High Level of Agreement Between Pretherapeutic ^{124}I PET and Intratherapeutic ^{131}I Imaging 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], and Sandra Rosenbaum-Krumme[1]

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

The aim of this retrospective study was to assess the level of agreement between PET and scintigraphy using diagnostic amounts of ^{124}I and therapeutic amounts of ^{131}I, respectively, in detecting iodine-positive metastases in patients with differentiated thyroid carcinoma. **Methods:** The study included patients who underwent PET/CT 24 and 120 h after administration of approximately 25 MBq of ^{124}I and subsequently underwent imaging 5–10 d after administration of 1–10 GBq of ^{131}I. For each patient, the intratherapeutic ^{131}I imaging comprised a whole-body scintigraphy scan and a SPECT/CT scan of the neck to distinguish between metastatic and thyroid remnant tissues. Iodine uptake was rated as a metastatic focus if located outside the thyroid bed. Lesion- and patient-based analyses were performed. **Results:** The study included 137 patients with 227 metastases iodine-positive on both functional imaging modalities. In the lesion-based analysis, ^{124}I PET and ^{131}I imaging detected 98% (223/227) and 99% (225/227) of the iodine-positive metastases, respectively; the level of agreement between ^{124}I PET and ^{131}I imaging was 97% (221/227). Four metastases (3 lymph node and 1 bone) in 4 patients were ^{124}I-negative but ^{131}I-positive, and 2 lymph node metastases in 2 patients were ^{131}I-negative but ^{124}I-positive. In the patient-based analysis, 61 of the 137 patients presented with iodine-positive metastases. ^{124}I PET and ^{131}I imaging detected at least one iodine-positive metastasis in 97% (59/61) and 98% (60/61) of the patients, respectively. The level of agreement was 95% (58/61). Both imaging modalities concordantly identified 76 of 137 patients without pathologic 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 individualized treatment planning.

Key Words: ^{124}I PET/CT; SPECT/CT; whole-body scintigraphy; thyroid cancer; radioiodine therapy

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Radioiodine therapy is an integral component in the treatment of differentiated thyroid cancer. The identification of iodine-positive metastases is crucial for therapy planning and patient management. The sensitivity for detecting metastases depends on the characteristics of not only the radioiodine isotopes but also the imaging device.

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 in order to optimize radioiodine therapy (*7–13*). The more frequent use of ^{124}I is related mainly to the higher scanner efficiency of ^{124}I PET/CT, the higher sensitivity for detection of iodine-positive foci when similar amounts of diagnostic activities are applied, and the higher quantitative capacity relative to ^{131}I whole-body scintigraphy (WBS) or SPECT/CT (*4,5,14*). Especially in high-risk patients, pretherapeutic ^{124}I PET/CT, either as part of a dosimetry approach or for imaging only, was found beneficial in detecting local and distant metastases and altered 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*) cast doubt on the benefit of ^{124}I PET/CT—compared with intratherapeutic ^{131}I imaging—in the detection of iodine-positive metastases. Lammers et al. reported that in a significant number of patients, PET/CT using a tracer amount (40 MBq) of ^{124}I failed to predict the uptake in metastatic tissue observed on intratherapeutic scintigraphy performed 7 d after administration of 3.7–7.4 GBq of ^{131}I. This finding of poor sensitivity in detecting iodine-positive metastases heavily contradicts the clinical experience and current literature (*7,10*).

For over a decade, we have been routinely applying ^{124}I PET with or without CT in high-risk differentiated thyroid cancer patients, including for pretherapeutic dosimetry to estimate the individual optimized therapeutic radioiodine activity. On the basis of these data, we analyzed the level of agreement between ^{124}I PET and intratherapeutic ^{131}I imaging in detecting iodine-positive metastases in a large patient cohort.

MATERIALS AND METHODS

Patients

All patients gave written informed consent, and the local medical research ethics committee approved the study. The study consisted of patients who underwent serial ^{124}I PET/CT (as part of the pretherapeutic dosimetry protocol) and, several days after the last ^{124}I PET/CT scan, radioiodine therapy that included intratherapeutic ^{131}I imaging. The patients

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For correspondence or reprints contact: Marcus Ruhlmann, Klinik für Nuklearmedizin, Universität Duisburg-Essen, Hufelandstrasse 55, D-45122 Essen, Germany.
E-mail: marcus.ruhlmann@uk-essen.de
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were asked to maintain a low-iodine diet for at least 4 wk before the examinations (verified by a urinary iodine level < 250 μg/g creatinine).

In total, 137 patients with differentiated thyroid cancer were included (110 with papillary carcinoma, 20 with follicular carcinoma, and 7 with poorly differentiated carcinoma). At the time of dosimetry, the mean age of the patients (90 female and 47 male) was 50 y (median, 51 y; range, 12–85 y). ^{124}I PET/CT dosimetry and radioiodine therapy were performed during 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.

Of the 137 patients, 106 underwent dosimetry 4 wk after thyroidectomy as a means of initial diagnosis because they were at high risk of differentiated thyroid cancer. In the remaining 31 patients, dosimetry was performed for tumor localization because of an increasing level of serum thyroglobulin or for evaluation of indistinct findings during the first radioiodine therapy. These 31 patients had already undergone 1.4 radioiodine treatments on average (median, 1; range, 1–6), with a mean applied cumulative activity of 6.7 GBq of ^{131}I (median, 3.0 GBq; range, 1.0–47.0 GBq) and a mean thyroglobulin level of 528 ng/mL (median, 16.0 ng/mL; range, 0.0–9304 ng/mL).

Pretherapeutic ^{124}I PET/CT

PET/CT was performed 24 and 120 h after oral administration 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 was expected that this low activity would not cause a significant stunning effect. The images were acquired on a Biograph Duo PET/CT scanner (Siemens Medical Solutions). The examinations included whole-body PET/CT scans from head to thigh using 5–8 bed positions. PET/CT scanning started with a spiral CT scan using low-dose technique (tube voltage, 110 kVp; tube current–time product, 15 mAs; beam pitch, 2.0; slice width, 5 mm; collimation, 4 mm; table feed, 16 mm). No contrast agent was applied. Subsequently, a PET scan was acquired with an emission time of 240 s per bed position.

After Fourier rebinning, the PET images were reconstructed using attenuation-weighted ordered-subset expectation maximization. Standard corrections for random coincidences, dead time, and scatter were performed. The images were corrected for attenuation using a CT-based method. For image assessment, the standard image reconstruction parameters were 2 iterations and 8 subsets, a postreconstruction 3-dimensional gaussian smoothing filter of 5 mm, and a reconstructed voxel size of 5.2 × 5.2 × 2.4 mm. The CT images were reconstructed with a voxel size of 1.0 × 1.0 × 5.0 mm and the standard reconstruction kernel, B30f.

Intratherapeutic ^{131}I Imaging

We prefer using the term *intratherapeutic* imaging instead of *posttherapeutic* imaging to avoid confusion with *follow-up* imaging. The intratherapeutic WBS was performed 5–10 d after radioiodine therapy (mean ^{131}I activity, 4.4 GBq; median, 3.0 GBq; range, 1.0–10.0 GBq) using a double-head γ-camera (Symbia S; Siemens) equipped with a high-energy, parallel-hole collimator. The table speed was 15 cm/min. The matrix was 256 × 1,024, resulting in 2.4 × 2.4 mm pixels.

All patients underwent SPECT/CT of the neck on a scanner (Symbia T2; Siemens) equipped with a high-energy, parallel-hole collimator. Low-dose CT for attenuation correction was performed without a contrast agent (tube voltage, 130 kVp; tube current–time product, 17 mAs; beam pitch, 1.5; slice width, 5 mm). The SPECT scan was acquired using 128 angles over 360° and 25 s per stop. Images were iteratively reconstructed and corrected for attenuation and scatter (Flash 3D [Siemens], 4 subsets and 8 iterations; gaussian intersliced smoothing filter; attenuation coefficient, 0.15 cm^{-1}). The image matrix was 128 × 128, resulting in a cuboid voxel length of 4.8 mm.

Lesion- and Patient-Based Analyses

Four experienced nuclear physicians separately interpreted the ^{124}I PET/CT, ^{131}I WBS, and ^{131}I SPECT/CT images in different sessions and with masking 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 focus of iodine uptake was classified as metastatic tissue if located outside the thyroid bed. Iodine-positive foci within the thyroid bed were classified as probable thyroid remnants and were not included. Lesion- and patient-based analyses 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.

The lesion-based analysis counted the total number of iodine-positive foci detected by both functional imaging modalities together. The level of agreement regarding concordantly detected foci on ^{124}I PET and ^{131}I images was determined. Some patients had multiple pulmonary and osseous metastases. In these cases, the number of pulmonary or osseous foci was restricted to 7 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 in one patient. The maximum signal and the signal-to-background ratios of the discordant foci were derived from the images.

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

RESULTS

In total, 227 metastases (91 lymph node, 76 lung, 55 bone, and 5 other tissue) were detected by the imaging modalities together. Seven or more pulmonary metastases and bone metastases were found in 8 patients and 5 patients, respectively. ^{124}I PET alone detected 223 metastases (98%), and ^{131}I imaging alone detected 225 (99%). The level of agreement between ^{124}I PET and ^{131}I imaging was 97% (221/227). Some properties of the 6 discordant foci, in 6 patients, are listed in Table 1. Four (foci 1–4) were before the first radioiodine treatment, and 2 (foci 5 and 6) were after radioiodine treatment. Two lymph node metastases (foci 1 and 2) were negative on ^{131}I imaging but positive on ^{124}I PET. Three lymph node metastases (foci 3, 4, and 6) and 1 bone metastasis (focus 5) in 4 patients were ^{124}I-negative but ^{131}I-positive. Figures 1 and 2 show foci 1 and 5, which were detected only on ^{124}I PET/CT and ^{131}I imaging, respectively.

In the patient-based analysis, 61 patients were categorized as iodine-positive: 59 (97%) on ^{124}I PET and 60 (98%) on ^{131}I imaging. The level of agreement between ^{124}I PET and ^{131}I imaging was 95% (58/61). Seventy-six patients were concordantly found to be without iodine-positive metastases by both imaging modalities.

DISCUSSION

Two published studies have found that after administration of radioiodine for diagnostic purposes, a higher number of iodine-positive foci are detected by ^{124}I PET than by ^{131}I WBS (*4,5*). The activity used in these studies varied between 63–74 MBq of ^{124}I (*4*) and 37–74 MBq of ^{131}I (*5*). Consequently, ^{124}I PET is considered the favored diagnostic tool for detection of metastatic foci. Several studies have also shown the superiority of ^{124}I PET over intratherapeutic ^{131}I imaging after application of a therapeutic amount of ^{131}I activity (*1,7,9*). However, other studies (*17,18*) have found that ^{124}I PET may be inferior.

The present study demonstrated, in a large patient cohort (including radioiodine-naive patients and patients previously treated with radioiodine), a high level of lesion-based and patient-based agreement between diagnostic ^{124}I PET and intratherapeutic ^{131}I imaging. Of the

TABLE 1
Properties of Discordant Metastases, Administered Therapeutic Activities, and Time Point of ^{131}I Images

Focus	Visible on…	^{124}I I_{max} (kBq/mL)		^{124}I activity (MBq)	^{131}I I_{max} (SPECT counts)	^{131}I activity (GBq)	Time point of ^{131}I images (d)
		Early (1 d)	Late (5 d)				
1	PET*	2.7 (15)	1.7 (96)	26	–	6	10
2	PET†	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	1,042 (104)	8	8
6	WBS, SPECT	–	–	22	225 (66)	10	10

*Focus observed on early (1 d) and late (5 d) images.
†Focus observed only on early image (1 d).
I_{max} data are maximum signal, followed by signal-to-background ratio within parentheses.

227 metastases found in 61 patients, only 6 iodine-positive metastases (foci 1–6) in 6 patients (Table 1) were discordantly detected. A possible explanation for foci 1 and 2 is that they were detected on ^{124}I PET/CT but not on ^{131}I WBS after therapeutic radioiodine application because of the fast iodine kinetics and the late time points (10 d and 7 d) of WBS. Regarding focus 6, it might have been observed only on ^{131}I images because of the high therapeutic activity, 10 GBq. Detection of the other 3 metastases (foci 3–5) only on ^{131}I images might have been due to slow iodine kinetics.

The findings of the present study are in contrast to those of recently published studies (*17,18*). Lammers et al. analyzed 30 patients, and their Table 1 indicates that only 7 of them underwent subsequent radioiodine treatment (*17*). The ^{124}I PET/CT results for the other 23 patients were compared with the results of noniodine imaging, such as CT or sonography, and with thyroglobulin values. Thus, a statement to a reliable detection of iodine uptake in metastases with ^{124}I PET/CT compared with noniodine imaging is inappropriate because the presence of iodine-negative lesions, especially in metastatic patients with long-term follow-up, is well known. Khorjekar et al., who also performed a patient-based assessment, reported that ^{124}I PET yielded ^{124}I-positive metastases in only 2 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 was narrowly selected: patients after initial ^{131}I therapy with iodine-positive lesions and elevated thyroglobulin levels. Thus, as stated by the authors, their results should not be generalized to a different patient population. Moreover, when we juxtaposed study designs, technical factors, and patient populations, we did not find any relevant characteristics that might lead to higher lesion detection with ^{124}I PET/CT in our study than in the studies of Lammers et al. and Khorjekar et al.

Finally, we should note 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 considered: the high therapeutic radioiodine activity and the superior scanner technology of PET/CT. In this study, applying about 30 MBq of ^{124}I and a median of 3,000 MBq of ^{131}I, and assuming equal pre- and intratherapeutic iodine kinetics and neglecting physical half-life differences between ^{124}I and ^{131}I, the total amount of uptake in metastases was approximately 100 times larger for ^{131}I than for ^{124}I. However, this advantage is nullified by the lower detection limit of scintigraphic systems. Our working group recently reported that a

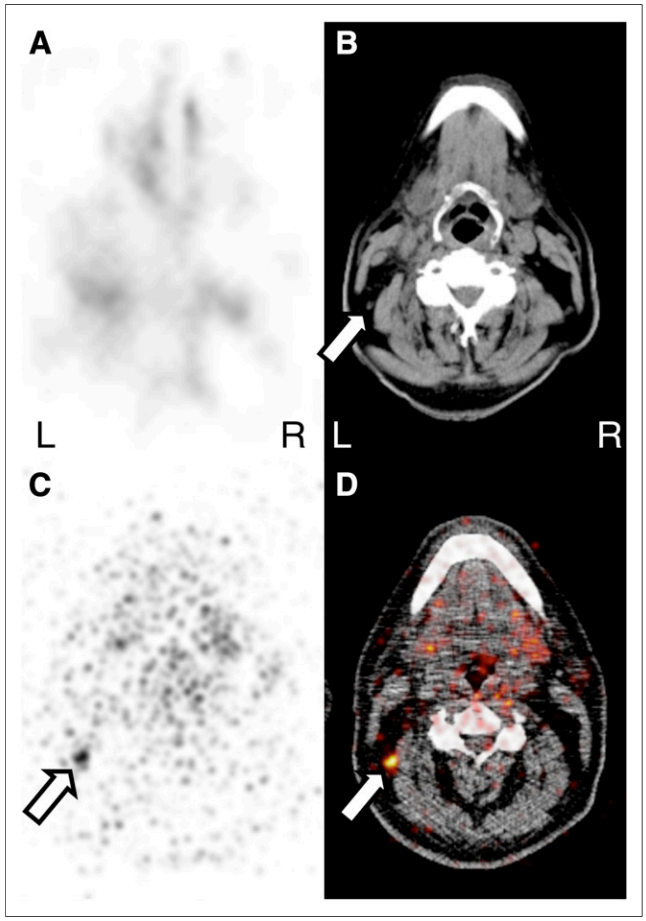

FIGURE 1. Patient with iodine-positive right nuchal lymph node metastasis (focus 1, arrows) detected by early ^{124}I PET/CT but not by ^{131}I SPECT/CT. Shown are axial cervical SPECT (A) and SPECT/CT (B) images, along with their corresponding PET (C) and PET/CT (D) images.

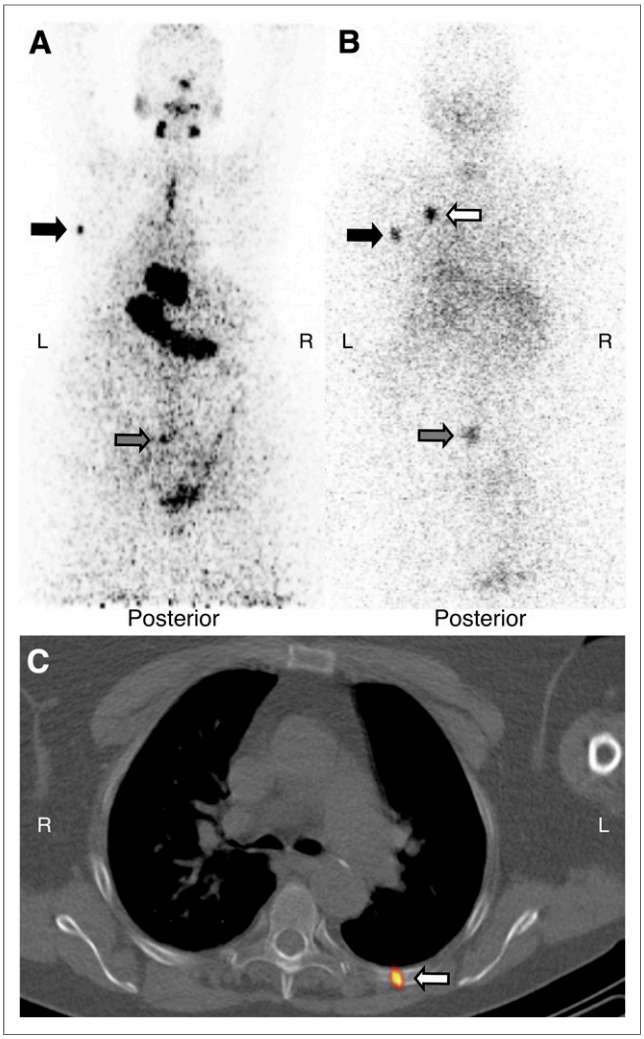

FIGURE 2. Patient with iodine-positive rib metastasis (focus 5, white arrows) detected not by maximum-intensity-projection ^{124}I PET (A) but by planar ^{131}I WBS (B) and axial SPECT/CT (C). Black arrows mark iodine-positive left scapula metastasis, and gray arrows lower lumbar spine metastasis.

^{124}I uptake of approximately 0.001% can be considered the detection limit for a 1-mL focus using 25 MBq of ^{124}I (*19*). In ^{131}I scintigraphy, it has been shown that the detection limit for a focus in the neck is also approximately 0.001% for therapeutic activities, which are 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 imaging (WBS and SPECT/CT of the neck). ^{124}I PET/CT can be used for individualized treatment planning and staging in thyroid cancer patients.

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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