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High Level of Agreement between Pretherapeutic ^{124}I PET and Intratherapeutic ^{131}I Images in Detecting Iodine-positive Thyroid Cancer Metastases

Marcus Ruhlmann[1], Walter Jentzen[1], Verena Ruhlmann[1], Cinzia Pettinato[2], Gloria Rossi[3], Ina Binse[1], Andreas Bockisch[1], Sandra Rosenbaum-Krumme[1]

[1] Department of Nuclear Medicine, University Hospital, University Duisburg-Essen
[2] Medical Physics Unit, Orsola-Malpighi University Hospital, Bologna, Italy
[3] Medical Physics Unit, Service Department Macerata Hospital, Macerata, Italy

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For correspondence:
Marcus Ruhlmann, MD
Klinik für Nuklearmedizin, Universität Duisburg-Essen
Hufelandstrasse 55
D-45122 Essen
Germany
FAX: +49-201-723-5964, Phone: +49-201-723-2032
email: marcus.ruhlmann@uk-essen.de

ABSTRACT

The aim of this retrospective study was to assess the level of agreement between **positron emission tomography (PET)** and scintigraphies using diagnostic tracer amounts of ^{124}I and therapeutic activities of ^{131}I, respectively, in detecting iodine-positive metastases in patients with differentiated thyroid carcinoma.

Methods: Patients were included who underwent two ^{124}I PET**/computed tomography (CT)** scans (24 and 120 h) after administration of approximately 25 MBq and subsequently received ^{131}I **images** 5–10 days after therapeutic activities (1–10 GBq). For each patient, intratherapeutic ^{131}I **images** comprised a whole body scintigraphy scan and, in addition, a **single photon emission computed tomography/CT** (SPECT/CT) scan of the neck to distinguish between metastatic and thyroid remnant tissues. Iodine uptake was rated as metastatic focus if the lesion was located outside the thyroid bed. A lesion-based and a patient-based analysis was performed.

Results: 137 patients were included with a total of 227 iodine-positive metastases detected by both functional imaging modalities together. In the lesion-based analysis, ^{124}I PET and ^{131}I **images** detected 98% (223/227) and 99% (225/227) iodine-positive metastases, respectively; the level of agreement between ^{124}I PET and ^{131}I **images** was 97% (221/227). 4 metastases (3 lymph nodes, 1 bone) in 4 patients were ^{124}I-negative findings but positive in ^{131}I **images**, and 2 lymph node metastases in 2 patients were ^{131}I-negative findings but positive in ^{124}I PET/CT. In the patient-based analysis 61/137 patients presented with iodine-positive metastases. ^{124}I PET and ^{131}I **images** detected 97% (59/61) and 98% (60/61) patients with at least one iodine positive metastasis, respectively. The level of agreement was 95% (58/61). Both imaging modalities concordantly identified 76 out of 137 patients without pathological iodine uptake.

Conclusion: Because of the high level of agreement, pretherapeutic ^{124}I PET/CT is an adequate methodology in the detection of iodine-positive metastases and can be used as a reliable tool for staging of thyroid cancer patients and individual treatment planning.

Keywords: ^{124}I PET/CT, SPECT/CT, whole body scintigraphy, thyroid cancer, radioiodine therapy

INTRODUCTION

Radioiodine therapy is an integral component in the treatment of differentiated thyroid cancer (DTC). The identification of iodine-positive metastases is crucial for therapy planning and patient management. The detection sensitivity of metastases depends besides biological factors on radioiodine isotopes and imaging device characteristics.

Over the last decade, the use of the positron-emitting ^{124}I with diagnostic activities of 20–80 MBq has become more frequent in staging (*1–7*) and in pretherapeutic dosimetry to estimate the absorbed doses of iodine-positive foci and of organs at risk to optimise radioiodine therapy (*7–13*). Its more frequent use is mainly related to the higher scanner efficiency of positron emission tomography/computed tomography (^{124}I PET/CT) and higher sensitivity for detection of iodine-positive foci when using similar diagnostic activities and its higher quantitative capacity relative to ^{131}I whole body scintigraphy (WBS) or single photon emission computed tomography/CT (SPECT/CT) (*4,5,14*). Especially in high-risk patients, a pretherapeutic ^{124}I PET/CT, either as part of a dosimetry approach or imaging only, was demonstrated to be beneficial in detecting local and distant metastases and resulted in an alteration of therapy management (*2,4,6,7,9–11*). Moreover, ^{124}I PET/CT has been mentioned in European and American guidelines (*15,16*).

However, a recent study by Lammers et al. (*17*) casted doubt on the benefit of ^{124}I PET/CT in the detection of iodine-positive metastases compared with intratherapeutic ^{131}I imaging. They reported, that ^{124}I PET/CT failed to predict uptake in metastatic tissue in a significant number of patients, observed in intratherapeutic ^{131}I scintigraphy acquired 7 days after administration of 3.7–7.4 GBq, indicating a poor sensitivity in detecting iodine-positive metastases using tracer amount of 40 MBq ^{124}I. This finding heavily contradicts the clinical experience and current literature (*7,10*).

For over a decade, we have been routinely applying ^{124}I PET(/CT) in high-risk DTC patients, including pretherapeutic dosimetry to estimate the individual optimised therapeutic radioiodine activity.

On the basis of these data, we analysed the level of agreement between ^{124}I PET and intratherapeutic ^{131}I **images** in detecting iodine-positive metastases in a large patient cohort.

MATERIALS AND METHODS

Patients

All patients gave their informed consent and the local medical research ethics committee approved the study. Patients were included, who underwent serial ^{124}I PET/CT scans (as part of the pretherapeutic dosimetry protocol) and subsequently radioiodine therapy several days after the last ^{124}I PET/CT scan, including intratherapeutic ^{131}I **images**. The patients were requested to maintain a low iodine diet for at least four weeks prior to the examinations (verified by urine iodine <250 µg/g creatinine).

137 DTC patients (110 papillary carcinomas, 20 follicular carcinomas and 7 poorly differentiated carcinomas) were included. At the time of dosimetry, the mean age of the patients (90 females and 47 males) was 50 years (median: 51 years; range: 12–85 years). ^{124}I PET/CT dosimetry and radioiodine therapy were performed in hormone withdrawal (n= 133) or with recombinant thyroid stimulating hormone (n=4). In all cases, the serum thyroid stimulating hormone value was at least 30 mU/L.

106/137 patients underwent dosimetry 4 weeks after thyroidectomy because of a high-risk DTC as initial diagnosis. Dosimetry was performed in the remaining 31/137 patients because of increasing serum thyroglobulin for tumour localization or indistinct findings during the first radioiodine therapy. In these 31 patients, the number of already performed radioiodine treatment was on average 1.4 (median: 1; range: 1–6) with mean applied cumulative activity of 6.7 GBq ^{131}I (median: 3.0 GBq; range: 1.0–47.0 GBq) and mean **thyroglobulin** value was 528 ng/mL (median: 16.0 ng/mL; range: 0.0–9304 ng/mL).

Pretherapeutic ^{124}I PET/CT

^{124}I PET/CT was performed 24 and 120 h after oral application of a mean ^{124}I activity of 24.1 MBq (median: 24.3 MBq; range: 20.2–28.5 MBq) according to our dosimetry protocol (8,12). It is expected that this low activity does not cause a significant stunning effect. The images were acquired on a Biograph Duo PET/CT scanner (Siemens Medical Solutions; Illinois, USA). The examinations included whole body PET/CT scans from head to thigh using 5–8 bed positions. PET/CT scans started with a spiral CT in low-dose technique (tube voltage of 110 kVp, tube current time product of 15 mAs, beam pitch of 2.0, and slice width of 5 mm, collimation 4 mm, table-feed 16 mm). No contrast agent was applied. Subsequently, PET scan was acquired with an emission time of 240 s per bed position.

The PET images were reconstructed after Fourier-rebinning. In the reconstruction, an attenuation-weighted ordered-subset expectation maximization algorithm was used. Standard corrections for random coincidence, dead time, and scatter were performed. Images were corrected for attenuation with a CT-based attenuation correction method. For image assessment, the standard image reconstruction parameters were 2 iterations and 8 subsets, a post-reconstruction 3D Gaussian smoothing filter of 5 mm, and a reconstructed voxel size of 5.2x5.2x2.4 mm^3. The CT images were reconstructed with a voxel size of 1.0 x 1.0 x 5.0 mm^3; the standard reconstruction kernel B30f was used.

Intratherapeutic ^{131}I Images

The authors prefer the term “intratherapeutic” **images** to be used instead of “postherapeutic” to avoid confusion with “follow-up” imaging. The intratherapeutic WBS was performed 5-10 days after radioiodine therapy (mean ^{131}I activity of 4.4 GBq; median: 3.0 GBq; range: 1.0–10.0 GBq) using a double-headed gamma camera (Symbia S; Siemens, Erlangen, Germany) equipped with a high-energy, parallel-hole collimator. The table speed was 15 cm/min. The matrix size was 256x1024, resulting in 2.4x2.4 mm^2 pixel size.

All patients underwent a SPECT/CT of the neck (Symbia T2; Siemens, Erlangen, Germany), equipped with a high energy, parallel-hole collimator. A low-dose CT for attenuation correction was conducted (tube voltage of 130 kVp, tube current time product of 17 mAs, beam pitch of 1.5, and slice width of 5 mm) without contrast agent. The SPECT scan was acquired using 128 angles over 360 degrees and 25 s per stop. Images were iteratively reconstructed and corrected for attenuation and scatter (iterative reconstruction Flash 3D, 4 subsets and 8 iterations, Gaussian inter-sliced smoothing filter, attenuation coefficient 0.15 cm^{-1}). The image matrix was 128x128, resulting in a cuboid-shaped voxel length of 4.8 mm.

Lesion-based and Patient-based Analysis

Four experienced nuclear physicians separately interpreted the ^{124}I PET/CT, ^{131}I WBS and ^{131}I SPECT/CT images in different sessions and blinded to each other. The findings derived from PET images were compared with the findings derived from **^{131}I images**. In cases of different observer ratings, a consensus was obtained in an additional session. A focal iodine uptake was rated as metastatic tissue if the focus was located outside the thyroid bed. Iodine-positive foci within the thyroid bed were rated as probably thyroid remnants and were not included. A lesion-based and a patient-based analysis were performed to assess the findings derived from ^{124}I PET and ^{131}I **images**. Foci were considered positive on ^{124}I PET if they were evident on early or late images.

In the lesion-based analysis, the total number of iodine-positive foci were counted, which were detected by both functional imaging modalities together. The level of agreement regarding concordantly detected foci in ^{124}I PET and ^{131}I **images** was determined. As demonstrated in the result section, there were multiple pulmonary and osseous metastases in some patients. In these cases, the number of pulmonary or osseous foci were restricted to 7 metastases in each patient to avoid selection bias. The limit of 7 foci was selected because, in the other patients, the highest number of distinguishable lung or bone metastases was 7 metastases in one patient. The maximum signal and the signal-to-background ratios of the discordant foci were derived from the images.

In the patient-based analysis, the number of iodine-positive patients were counted that were detected by both functional imaging modalities together. The level of agreement regarding iodine-positive patients observed in each modality was determined.

RESULTS

Lesion-based and Patient-based Assessment

A total of 227 metastases (91 lymph nodes, 76 lung metastases, 55 bones, 5 other tissue) were detected by the imaging modalities together. Many pulmonary and bone metastases (≥ 7) were found in 8 patients and 5 patients, respectively. ^{124}I PET alone detected 223/227 (98%) metastases and ^{131}I **images** found 225/227 (99%) metastases. The level of agreement between ^{124}I PET and **images** was 97% (221/227). Important properties of the six discordant foci of 6 patients are listed in Table 1. There were 4 foci (nos. 1–4) before the first radioiodine treatment and 2 foci (nos. 5 and 6) after radioiodine treatment. 2 lymph node metastases (nos. 1, 2) were ^{131}I-negative findings and only conspicuous by ^{124}I PET. 3 lymph node metastases (nos. 3, 4, 6) and 1 bone metastases (no. 5) in 4 patients were ^{124}I-negative findings but positive in ^{131}I **images**. The images of the lesions nos. 1 and 5 are illustrated in the Figures **1** and 2, showing metastases only detected by ^{124}I PET/CT and ^{131}I **images**, respectively.

In the patient-based assessment, a total of 61 patients were categorized as iodine-positive. ^{124}I PET detected 59/61 (97%) patients and ^{131}I **images** 60/61 (98%) patients as iodine-positive. The level of agreement between ^{124}I PET and **^{131}I images** was 95% (58/61). A total of 76/137 patients were concordantly without iodine-positive metastases by both imaging modalities.

DISCUSSION

When administering radioiodine activities for diagnostic purposes, ^{124}I PET has been proven to detect more iodine-positive foci relative to ^{131}I **WBS** (*4,5*). The amount of activities used in these published studies was 63-74 MBq ^{124}I and 37-74 MBq ^{131}I, respectively. Consequently, ^{124}I PET is considered the favourable diagnostic tool to detect metastatic foci. When applying a therapeutic amount of ^{131}I activity, several studies (*1,7,9*) have also shown the superiority of ^{124}I over intratherapeutic ^{131}I **images**. However, two studies (*17,18*) reported that ^{124}I PET may be inferior.

The present study demonstrates in a large patient cohort (including radioiodine naive patients and patients with previous radioiodine treatment) a high level of lesion-based and patient-based agreement between diagnostic ^{124}I PET and intratherapeutic ^{131}I **images**. Only 6 iodine-positive metastases in 6 patients (Table 1) were discordantly detected out of 227 metastases found in 61 patients. Possible reasonable explanations could be as follows: Metastasis no. 1 was only detected by ^{124}I PET/CT and not seen on ^{131}I **WBS** performed 10 days after therapeutic radioiodine application. This could be due to fast iodine kinetics and the late time point of **WBS**. Metastasis no. 2 could probably not been seen in ^{131}I **WBS** 7 days after treatment but in early ^{124}I PET/CT because of fast iodine kinetics, too. Metastas**i**s no. 6 could be only observed in **^{131}I images** due to the high therapy activity of 10 GBq. The other three metastases (nos. 3-5) were only detected in ^{131}I **images**. Slow iodine kinetics could be an explanation.

The findings in the present study are in contrast to recently published studies (*17,18*). Lammers et al. analysed 30 patients, whereof only 7 patients underwent a subsequent radioiodine treatment (see Table 1 of reference (*17*)). The ^{124}I PET/CT imaging of the other 23 patients were compared to non-iodine imaging, such as CT or sonography and **thyroglobulin** values. Thus, a statement to a reliable detection of iodine uptake in metastases with ^{124}I PET/CT compared to non-iodine imaging is inappropriate as the presence of iodine-negative lesions, especially in metastatic patients with long-term follow-up, is well known. Khorjekar et al. also performed a patient-based

assessment and reported, that ^{124}I PET yielded ^{124}I-positive metastases in only 2 out of 12 patients with ^{131}I-positive lesions (*18*). **However, the authors could not explain the low number of ^{124}I-positive findings and mentioned that their patient population is very selected: patients after initial ^{131}I therapy with iodine-positive lesions and elevated thyroglobulin. Thus, as stated by the authors (*18*), their results should not be generalized to a different patient population. Moreover, by juxtaposing study designs, technical factors and patient populations, we did not find any relevant characteristics that may lead to a higher lesion detection with ^{124}I PET/CT in our study compared to the studies by Lammers et al. (*17*) and Khorjekar et al. (*18*).**

It should be finally noted that the high level of agreement in the present study could be explained by a simplistic approach. There are two main counteracting effects that have to be taken into account: the high therapeutic radioiodine activity and the superior scanner technology of PET/CT. In this study, applying about 30 MBq ^{124}I and a median activity of 3,000 MBq ^{131}I, assuming equal pre- and intratherapeutic iodine kinetics and neglecting physical half-life differences between ^{124}I and ^{131}I, the total amount of ^{131}I in metastases is approximately 100 times larger than of ^{124}I. However, this advantage is nullified by the lower detection limit of scintigraphic systems. Our working group recently reported (*19*), that a percentage ^{124}I uptake of approximately 0.001% can be considered as the detection limit for a 1-mL focus using 25 MBq ^{124}I. In ^{131}I scintigraphy, it has been shown that the detection limit for a focus located in the neck is also approximately 0.001% for therapy activities, being approximately 100 times larger than the diagnostic activity (*20*). Taken together, a diagnostic activity of approximately 1% of the therapeutic activity may be sufficient to achieve a high level of agreement between ^{124}I PET/CT and ^{131}I WBS including SPECT/CT.

CONCLUSION

As demonstrated in our large patient population, ^{124}I PET/CT is reliable in detecting iodine-positive metastases and provides in overall good match with intratherapeutic **^{131}I images** (WBS and

SPECT/CT of the neck). ^{124}I PET/CT can be used for individual treatment planning and staging of thyroid cancer patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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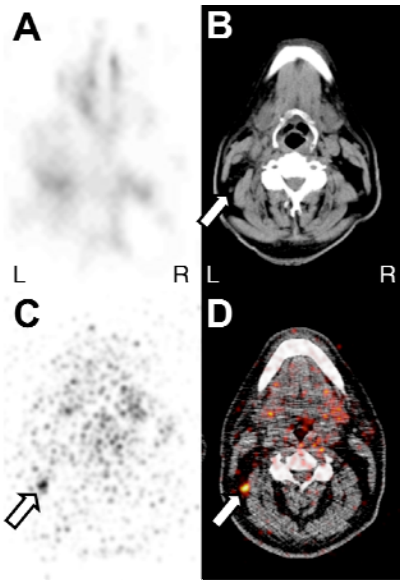

FIGURE 1. Patient with an iodine-positive metastasis (no. 1), which was only detected by early ^{124}I PET/CT (C: axial cervical PET, D: corresponding fused PET/CT) but not discernible by ^{131}I SPECT/CT (A: axial cervical SPECT corresponding to C, B: corresponding SPECT/CT). The white arrows mark the lymph node metastasis right nuchal.

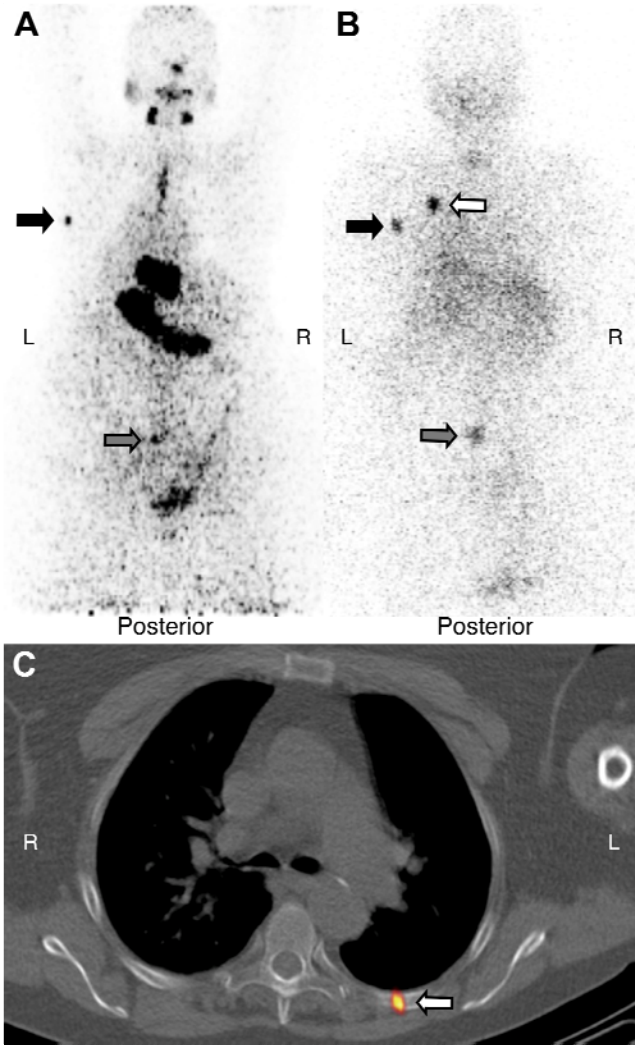

FIGURE 2. Patient with one iodine-positive metastasis (no. 5), which was not detected by ^{124}I PET (A, MIP, posterior view) but by ^{131}I WBS (B, planar posterior image) and SPECT/CT (C, axial). The black arrows mark an iodine-positive metastasis in the left scapula and the grey arrows a metastasis in the lower lumbar spine. The white arrow in images (B, C) points at a metastasis in a rib, only detected by ^{131}I **images**.

Tables

TABLE 1.

Important Properties of the Discordant Metastases, Administered Therapeutic Activities, and Time Point of **^{131}I images**

Focus	Visibility	Early ^{124}I I_{max} (kBq/mL) [a]	Late ^{124}I I_{max} (kBq/mL) [a]	^{124}I Activity (MBq)	^{131}I I_{max} (**SPECT Counts**) [a]	^{131}I Activity (GBq)	Time point of **^{131}I images** (d)
1	PET [b]	2.7 (15)	1.7 (96)	26	–	6	10
2	PET [c]	1.8 (13)	–	22	–	3	7
3	WBS, SPECT	–	–	23	37 (26)	3	7
4	WBS, SPECT	–	–	23	133 (19)	3	7
5	WBS, SPECT	–	–	28	1042 (104)	8	8
6	WBS, SPECT	–	–	22	225 (66)	10	10

[a] Maximum signal I_{max} and the respective signal-to background ratio (within parentheses); an early (1 d) and late signal (5 d) are given PET. [b] Focus observed in early (1 d) and late images (5 d). [c] Focus observed only in early image (1 d).