^{124}I Positron Emission Tomographic Dosimetry and Positron Emission Tomography/ Computed Tomography Imaging in Differentiated Thyroid Cancer

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7.1 Introduction

Patients with well-differentiated thyroid cancer (DTC) of follicular origin usually undergo total thyroidectomy and at least one radioiodine therapy using ^{131}I. Besides the therapeutic effect, ^{131}I whole body imaging offers excellent accuracy for the detection of DTC metastases; however, it is limited only for those accumulating iodine. Additional useful diagnostic tools in the follow-up of thyroidectomized patients with DTC are thyroglobulin, ultrasonography (US), US-guided fine-needle biopsy, and [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) [1–6]. Recent studies show that FDG-PET leads to changes in approaches to surgical treatment plans in a significant number of patients. In detail, in cases with poor tumor differentiation, reduced or lost iodine-accumulating ability leads to false-negative ^{131}I scanning results [1–3].

In the majority of patients, however, iodine uptake in the tumor is adequate for scintigraphy and somewhat less frequent for radioiodine therapy. Although ^{131}I therapy and diagnostics are not only well established but also very successful, they suffer from two drawbacks. Due to physical restrictions of gamma cameras used for ^{131}I imaging, the special resolution is limited and there is significant septa penetration degrading the scintigram. Therefore, in the presence of the extremely high uptake of thyroid remnant, many local metastases may not be detected by the scintigraphy following the first therapy. The resulting uncertainty in staging probably requires in a certain way an overtreatment. The second drawback in conventional therapy is the unfeasible or inaccurate dosimetry. Iodine imaging is very selective and therefore the morphological correlate is often missing. In the face of the unknown depth of the lesion, attenuation correction cannot be applied and, in addition, due to the missing volume information, dosimetry is completely impossible. Therefore, the usual radioiodine therapy is performed using risk-adapted standard activities.

7.2 ^{124}I Characteristics

The above-mentioned drawbacks may be mostly overcome by replacing the gamma camera by PET using ^{124}I. ^{124}I is a positron emitter with a half-life of 4.2 days, but only 23% of the transition results in positron emission. The complex decay scheme of ^{124}I includes several high-energy gamma rays, making ^{124}I imaging a challenge even for high-quality PET systems. There are single gamma quanta – in cascade with positron emission – with energies of 603 keV and 723 keV and abundance of 62% and 10%, respectively. Since the typical discriminator energy window of PET ranges from 350 to 650 keV, additional random counts resulting from gamma coincidences, scatter (versus the annihilation coincidences) will occur and result in lower image contrast. The mean positron energy is less than 1 MeV; therefore, a degradation of image resolution caused by long-range positrons does not occur.

Widespread application is hampered today by its very restricted availability. ^{124}I is preferably produced using a high-energetic cyclotron. We apply the ^{124}Te(d,2n)^{124}I reaction using a 14-MeV deuteron beam (a detailed description of the radiopharmaceutical production, preparation, and its impurities is given elsewhere [7]). A variety of PET scanners have been characterized for the use of ^{124}I, and satisfactory imaging results can be achieved in realistic settings [13, 15–19]. Thus, ^{124}I is suitable for quantitative PET imaging and has been used for dosimetry [8–14].

The requested high specificity of the tracer that makes it ideal for detecting lesions results in a lack of identifiable anatomical structures, thus making an accurate localization of foci of tracer uptake highly problematic [20, 22]. This disadvantage is overcome by correlating the PET information with available anatomical background information obtained, for instance, from a combined PET/CT.

We propose to apply 50 MBq ^{124}I for dosimetric purposes and 25 MBq if only cervical imaging is intended. After oral administration measurements after 4, 24, 48, 72, and 96 h are proposed for accurate dosimetry. We expect that a single uptake measurement (after 2 or 3 days) may replace the multiple measurements that have already been proven for benign thyroid diseases [21]. In spite of the above-mentioned randoms due to high-energy gamma rays, it could be proven that the use of the three-dimensional (3D) mode is appropriate [16–19], and acquisition times of 5-min emissions per bed position are suitable. Therefore, a whole body scan in the PET/CT requires approximately 30 min. It has to be said that if PET/CT scans are performed the application of iodinated contrast agents is strictly forbidden.

7.3 Metastases Dosimetry Using ^{124}I PET

Furhang and coworkers [23] published a reasonable procedure for dosimetry using ^{124}I PET. Our modifications have resulted in a quite complex bundle of measurements. There are two targets for dosimetry: determining the lesion

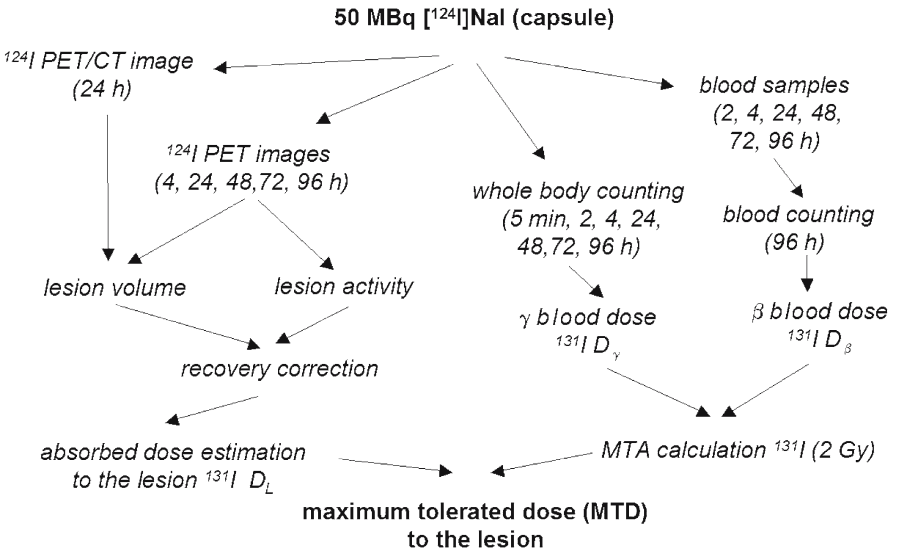

Fig. 7.1 The radioiodine dosimetry procedure for differentiated thyroid cancer (DTC) using ^{124}I (MTA maximum tolerated activity)

dose and the dose deposited in the bone marrow that is the organ at risk. Blood is taken as the surrogate marker for bone marrow toxicity. Parallel to external beam radiation, 2 Gy is used as dose constraint to the bone marrow. Thus, 2 Gy to the blood is used to calculate the maximum tolerated activity (MTA) assuming that the iodine kinetics during the ^{124}I dosimetry is similar to that of the ^{131}I under therapeutic conditions. Finally, using the calculated MTA, the maximum potential dose in each lesion is calculated. Depending on the result, the indication for radioiodine therapy is derived. Apart from small local metastases, absorbed doses well above 100 Gy are needed for cure. Absorbed doses below 30 Gy usually have only limited effect.

As illustrated in Fig. 7.1, the radioiodine dosimetry procedure consists of two parts: blood and whole-body counting as well as PET(/CT) imaging. The blood and whole-body counting monitors the respective radioiodine kinetics. The time activity curves are then used to estimate the absorbed dose to blood per unit of administered activity to the lesion.

Specifically, the patient was given an activity of about 50 MBq of ^{124}I. The blood dose is derived from measurements of daily blood samples. In addition, whole-body clearance measurements need to be carried out, e.g., employing an uncollimated gamma camera with the patient standing a large distance away (4 m). The measurements need to be taken in anterior and posterior view to account for absorption. The blood dose per unit of administered activity consists of two components, β blood and γ blood dose, and are estimated using their corresponding time-activity curves. PET imaging is performed using (single) PET and combined PET/CT. The daily whole-body measurements were carried out

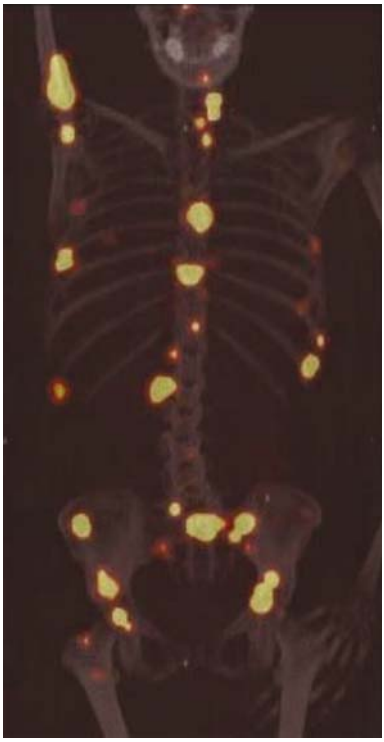

Fig. 7.2 ^{124}I PET/CT image acquired 24 h after oral administration of 45 MBq shows multiple bone metastases

with PET, and after 24 h one PET/CT image was taken. Both sets of images were used to obtain the lesion volume, either from PET images using the threshold technique [24] and/or directly from the CT images. The lesion activity corrected with the measured recovery coefficient was used to estimate the absorbed dose per unit of administered activity of each lesion.

In summary, the absorbed dose to the lesions per unit of administered activity and the MTA are used to calculate the maximum tolerated dose (MTD) to the DTC lesions that is essential in estimating the success of radioiodine therapy. A clinical example illustrates the usefulness of the ^{124}I dosimetry.

A 49-year-old woman suffered from a pathological fracture of the right humerus. The following clinical workup resulted in an advanced follicular thyroid carcinoma (pT4 pN1 M1 os). Three weeks after thyroidectomy, the patient presented with severe bone pain, and multiple bone metastases were seen in bone scintigraphy. Blood concentration of thyroglobulin was 16,800.0 ng/ml with undisturbed recovery test and negative thyroglobulin antibodies. As desired was risen to TSH 43 mU/l. Due to the extent of the disease, the patient received ^{124}I dosimetry in order to apply maximum activity.

^{124}I PET imaging showed multiple iodine-avid bone metastases (see Fig. 7.2). Lesion dosimetry yielded a dose of 30–150 Gy/GBq and a MTA of 5 GBq, thus revealing a MTD of 150–750 Gy. As this high-risk patient had a poor prognosis

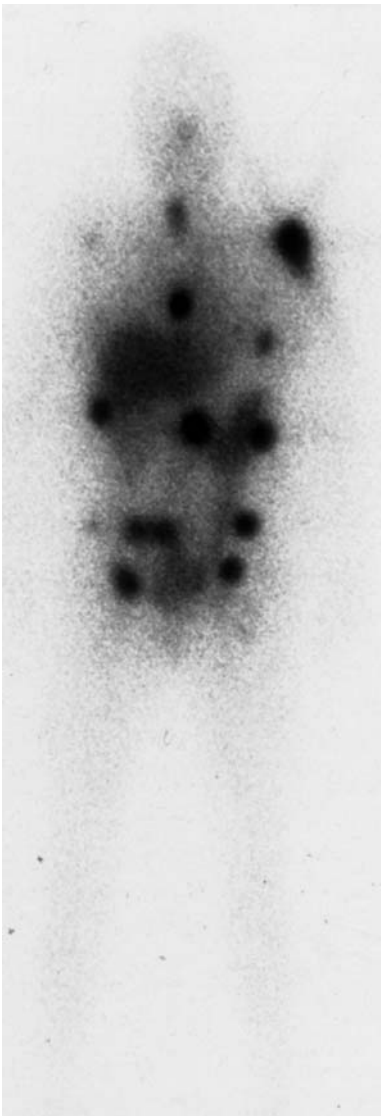

Fig. 7.3 ^{131}I whole-body scan acquired 10 days after oral administration of 10 GBq showing bone metastases

and the algorithm to qualify the MTA is conservative, the patient was treated with 10 GBq of ^{131}I with a hematological backup. Side-effects of this high-dose therapy were transient decrease in lymphocytes (from 2.1/nl to a minimum of 0.2/nl on posttherapy day 6), recurrent fever requiring antibiotic therapy and intermittent worsening of bone pain resulting in morphine therapy. The ^{131}I whole-body scan 10 days after application of 10 GBq ^{131}I demonstrated an extensive activity retention in the lesions known from the ^{124}I PET (see Fig. 7.3). At

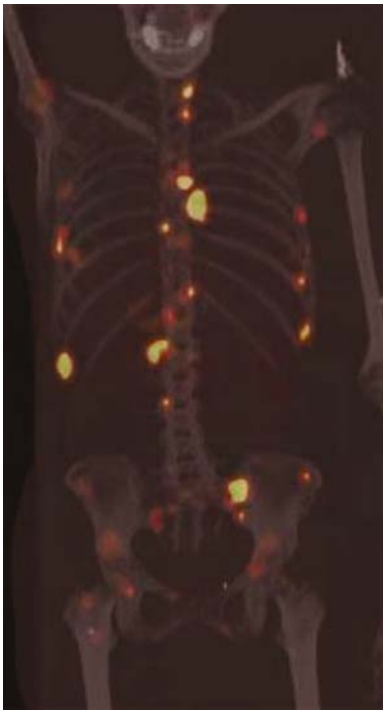

Fig. 7.4 ^{124}I PET/CT image acquired 24 h after oral administration of 48 MBq shows multiple, clearly declining bone metastases (see Fig. 7.2)

that time the patient already recovered from the bone pain that was increased as a flair phenomenon.

Four months posttherapy, the patient was readmitted for a second radioiodine dosimetry and subsequent radioiodine therapy. She was in good general health. Thyroglobulin was decreased to less than 10% of the initial value (1,240.0 ng/ml), again undisturbed, TSH 52 mU/l. ^{124}I PET(/CT) had a considerable effect on patient management, resulting in complete remission in many lesions and a dramatic decrease in iodine uptake in most other metastases (see Fig. 7.4). As a consequence of the second dosimetry, radioiodine therapy with 8 GBq ^{131}I was given.

7.4 PET/CT Imaging with ^{124}I

As of February 2005, there have been no studies examining the impact of ^{124}I PET on the management of differentiated thyroid cancer, although ^{124}I PET has been shown to be an useful imaging technique for the diagnosis and management of thyroid diseases [13]. However, interpreting PET scans with highly specific tracers such as ^{124}I is challenged by the lack of identifiable anatomical

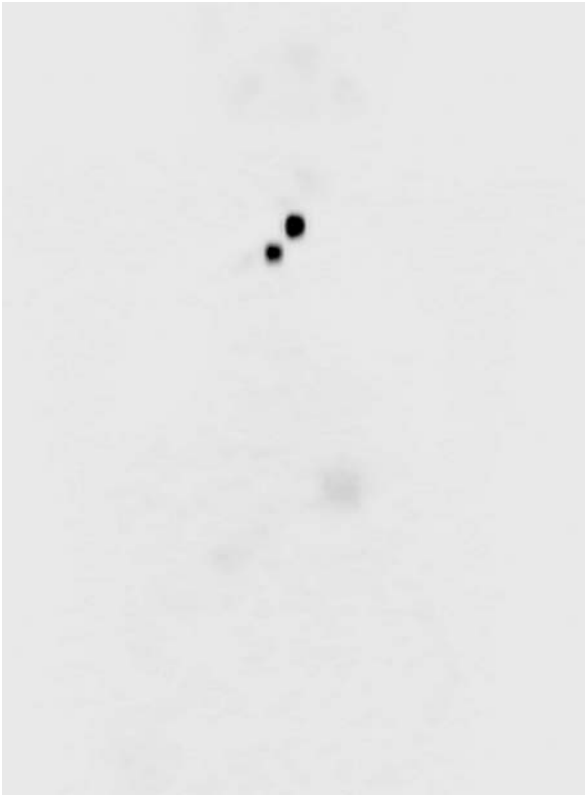

Fig. 7.5 ^{124}I PET acquired 24 h after oral administration of 50 MBq showing pathological tracer uptake cervically or mediastinally

structures in PET images. This shortcoming of diagnostic procedures using radioactive iodine is reduced by PET/CT.

An example illustrates this finding. A 54-year-old man with a history of well-differentiated (G1) follicular thyroid carcinoma (1 cm in diameter, with penetration of the thyroid capsule, pT4 pN0 MX) developed an increased thyroglobulin blood concentration of 1.8 ng/ml; recovery test 68%; thyroid stimulating hormone 68 mU/l, fT3 2.9 ng/ml, and fT4 2.8 ng/ml. Cervical ultrasonography showed no pathological structures. Prior to further treatment, an accurate staging was desired.

Images on a combined PET/CT system were acquired (Biograph, Siemens) 24 h after oral administration of 50 MBq of ^{124}I. Projections from head to pelvis were obtained. The PET scan alone showed pathologically increased tracer uptake in two foci located cervically or mediastinally (see Fig. 7.5). An accurate anatomical localization of these foci was not completely possible as the tracer is highly specific. The CT scan alone showed no pathology. Image fusion of PET and the coregistered CT enabled to attribute the pathological tracer uptake to an area close to the aorta representing mediastinal micrometastases (see Fig. 7.6).

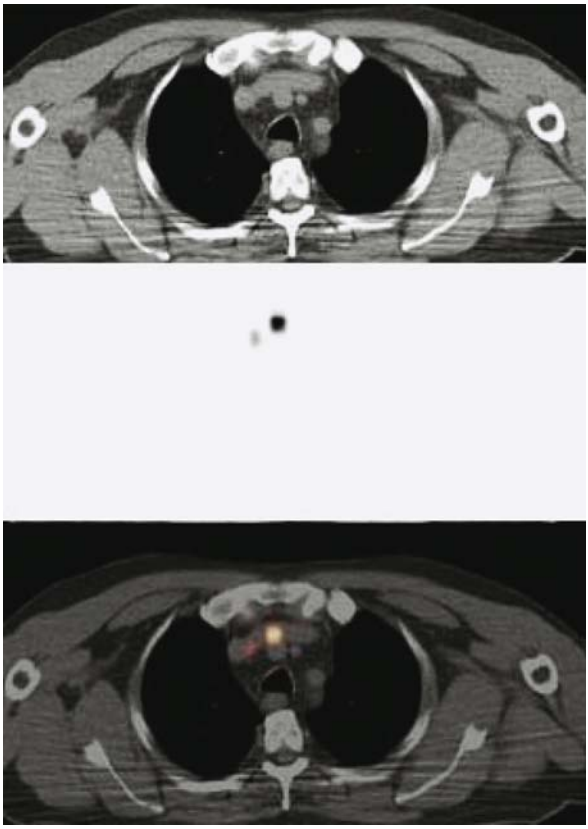

Fig. 7.6 ^{124}I PET (A), CT (B), and PET/CT (C) acquired 24 h after oral administration of 85 MBq pathological tracer uptake mediastinally, representing mediastinal micrometastases close to the aorta

This case illustrates the potential of ^{124}I PET/CT in exact anatomical localization of DTC metastases.

In a pilot study, we showed the clinical usefulness of ^{124}I PET/CT with lesion detection rates of 97% compared with high-dose ^{131}I whole-body scan with lesion detection rates of 83% [19]. PET/CT not only adds the morphological information to the ^{124}I PET, but also has the power to assess iodine-negative metastases. Due to the small patient group, the impact of ^{124}I PET/CT on patient management could not be evaluated. However, with ^{124}I PET/CT being superior to ^{131}I whole-body scan with respect to lesion detectability on a lesion-by-lesion basis, an impact on patient management appears to be likely. Several case reports support this finding [16–20, 25].

Another advantage of combined ^{124}I PET and CT are synergistic effects. Although the combined assessment of fused PET and CT images in a fusion display does not reveal additional tumor manifestations compared with PET and CT alone, the accurate topographic localization of the tumor can result in a change of staging and in therapy management [16–19, 25]. From these consid-

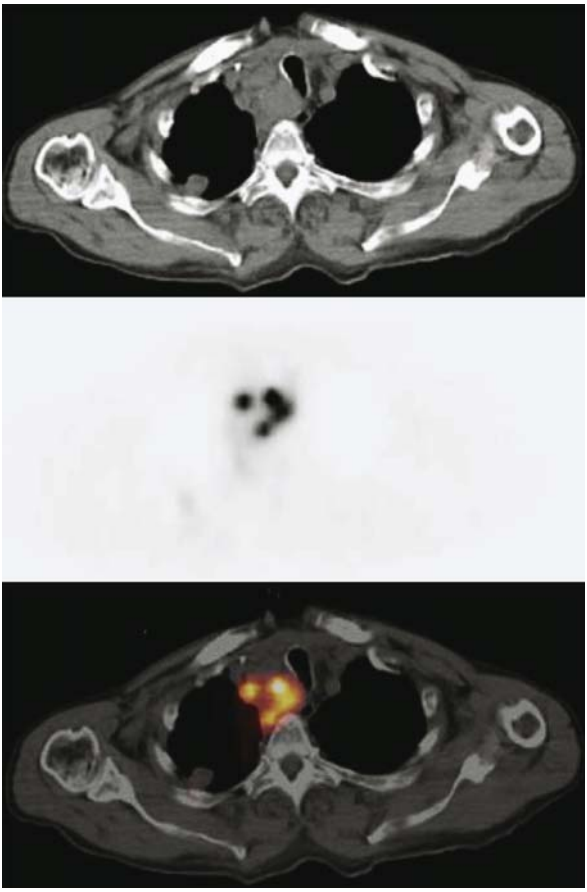

Fig. 7.7 ^{124}I PET (A), CT (B), and PET/CT (C) images acquired 24 h after oral administration of 50 MBq show pathological tracer uptake mediastinally representing four iodine-avid mediastinal metastases. Additional non-iodine-avid metastases were found in the mediastinum and lung

erations, it is clear that ^{124}I PET/CT may provide incremental diagnostic value over the individual imaging modalities.

As an example, a 46-year-old man with advanced papillary thyroid carcinoma (pT4 pN1 MX) was referred to the Department of Nuclear Medicine for radioiodine therapy. The physical examination showed a patient in good general health. On admission, the following pathological laboratory values were seen: thyroglobulin 29.0 ng/ml; recovery test 81%; thyroid-stimulating hormone 51 mU/l, fT3 2.3 ng/ml, and fT4 2.5 ng/ml. Results of cervical ultrasonography suggested a cervical metastasis. Prior to therapy, this high-risk patient received ^{124}I dosimetry to allow individual treatment planning. Images on a combined PET/CT system were acquired (Biograph, Siemens) 26 h after oral administration of 50 MBq ^{124}I. The PET scan alone showed pathologically increased tracer uptake in four mediastinal metastases (see Fig. 7.7); however, the additional CT and subsequent PET/CT showed additional, non-iodine-avid metastases (mediastinal and pulmonary). The patient was referred to the Department of Radia-

tion Therapy for further treatment and underwent external beam radiotherapy. Hence, PET/CT allowed fast treatment stratification and therapy.

In addition, logistics and economics of the diagnostic tests have to be analyzed. PET/CT certainly adds significant costs to the diagnostic workup; nevertheless, there are savings too from shortening the workup and keeping the patient at work. ^{124}I PET/CT can be performed on a outpatient basis – another economic factor. A high-dose, whole-body scan is typically performed 3–8 days after the administration of ^{131}I. Nevertheless scanning can be difficult in terms of septal penetration at high ^{131}I activity. Sometimes a secondary scan, e.g., 4–5 days later, may be necessary to obtain higher-quality ^{131}I images. This implies a separate visit to the hospital for patients who often live far from the treatment center (low prevalence of thyroid cancer). In contrast, ^{124}I PET/CT allows us to complete diagnostic imaging in a much shorter time span without sacrifice in diagnostic accuracy compared with high-dose ^{131}I whole-body scan. As a consequence, faster treatment stratification is possible, e.g., initiation of surgery for the removal of easily accessible tumor manifestations or external beam radiation for metastases with insufficient uptake for radioiodine therapy.

Moreover, a radiation exposure of 5 mSv from the administration of 50 MBq of ^{124}I compares favorably with 60 mSv from 1,000 MBq ^{131}I [26]. Our data showed the superiority of ^{124}I PET over planar ^{131}I whole-body scan even at lower ^{124}I activities. Thus, ^{124}I PET presumably is a suitable alternative for high-dose diagnostic ^{131}I whole-body scan [27] in follow-up of DTC that is less time-consuming and more convenient for the patient.

7.5 Conclusions

^{124}I is an efficient diagnostic tool in DTC and allows not only sensitive imaging but also precise dosimetry. The dosimetry procedure using ^{124}I allows estimation of the maximum tolerated dose to the lesions with acceptable accuracy. In contrast to the conventional procedures using, for instance, gamma cameras, it allows absolute quantification. The ^{124}I dosimetry has been clinically proven to be useful. It is a promising approach in patients suffering from advanced DTC before radioiodine therapy and patients with suspected recurrence and/or metastases.

In addition to the synergistic effects of combining morphological imaging with highly specific functional imaging, ^{124}I PET/CT represents a suitable, low-dose alternative to the clinical standard of high-dose ^{131}I whole-body scan in follow-up of patients with DTC. The diagnostic and logistic advantages of ^{124}I PET dosimetry and PET/CT imaging can only be utilized clinically if ^{124}I becomes more widely available.

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