No information was obtained about the effective half-life aspect of RAIU. The goals of this study were to assess a hypothetical minimum activity that will achieve comparable results between ^{124}I RAIU measurement and the clinical standard, ^{131}I RAIU measurement; to determine the influence of different reconstruction algorithms on ^{124}I RAIU measurement; and to evaluate pixel noise as a parameter for image quality.

MATERIALS AND METHODS

Patients and Ethics

The study included consecutive patients with benign thyroid diseases referred to our institution from April 2012 to June 2014 in preparation for RAIT. The study was designed as a subanalysis within a larger prospective study approved by the local ethics committee and the German Federal Office of Radiation Protection. All participants signed a written informed consent form.

Study Protocol

Thyroid Diagnostics. The initial thyroid diagnostic was performed according to current guidelines (anamnesis; measurement of thyroid-stimulating hormone, free T₃, and free T₄; neck ultrasound; and planar $^{99\text{m}}\text{Tc}$ -pertechnetate scintigraphy) (8–10).

Inclusion and Exclusion Criteria. Criteria for inclusion were the diagnosis of a benign thyroid disease potentially requiring treatment (e.g., RAIT with the aim of volume reduction). Patients were excluded if they had received thyroid-specific treatment in the previous 12 wk, if their anamnesis was positive for iodine contamination, or if a

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relevant change in thyroid metabolism (as assessed by thyroid-stimulating hormone levels) occurred between the investigations.

Tracer Preparation. Sodium- ^{131}I solution (GE Healthcare) and sodium- ^{124}I tracer solution (BV Cyclotron VU) were poured into identical capsules (HGK, size 3; GE Healthcare) on a crystalline carrier. The tracer activity of the test capsules was measured using a dose calibrator (Isomed 2010; MED Nuklear-Medizintechnik).

Tracer Administration and RAIU Measurement Schedule. Oral administration of ^{131}I capsules (3 MBq) was performed first; ^{124}I capsules (1 MBq) were administered 7–14 d later. Each RAIU was measured 30 h after administration. Before this study, phantom experiments demonstrated that residual ^{131}I does not interfere with quantification of ^{124}I in PET/CT examination (2).

^{131}I Probe Measurement. The activity in patients was measured using an ISOMED 2162 thyroid uptake counter (MED Nuklear-Medizintechnik). The measuring distance between detector and neck was kept at 45 cm using a spacer. The detector fitted with an NZ-136-01 collimator (MED Nuklear-Medizintechnik) had dimensions of 5×5 cm and was connected to a multichannel analyzer through a photomultiplier tube. For quality assurance purposes, each measurement was preceded by a check of the energy spectrum using a ^{137}Cs test source, as well as by measurement of the background activity. The determined lower limit of detectability was 7 kBq.

^{124}I PET/CT. ^{124}I PET/CT scans were acquired using a Biograph mCT 40 system (Siemens). The scans were scheduled late in the afternoon following clinical routine to ensure a high adherence to the appointed date. ^{124}I PET imaging was performed in list-mode acquisition by continuous scanning for 600 s, with every measured value stored as raw data with an exact time stamp to allow reconstruction of intervals of different length as static images, simulating scan intervals of different length.

Patients were scanned supine at one bed position. The scan region included the whole neck and the upper thorax. Anatomic coregistration and attenuation correction were performed using a native CT scan at its lowest tube setting (30 mA), with 120-kV tube voltage, 3-mm scan slice width, and 1.2 pitch. The PET system showed a 3-dimensional sensitivity of 9.5 cps/kBq/mL. At 1 cm, the axial resolution was 4.4 mm and the transverse resolution 4.5 mm. The scatter fraction was below 36%. Quality control was performed daily and weekly according to the standards of the National Electrical Manufacturers Association.

^{124}I PET Reconstruction Intervals (RI). List-mode data were reconstructed using the software HD-TrueX (Siemens), with 15 RIs of different lengths, that is, 600 s, 540 s, 480 s, 420 s, 360 s, 300 s, 240 s, 180 s, 120 s, 60 s, 50 s, 40 s, 30 s, 20 s, and 10 s.

^{124}I PET Reconstruction Algorithms. Images were reconstructed using 2 different processes, that is, filtered backprojection (FBP) and iterative technique (IT). The IT consisted of different combinations of the 4 reconstruction parameters, image matrix, iterations, subsets, and zoom. One or maximally 2 parameters were changed according to the locally established reconstruction algorithm (IT-1) (Table 1) (2–4). Each RI was reconstructed with the 5 different reconstruction algorithms.

Quantitative Analysis

^{131}I RAIU Measurement. The computer-based assessment proceeded by means of the dedicated standard software UPT 2000 (MED Nuklear-Medizintechnik). The thyroid activity was calculated as ratio of counts measured in the patients' field of view versus the counts measured in a standard phantom, in both cases after subtraction of the background counting rate. ^{131}I RAIU was calculated by dividing measured counts by applied activity, considering decay correction and calibration of the ^{131}I probe.

^{124}I RAIU Measurement. The ^{124}I PET and CT datasets were fused using the software PMOD, version 3.408 (PMOD Technologies Ltd.), and quantified using the volume-of-interest (VOI) technique. A cylinder-shaped VOI was placed on the neck, ensuring that the mandible and any

TABLE 1

Overview of Reconstruction Algorithms and Parameters

Parameter	FBP	IT-1	IT-2	IT-3	IT-4
Matrix	512	512	512	128	512
Iterations	NA	4	4	4	1
Subsets	NA	24	24	24	12
Zoom	2	2	1	1	2

NA = not available.

retrosternal thyroid parts were included, enabling the measurement of any activity within this region (Fig. 1) (2). Mean activity concentration (kBq/mL) and its SD were measured in each VOI. A background correction VOI was not used because of the high specific uptake within the thyroid compared with surrounding tissue. ^{124}I RAIU was calculated by dividing measured activity within the VOI by applied activity. In analogy to other studies, a correction of the measured activities based on the difference in decay between ^{124}I and ^{131}I was performed, allowing a comparison of the activities of the two radionuclides (2).

Data Analysis

Comparison of ^{131}I RAIU and ^{124}I RAIU. The impact of the length of RI (as a surrogate for the scanning duration) was assessed for the 5 ^{124}I PET reconstruction algorithms in terms of consistency with the ^{131}I RAIU measurement (Fig. 2). A slightly modified version of the Bland–Altman method was applied to estimate the degree of consistency between the ^{131}I RAIU and ^{124}I RAIU determined by means of the 5 different reconstruction algorithms (11). In short, relative uptake differences were calculated between ^{124}I RAIU and ^{131}I RAIU. A subanalysis was performed splitting the patients into 2 subgroups, one without and the other with retrosternal thyroid tissue (Figs. 2B and 2C).

Image Quality. Two image quality aspects were considered. First, visual inspection of the ^{124}I PET/CT images was performed for the different RI and reconstruction algorithms but not routinely analyzed in terms of visual scoring, because visual assessment is subjective. Therefore, we decided to use a second, objective parameter.

It is generally accepted that high pixel noise contributes to low image quality (12). In our setting, reducing the RI leads to an increase in pixel noise and in turn a decrease in image quality. As an approach to objectify pixel noise, we measured the SD of the activity concentration within the VOI. Finally, SD and pixel noise were observed to increase in this study, corresponding with low image quality. This is exclusively influenced by length of RI and reconstruction algorithm. Since the experience in our institution shows that 1 MBq of ^{124}I at a 600-s scan time provides sufficient images in all cases, it serves as a reference for image quality in this study (2,3). We tested a limit of 10% change in SD to obtain

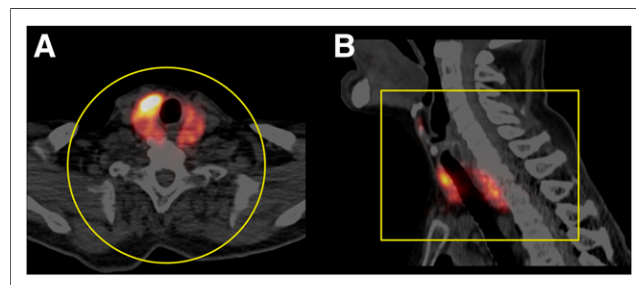


FIGURE 1. Transversal (A) and sagittal (B) ^{124}I PET/CT images (IT-1 reconstruction; 600 s), with cylinder-shaped VOI indicated by yellow line.

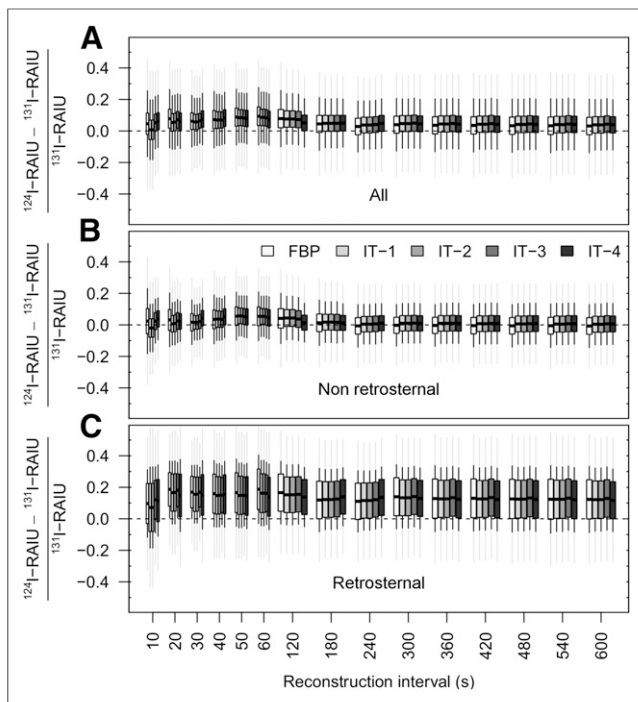


FIGURE 2. Modified Bland–Altman plots showing relative differences in uptake between ^{124}I PET and ^{131}I probe (clinical standard, line of equality at 0) for all patients (A) and for subgroups without (B) and with (C) retrosternal tissue, using 5 different ^{124}I PET reconstruction algorithms at 15 RIs. Boxes and horizontal lines indicate mean and its 95% confidence interval. If box includes line of equality, there is no systematic over- or underestimation. Gray whiskers indicate 95% limits of agreement according to Bland–Altman (1.96-fold SD), whereas black whiskers indicate common SD.

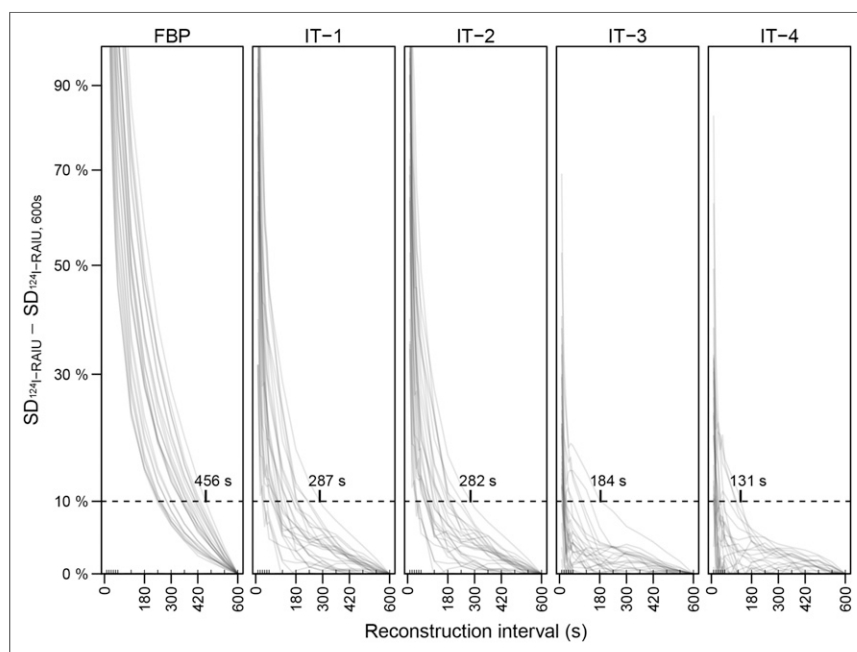


FIGURE 3. Difference between SD of ^{124}I RAIU and SD of ^{124}I RAIU at 600 s depending on length of RI and reconstruction algorithm. Each patient was plotted separately as single gray line. Image quality was considered acceptable if increase in SD of all scans remained $\leq 10\%$; length of RI at which this criterion was met was defined as RI_{acc} .

images with probable acceptable quality. The length of the RI at an SD increase of 10% or less was defined as the RI of acceptability (RI_{acc}), and this corresponds to a hypothetical minimum activity (Fig. 3; Table 2). The image quality is proportional to the PET scanning time and the activity contained in the scan field of view. Doubling the activity of a PET radiopharmaceutical leads to halving the scanning time, and halving the activity contained in the scan volume requires doubling the scanning time, resulting in the same image quality (13). Accordingly, the determination of RI_{acc} allows the calculation of a hypothetical minimum activity (A_{min}) by means of a proportion equation (Eq. 1):

$$A_{\text{min}} = \frac{1 \text{ MBq}}{600 \text{ s}} \cdot \text{RI}_{\text{acc}}.$$

Therefore, in the presented setting of 600 s and 1 MBq of ^{124}I , an RI_{acc} of 300 s is equal to a hypothetical activity of 0.5 MBq of ^{124}I .

RESULTS

Patients

Of 97 patients screened, 56 fulfilled the inclusion criteria and 37 agreed to participate in the study (Table 3). Part of the data was reported in a previous study (2). All participants were fully examined according to protocol. The mean orally administered activities were 3.03 ± 0.13 MBq for ^{131}I and 1.02 ± 0.03 MBq for ^{124}I . The interval between administrations was 10.0 ± 3.1 d. On average, the ^{131}I RAIU measurements took place at $30 \text{ h} \pm 2 \text{ min}$ after oral administration of the tracer, and the ^{124}I RAIU measurements took place at $30 \text{ h} \pm 5 \text{ min}$. The mean ^{131}I RAIU measured after 30 h was $29.1\% \pm 9.8$, and the mean ^{124}I RAIU (IT-1; 600-s RI) measured after 30 h was $29.6\% \pm 9.1$.

Comparison of ^{131}I RAIU and ^{124}I RAIU

A comparison of ^{131}I RAIU and ^{124}I RAIU for all patients showed a trend toward overestimation by ^{124}I PET/CT (Fig. 2A). Therefore, a subanalysis of patients without (Fig. 2B) and with (Fig. 2C) retrosternal tissue was performed. The nonretrosternal subgroup showed a good agreement between the 2 RAIU measurements. There was hardly any systematic variability irrespective of the RI and algorithm. The retrosternal subgroup displayed higher ^{124}I RAIU levels for all reconstruction algorithms, revealing a systematic overestimation.

For ^{124}I PET reconstruction algorithms in all patients (Fig. 2A) and in the non-retrosternal subgroup (Fig. 2B), the limits of agreement were fairly concordant; however, a slight enlargement was observed for the RI between 10 and 60 s. In general, the reconstruction data obtained with the FBP showed a more pronounced enlargement of the limits of agreement than did the data obtained by IT (Fig. 2).

Image Quality

Figure 3 shows an exponential increase in SD at shorter RIs. This increase was more pronounced for FBP than for IT. The RI_{acc} was reached from 131 s to 456 s, and the calculated hypothetical minimum activity was reached from 0.22 MBq to 0.76 MBq (Fig. 3; Table 2). Image quality was still good at 300 s (Fig. 4A), but reducing the number

TABLE 2

RI_{acc} and Calculated Hypothetical Minimum Activity for Different Reconstruction Algorithms

Algorithm	RI_{acc} (s)	Calculated hypothetical minimum ^{124}I activity (MBq)
FBP	456	0.76
IT-1	287	0.48
IT-2	282	0.47
IT-3	184	0.31
IT-4	131	0.22

of subsets (IT-4) as well as using FBP lowered image quality visually (Fig. 4B).

DISCUSSION

Different radioiodine isotopes are available for thyroid diagnostics. Hybrid imaging leads to additional benefits (connection between anatomic and functional imaging). ^{123}I and ^{131}I require a SPECT/CT scanner and ^{124}I a PET/CT scanner. However, in many institutions only one of these two types of scanners is available. If it is not possible to use SPECT/CT, ^{124}I PET/CT forms a suitable alternative.

As the thyroid RAIU is comparably specific and intense, ^{124}I PET/CT images obtained with low activity are of good visual quality compared with ^{124}I PET/CT performed in patients with metastasized differentiated thyroid cancer after thyroid removal or remnant ablation. Moreover, recent ^{124}I RAIU measurement studies indicate that an activity of 1 MBq and a scan time of 600 s generate a visually sufficient image for diagnostics and allow reliable RAIU measurement (2,3). Concerning radiation exposure of ^{124}I RAIU evaluation with 1 MBq, a thyroid uptake of 25% is associated with an effective whole-body equivalent dose of about 6.5 mSv considering that about 0.3 mSv is contributed by the low-dose CT and the thyroid organ dose is 260 mGy (8,14). In comparison, the effective whole-body equivalent dose resulting from ^{131}I RAIU evaluation with 3 MBq is about 33 mSv, and the thyroid organ dose is 1,290 mGy (8,14). Therefore, radiation exposure caused by ^{124}I RAIU measurement is approximately one fifth of that of ^{131}I RAIU measurement. However, the radiation exposure aspect is somewhat relative concerning the following RAIT. Moreover, in the past, activities of as low as 0.2 MBq have been shown to be sufficient for ^{131}I RAIU measurement (15). In the presented setting, standard activities of 3 MBq of ^{131}I were used according to current guidelines (9,10). However, ^{124}I activity reduction may be desirable for decreasing the inherent material costs. The present study sought to verify the effects of a hypothetical reduction of ^{124}I activity on ^{124}I RAIU and pixel noise, as well as the role of different reconstruction algorithms. The investigational use of different activities was not feasible because of the clear methodologic constraints caused by the additional exposure for individual participants; therefore, we chose an indirect methodologic approach determining hypothetical minimum activities.

Simulating different scan times with the help of list-mode data has already been used in studies aimed at assessing the optimal activity for pediatric ^{18}F -FDG-PET; however, the reconstruction times were limited to 1–5 min (13). A phantom study with ^{18}F -FDG examined the relationship between image quality and (simulated) acquisition

times, but only at intervals of 1–4 min (16). The present study differed from those publications in that not only was ^{124}I used but also a larger time span with more time intervals.

Comparison of ^{131}I RAIU and ^{124}I RAIU

Mean ^{124}I RAIU and ^{131}I RAIU were fairly concordant. Length of RI and reconstruction algorithms influenced neither the level of agreement nor the SD of the measured RAIU (Fig. 2). An RI of as short as 10 s (corresponding to an activity of 0.017 MBq of ^{124}I ; Eq. 1) did not show a difference between mean ^{124}I RAIU and ^{131}I RAIU. However, images of the 10-s RI are visually insufficient (Fig. 4A). Therefore, the difference between ^{124}I RAIU and ^{131}I RAIU cannot be used as a parameter to determine a reasonable lower limit for ^{124}I activity.

The subgroup analysis separately investigating patients without and with retrosternal thyroid tissue proved that the slight trend toward higher ^{124}I RAIU is caused by patients with retrosternal tissue only (Fig. 2). In fact, ^{131}I RAIU measurement may be associated with some γ -absorption in the sternum and hence in underestimation of RAIU. In addition, ^{131}I RAIU measurement may not completely include the whole retrosternal part because positioning is not image-guided, probably resulting again in underestimation of the RAIU. ^{124}I RAIU measurement, in contrast, always identifies possible retrosternal portions and includes them in the RAIU measurement. The trend toward higher ^{124}I RAIU was more pronounced at shorter RIs (10–60 s), leading to a slight statistical deviation. This finding is difficult to assess; a conceivable explanation lies in the IT calculation model.

TABLE 3
Patient Characteristics

Characteristic	Value
Age (y)	
Median	75 (52–85)
Mean \pm SD	73.3 \pm 7.3
Female (n)	24 (64.9%)
Thyroid disorder (n)	
Unifocal autonomy	6 (16.2%)
Multifocal autonomy	18 (48.6%)
Nontoxic goiter	13 (35.2%)
Thyroid volume (mL)	
Median	87.5 (24–299)
Mean \pm SD	103 \pm 60
Retrosternal part (n)	12 (32.4%)
Thyroid-stimulating hormone (mU/mL)	
Median	
Before ^{131}I RAIU measurement	0.33 (0.01–2.86)
Before ^{124}I RAIU measurement	0.33 (0.01–2.71)
Mean \pm SD	
Before ^{131}I RAIU measurement	0.54 \pm 0.84
Before ^{124}I RAIU measurement	0.52 \pm 0.77

Data in parentheses are range or percentage.

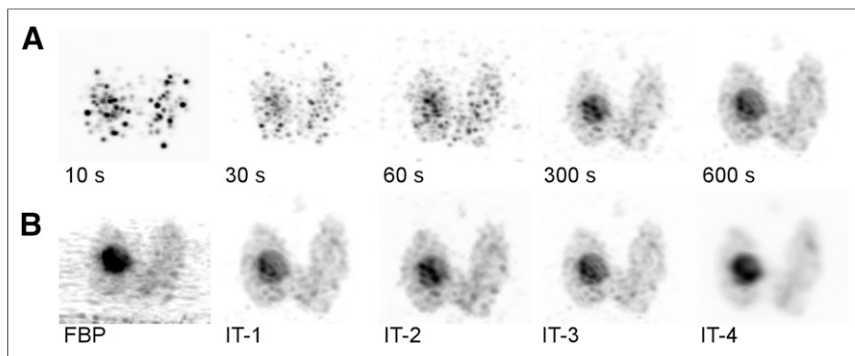


FIGURE 4. Maximum-intensity projection of ^{124}I PET for patient with autonomous adenoma according to RI (A) and algorithm (B).

Image Quality

The impact of the RI length on the increase in pixel noise was examined as a parameter of image quality, given that very short scanning times (simulated by short RIs) are associated with a higher background noise and poorer image quality (17–20). The concept of using an increase in SD as a parameter of image quality was chosen because an exact assessment of image quality with parameters such as spatial resolution, signal-to-noise ratio, or noise-equivalent counting rate was not applicable to the underlying in vivo data (21,22). These parameters can reliably be determined only by using a phantom with defined focal hot and cold spots of different sizes. A modified neck-shaped Jaszczak-phantom meeting the needs of the proposed study setting is currently being constructed in our clinic, and corresponding studies are planned.

During the last few years, we used 1 MBq of ^{124}I for imaging of benign thyroid diseases in unclear situations with guideline-conforming thyroid diagnostics (2,3). Through these experiences, we know that activities of as low as 1 MBq produce high-quality PET/CT images that clearly depict thyroid metabolism and are sufficient for image fusion with ultrasound (23,24). Because a deviation of $\pm 10\%$ in terms of applied activity is usually accepted in nuclear medicine, we allowed a 10% increase in the SD of mean uptake with regard to the 600-s RI, which is the locally established reconstruction algorithm. An increase in SD was considered a surrogate parameter for pixel noise and, thus, representative of image quality. The length of the RI at which all patients show an SD increase of no more than 10% is 287 s for IT-1, and this corresponds to a hypothetical minimum activity of 0.48 MBq (Table 2). Thus, it can be concluded that activities of as low as 0.5 MBq might be sufficient for good-quality images.

Visual interpretation in terms of visual scoring was not a focus of the current study. However, it is important to look at these images because diagnostics rely on visual assessment. An example of the influence of different RI and reconstruction algorithms is shown for one patient in Figure 4. Given that ^{124}I PET/CT can be used for PET/ultrasound fusion imaging, it is important to obtain a sufficiently high image quality (23,24). Images with an RI of 300 s still are appropriate to clearly define thyroid metabolism in the chosen example (Fig. 4A). Decreasing the RI length leads to a significant loss in image quality. As expected, it can be concluded that FBP is inferior to IT with regard to image quality, as has been extensively reported previously (25,26). Additionally, the reduc-

tion of equivalent iterations, that is, the product of iterations and subsets (IT-4), softens the image on the one hand but leads to increased blurring and therefore reduced image quality on the other hand (27–29). IT-1 to IT-3 do not differ with regard to image quality; therefore, we assume that zoom and matrix do not directly influence the image quality.

Limitations

The present study had some clear limitations. The number of patients was limited, and the benign thyroid diseases were of different types. Because this research was designed as an initial subanalysis within a larger study, results were valid only for a

time point of 30 h after radioiodine administration. Kinetic information (i.e., information on effective half-life) that would be available in the case of multiple RAIU measurements was not obtained with the present data. Because a comparison with intratherapeutic measurements was not performed, conclusions on the superiority of ^{124}I RAIU over ^{131}I RAIU are not possible. Because the study focused on activity, the functional topography of hypo- or hyperfunctional areas was not systematically considered. These aspects are nonetheless important for the use of PET/CT or PET/ultrasound image fusion. Finally, a routine ^{124}I RAIU measurement is hindered by several factors. The use of ^{124}I PET/CT is complex and not ubiquitously available and, compared with a ^{131}I probe, considerably more expensive regarding the length of the examination and the price of ^{124}I , which in our institution is about 20% higher than the price of ^{131}I . The use of very low activities might lower the cost (2).

CONCLUSION

The present study confirmed the potential of ^{124}I PET/CT as an alternative method for RAIU measurement in patients with benign thyroid diseases, and this irrespective of additional benefits such as improved information on functional anatomy, reliable volumetry, and the possibility of performing image fusion with ultrasound. A hypothetical activity reduction to approximately 0.5 MBq of ^{124}I obtained with the locally established reconstruction algorithm IT-1 appeared sufficient when considering pixel noise in parallel. Further studies with more time points, higher patient numbers, and clearly defined disease groups divided by uptake level are warranted, especially if validated by intratherapeutic measurements.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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