Dose–Response Relationship in Differentiated Thyroid Cancer Patients Undergoing Radioiodine Treatment Assessed by Means of [124]I PET/CT

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The dose–response relationship in a fixed-activity approach generally applied in the treatment of differentiated thyroid cancer was assessed using [124]I PET/CT. **Methods:** Pretherapeutic [124]I PET/CT images of 47 patients scheduled for radioiodine therapy were retrospectively analyzed. [124]I PET/CT images were acquired 24 and 96 h after oral administration of approximately 28 MBq of [124]I-sodium iodide. Lesions were identified as thyroid remnants or metastases (lymph node, lung, bone). After a neoteric segmentation technique allowing accurate volume estimation down to the [124]I PET spatial resolution of 0.15 mL was applied, lesions were divided into a known-volume group and a small-volume group. For the known-volume group, average lesion-absorbed dose (AD) values were calculated, whereas for the small-volume group a minimum lesion AD was estimated. Lesion response was determined on the basis of [124]I PET/CT and ^{131}I SPECT/CT follow-up images. A lesion not detectable on any of the follow-up images was considered a completely responding lesion. Differences in lesion AD estimations between completely and incompletely responding lesions were evaluated by Mann–Whitney U test. Moreover, receiver-operating-characteristic curves were used to test the performance of pretherapeutic [124]I PET/CT lesion AD for prediction of complete lesion response. **Results:** In the approach of fixed radioiodine activity (3.0 ± 1.0 GBq), 89% of thyroid remnants and 69% of metastases responded completely. Except for the small-volume groups, the lesion AD of completely responding lesions was significantly higher than that of incompletely responding lesions. Using receiver-operating-characteristic curve analysis, it was shown that for the known-volume group, pretherapeutic [124]I PET/CT lesion dosimetry can be used as a prognostic tool to predict lesion-based ^{131}I therapy response with an area under the curve of 0.76 for remnants and 0.97 for metastases. The corresponding lesion AD threshold value maximizing correct complete response prediction was 90 Gy for remnants and 40 Gy for metastases. **Conclusion:** In a fixed-activity approach, a statistically significant dose–response relationship for both thyroid remnants and metastases using pretherapeutic [124]I PET/CT lesion dosimetry was found. The findings may be useful in patient management.

Radioiodine therapy is the standard adjuvant therapy after total thyroidectomy in patients with differentiated thyroid cancer (DTC) (*1,2*). The purpose of radioiodine therapy is 2-fold: ablation of thyroid remnants and treatment of radioiodine-avid metastases.

The generally accepted threshold for lesion-absorbed dose (AD) to achieve high therapy response is 85 Gy for metastases and 300 Gy for thyroid remnants (*3,4*). To predict therapy response, a reliable AD estimation requires, inter alia, accurate lesion volume determination, which is hampered by the often small lesion volumes with respect to the spatial resolution of ^{131}I scintigraphy and lesion segmentation difficulties encountered in ultrasonography, CT, or other imaging modalities (*1,5*). As a result, personalized radioiodine therapy based on lesion dosimetry is not globally adopted. In general, a fixed ^{131}I activity is administered on the basis of disease characteristics and patient age, with the risk of under- or overtreatment (*6*).

Several groups have concluded that quantitation of [124]I PET images is feasible (*7–11*). Compared with ^{131}I SPECT, [124]I PET imaging offers a higher image spatial resolution, increased counting rate sensitivity, and higher quantitative capacity, resulting in the application of pretherapeutic [124]I PET/CT–based lesion dosimetry (*12–17*).

To date, the only study assessing the dose–response relationship using [124]I PET/CT in a larger number of patients was recently published by Jentzen et al. (*17*). Pretherapeutic [124]I PET/CT lesion AD estimation and toxicity assessment were taken into consideration in patient management, allowing the administration of an optimized therapeutic activity (8.0 ± 4.3 GBq). However, using a fixed-activity approach in the absence of toxicity assessment generally results in lower administered ^{131}I activity than the optimized therapeutic activity. Consequently, it is expected that the lesion ADs in the fixed-activity approach are lower than the values published by Jentzen et al. (*17*), possibly resulting in more lesions that receive a lesion AD below the established threshold values.

Therefore, the aim of this study was to assess the dose–response relationship in an approach of a fixed therapeutic ^{131}I activity in a large group of patients using pretherapeutic [124]I PET/CT lesion dosimetry. Moreover, a new segmentation technique allowing volume

estimation down to the PET spatial resolution of [124]I was used (18). In addition, we assessed the feasibility of performing pretherapeutic [124]I PET/CT lesion dosimetry as a prognostic tool to predict therapy response in DTC patients in a fixed-activity approach.

MATERIALS AND METHODS

Patient Population

This study was approved by the institutional review board, and the requirement to obtain informed consent was waived. In the Maastricht University Medical Centre, pretherapeutic imaging with [124]I was introduced as a clinical standard in 2007. A retrospective analysis of DTC patients who underwent [124]I PET/CT examinations, followed by ^{131}I therapy, between January 2007 and December 2012 was performed. All patients had histologically confirmed papillary or follicular DTC and underwent total thyroidectomy before [124]I PET/CT examinations. None of the patients received additional treatment such as surgery or external-beam radiation therapy. Patients were included if (posttherapy) follow-up imaging with either (pretherapeutic) [124]I PET/CT or ^{131}I planar whole-body scintigraphy and ^{131}I SPECT/CT as part the radioiodine therapy was available. For patients who underwent multiple radioiodine therapies preceded by [124]I PET/CT examinations, only the data of the first radioiodine therapy were included. Patient TNM status was characterized in 4 stages according to the American Joint Committee on Cancer Staging Atlas (19). Moreover, the maximum thyroglobulin value recorded within 1 y after ^{131}I ablation therapy was reported. Until March 2011, thyroglobulin was measured using a time-resolved fluoroimmunoassay (Autodelfia; PerkinElmer) with a limit of detection of 0.5 pmol/L. From March 2011, thyroglobulin was measured using a time-resolved amplified cryptate emission assay (Brahms GmbH; Thermo Fisher) with a limit of detection of 0.25 pmol/L. Abnormal (positive) results were recorded if thyroglobulin was greater than 1.5 pmol/L. In the case of incomplete recovery of the antibody used in the assay, additional testing was done for specific antithyroglobulin antibodies.

Patient preparation was done by thyroid hormone withdrawal or recombinant human thyroid-stimulating hormone (rhTSH) and was similar for the pre- and follow-up [124]I PET/CT examinations. In the case of thyroid hormone withdrawal, patients were withdrawn from thyroxine medication for 4–6 wk or remained without medication postoperatively. In the cases of rhTSH preparation, 0.9 mg of thyrotropin alfa or rhTSH (Thyrogen; Genzyme Ltd.) was injected intramuscularly on days 1 and 2, afterward [124]I was orally administered on day 4, and [124]I PET/CT was performed on day 5 (24 h after [124]I administration) and day 8 (96 h after [124]I administration). For radioiodine therapy, a fixed-activity protocol was performed according to the Dutch guidelines, using 2.8 GBq (75 mCi) for simple thyroid remnant ablation and 5.6 GBq (150 mCi) for regional nodal disease or distant metastases.

Image Acquisition and Reconstruction

[124]I PET/CT was performed in 3-dimensional mode using a PET camera equipped with time-of-flight (Gemini TF PET/64-slice CT scanner; Philips) at 24 and 96 h after oral administration of 28.0 ± 3.3 MBq of [124]I-sodium iodide. [124]I radioactivity was measured using a 3-mL syringe filled with approximately 1 mL of [124]I solution that was placed in a validated dose calibrator (Isomed 2000; Nuklear Medizin Technik GmbH). [124]I PET scans were acquired from the head, neck, and thorax comprising 4–5 bed positions of 4 min each. In selected cases, imaging was continued until the pelvis. A low-dose spiral CT scan from the head to thigh was acquired (tube voltage, 120 kVp; effective tube current, 30 mAs; slice thickness, 4 mm), followed by the PET acquisition and supplemental high-dose CT without contrast (neck, 120 keV; 150 mAs; slice thickness, 2 mm; increment, 1.8; and thorax, 120 keV; 175 mAs;

slice thickness, 5 mm; increment, 4.0). All CT images were reconstructed using the filtered backprojection algorithm. PET images were reconstructed using the line of response–based, time-of-flight reconstruction algorithm provided by the manufacturer with a voxel size of $4 \times 4 \times 4$ mm^3. In addition, for accurate lesion volume assessment and quantification purposes, PET images were retrospectively reconstructed with a voxel size of $2 \times 2 \times 2$ mm^3. For all PET images, standard corrections for attenuation, scatter, decay, and dead-time were performed.

The ^{131}I whole-body scintigraphy was made as a total-body scan from top until toe using a table speed of 10 cm/min. SPECT/CT was acquired immediately after whole-body scintigraphy. [131]I SPECT/CT was acquired using a standard SPECT/CT camera (Precedence SPECT/6-slice CT scanner; Philips) equipped with dual 1.6-cm γ-detectors with high-energy general-purpose collimators. SPECT data were obtained by a noncircular orbit, a 128×128 matrix (voxel size, $4.7 \times 4.7 \times 4.7$ mm^3), and 32 angles over 180° and 45 s per stop, using a 364-keV photo peak with 10% window (total acquisition time, 24 min). Reconstruction space and width was 3 mm using the Philips Astonish algorithm.

Lesion Volume Calculation

The volume of each lesion with focal uptake, present on both of the pretherapeutic [124]I PET images (24 and 96 h after administration), was semiautomatically determined using an in-house–built software algorithm (Matlab; The MathWorks) based on a recently published iterative thresholding method (18). The method assumes a spherically shaped lesion with homogeneous [124]I uptake. Accounting for the reconstructed [124]I PET spatial resolution of 6.7 mm (expressed as full width at half maximum), background-corrected relative boundary–reproducing values used for lesion delineation were calculated. The smallest diameter or volume that can be determined using this method corresponds to the PET spatial resolution or its equivalent sphere volume of 0.15 mL. Consequently, lesions were classified into 2 groups in line with a previous study (17): lesions with reliable volume estimation larger than 0.15 mL, the so-called known-volume group, and lesions with a volume smaller than 0.15 mL, the small-volume group. For the known-volume group, the lesion volume was calculated as the average value of the lesion volume determined on the 24- and 96-h [124]I PET images. Lesions for which the average lesion volume differed more than 30% with respect to the 24- or 96-h volume were excluded. Lesions for which either the 24- or the 96-h volume was smaller than 0.15 mL were classified into the small-volume group. For the small-volume group, the lesion volume used for lesion AD estimation was assumed to be equal to the PET spatial resolution volume of 0.15 mL.

Lesion-Absorbed Dose Estimation

For each [124]I PET image, lesion uptake was calculated as the average activity concentration of the segmented volume, corrected for partial-volume effect, using measured (absolute) recovery coefficients (18), which effectively corrects for prompt γ-coincidence effect as well (20). Assuming identical [124]I and ^{131}I pharmacokinetics, half-life correction was performed on the [124]I activity concentration to assess the projected ^{131}I activity concentration. [131]I residence time was determined according to the adapted 2-points approach (21). In the case the effective half-life was less than the physical ^{131}I half-life, the lesion time–activity curve was parameterized using a combination of a linear uptake function and a monoexponential decay function (interception time at 8 h after ^{131}I administration). In the case the effective half-life was greater than the ^{131}I physical half-life, physical decay was assumed beyond the 96-h time point. The (self-irradiation) lesion AD was calculated using the sphere model in the Olinda software package (Olinda version 1.1; Vanderbilt University) (22). For all lesions, a density of 1.0 g/mL was used, resulting in an average and a minimum lesion AD per administered ^{131}I activity for the known-volume and small-volume

groups, respectively. The predicted average and minimum lesion AD delivered in radioiodine therapy were estimated by multiplication with the therapeutic ^{131}I activity.

Therapy Response Assessment

Lesion-Based Analysis. Lesions were classified as either thyroid remnants or metastases including lymph node or distant metastases (lymph node, lung, bone). Both the thyroid remnants and the metastases were subdivided into a known-volume group and a small-volume group. Each individual lesion was defined either as completely or as incompletely responding by an experienced nuclear medicine physician and medical physicist. Specifically, the completely responding lesion did not show ^{124}I uptake on subsequent follow-up scanning within 1 y and no ^{131}I uptake on subsequent posttherapeutic planar and SPECT/CT scanning. In contrast, the incompletely responding lesion did show focal ^{124}I or ^{131}I uptake on the day-4 scan (in the absence of significant level of background noise), not contributable to physiologic uptake according to visual assessment. For each lesion group, the predicted lesion AD in radioiodine therapy of the completely responding lesions was compared with that of the incompletely responding lesions. Moreover, the performance of pretherapeutic ^{124}I PET/CT to predict complete lesion response was assessed using receiver-operating-characteristic (ROC) curve analysis (*23*).

Patient-Based Analysis. Patients were classified as incompletely responding if persisting disease after radioiodine therapy was demonstrated, either by functional imaging (^{124}I PET/CT, ^{131}I SPECT/CT, ^{18}F-FDG), anatomic imaging (ultrasonography, MRI), histology, or increased thyroglobulin value. Otherwise patients were classified as completely responding. The average patient-based lesion AD was calculated as the mean lesion AD of all radioiodine-avid lesions observed per patient.

Statistics

Statistical analysis was performed using SPSS version 22 (IBM Corp.). Descriptive data are shown as mean ± SD (median; range). Differences between 2 groups were assessed using the Mann–Whitney *U* test. Values for *P* less than 0.05 were considered statistically significant. ROC curves were used to test the performance of pretherapeutic ^{124}I PET/CT lesion AD for the prediction of complete lesion response.

RESULTS

Patient and Lesion Characteristics

Detailed patient characteristics are provided in Table 1. Of the in total 67 patients satisfying the inclusion criteria, 1 patient was excluded because this patient received a diagnostic CT with iodine-containing contrast agent before the ^{124}I PET/CT scan. Three patients were excluded because of the lack of either the 24- or the 96-h ^{124}I PET/CT examination. Furthermore, 12 patients were excluded because of the unavailability of the PET raw data required for the additional retrospective $2 \times 2 \times 2$ mm^3 voxel image reconstruction. Four patients did not show any visible lesions on the ^{124}I PET images. Of the remaining 47 patients, 29 patients were classified as completely responding and 18 patients as incompletely responding.

TABLE 1
Characteristics of Analyzed (*n* = 47) Patients

Characteristic	Completely responding	Incompletely responding
Age (y)	51 ± 11 (52; 23–70)	50 ± 18 (53; 18–79)
Sex		
Male	4	7
Female	25	11
Number of lesions		
Thyroid remnants	74	49
Metastases	6	39
Variant		
Papillary	21	11
Follicular	21	11
TNM stage		
1	13	8
2	4	—
3	12	4
4	—	6
Maximum thyroglobulin value in FU (pmol/L)	11 ± 55 (<0.5; 0.25–290)	$2.5 \cdot 10^3 \pm 7.0 \cdot 10^3$ (5.7; < 0.2–$2.5 \cdot 10^4$)
First ^{131}I radionuclide therapy		
Yes	26	16
No	3	2
Single therapeutic ^{131}I activity (GBq)	3.0 ± 0.7 (2.8; 2.8–5.5)	3.0 ± 1.0 (2.8; 1.1–5.5)
Follow-up period (mo)	19 ± 16 (10; 4.5–61)	17 ± 17 (9; 3.5–64)

Descriptive data are shown as mean ± SD, with median and range in parentheses.

TABLE 2
Overview of Analyzed Lesions

Characteristic	Completely responding	Incompletely responding
Thyroid remnants	109	14
Known-volume group	39	8
Paratracheal	12	5
Thyroid bed	7	—
Cervical high	20	3
Small-volume group	70	6
Paratracheal	45	1
Thyroid bed	11	1
Cervical high	14	4
Metastases	31	14
Known-volume group	6	12
Thyroid bed	—	—
Neck lateral (II–V)	5	1
Cervical high	—	—
Cervical low (VI)	1	—
Distant	—	11
Small-volume group	25	2
Thyroid bed	2	1
Neck lateral (II–V)	18	—
Cervical high	4	—
Cervical low	1	—
Distant	—	1

Detailed lesion characteristics are given in Table 2. In total, 168 lesion were suitable for AD estimation. Nine lesions were excluded because of lesion volume discrepancies between the 24- and 96-h scans. For the thyroid remnants and metastases, 89% (109/123) and 69% (31/45) of the lesions showed a complete response, respectively.

Lesion-Based Therapy Response

Figure 1 illustrates the calculated lesion AD in radioiodine therapy for both thyroid remnants and metastases for all lesions (including known- and small-volume group), the known-volume group, and the small-volume group. A statistically significant higher lesion AD was observed for the completely responding lesions than the incompletely responding lesions for all lesions and the known-volume group, but not for the small-volume remnants group. Because there were only 2 incompletely responding lesions in the small-volume metastases group, no statistical tests were performed for this group. Detailed lesion data are provided in the supplemental materials (available at http://jnm.snmjournals.org).

Figure 2 shows the ROC curves for both the thyroid remnants and the metastases. Except for the metastatic small-volume group, all area under the curve values were significantly higher than 0.5. The area under the curve values were highest for the known-volume group. The arrow in Figure 2 corresponds to the established threshold values for the lesion AD of 300 Gy for thyroid remnants and 85 Gy for metastases (3,4). For the known-volume group, these threshold values resulted in sensitivity values of 0.69 and 0.67 and specificity values of 0.75 and 0.92 for the thyroid remnants and metastases, respectively. The Youden index (24), defined as the value that gives the maximum correct classification, was calculated as being 90 Gy for thyroid remnants and 40 Gy for metastases, resulting in respective sensitivity values of 0.85 and 1.0 and specificity values of 0.75 and 0.92.

Patient-Based Therapy Response

In Table 1, it can be derived that the incompletely responding patients had a higher TNM status and considerably more radioiodine-avid metastases than the completely responding patients. The median patient-based thyroid remnant lesion AD was higher for the completely responding patients (370 Gy) than the incompletely responding patients (180 Gy), but this was not statistically significant. For metastases, the median patient-based lesion AD was higher for the incompletely responding patients (63 Gy) than the completely responding patients (39 Gy) but also not statistically significant. In 7 patients, a complete response of all radioiodine-avid lesions was seen at the lesion-based analysis. However, in the patient-based analysis these did not have a complete response because during follow-up new lesions in other anatomic areas were detected with ^{18}F-FDG PET/CT, ^{124}I PET/CT, or ultrasound in combination with cytology.

DISCUSSION

Maxon et al. (3,4) demonstrated that a lesion AD threshold of 300 Gy for thyroid remnants and 85 Gy for lymph node metastases was associated with a high complete lesion response rate of 80%–90%, establishing the lesion AD as an important quantity for prediction of lesion response in radioiodine treatment. Several groups
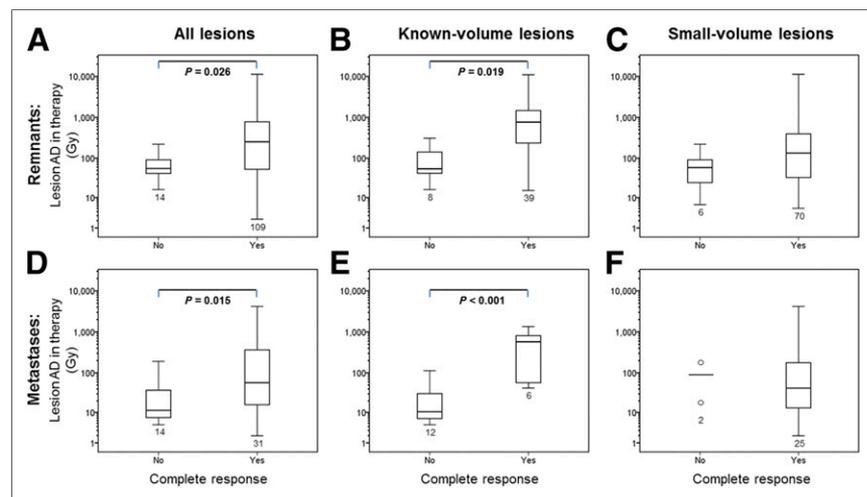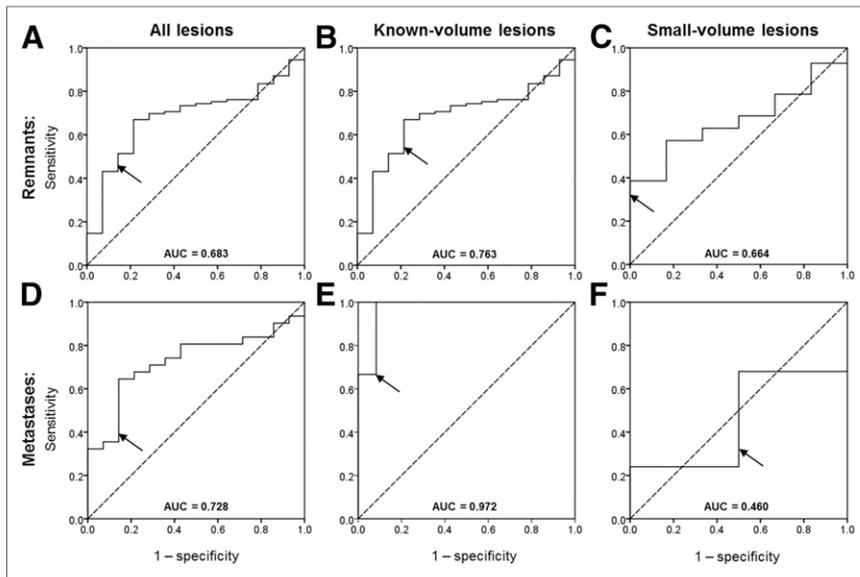

FIGURE 1. Box plots of lesion AD for both remnants (A–C) and metastases (D–F). Box plots are provided for all lesions (A and D), known-volume group (B and E), and small-volume group (C and F). Statistically significant differences are characterized by P < 0.05. Numbers close to whiskers represent number of lesions.

FIGURE 2. ROC curves for both remnants (A–C) and metastases (D–F). ROC curves are provided for all lesions (A and D), known-volume group (B and E), and small-volume group (C and F). Arrows correspond to threshold value of 300 Gy for remnants and 85 Gy for metastases. Dashed line represents line of equality.

have identified ^{124}I PET/CT as a promising modality for performing lesion-based dosimetry (*12–17*). Applying an empirically fixed radioiodine activity approach, Flower et al. (*12*) were the first to assess lesion AD in 3 patients using ^{124}I PET. In agreement with our findings, they reported that the administration of fixed activities (3.0–5.5 GBq) resulted in a large variation of lesion AD to both thyroid remnants (16–400 Gy) and involved neck nodes (2.5–33 Gy). In contrast, Erdi et al. (*13*) developed a method to estimate lesion AD of thyroid remnants based on pretherapeutic ^{124}I PET imaging at a maximum-tolerated activity of ^{131}I using a dose constraint of 2 Gy to blood. Performing this method in 3 patients, they observed a large lesion AD range (5–248 Gy) at maximum-tolerated activity (10–15.5 GBq). Indeed, an approach of maximum-tolerated activity applying a maximum blood dose of 2 Gy has been reported to be safe and well tolerated (*25–27*). Alternatively, several groups have reported an optimal activity approach using pretherapeutic ^{124}I PET/CT lesion AD calculations (*14–16*). In this approach, ^{131}I therapeutic activity was chosen to achieve lesion AD values above the established threshold values, considering toxicity estimations. Although this approach has been reported to result in change in patient management in 25%–50% of DTC patients (*14,16*), the biologic effectiveness of dosimetry-guided approaches is not proven yet (*1*).

To date, the only study assessing the dose–response relationship by means of ^{124}I PET/CT in a larger number of patients was recently published by Jentzen et al. (*17*). Therapy response for thyroid remnant and metastatic lesions above the accepted lesion AD was assessed using an optimum activity approach. This approach resulted in relatively high therapeutic ^{131}I activity (median, 10 GBq; range, 2–20 GBq), and most lesions, as expected, received an AD above the established threshold values. In our study, therapeutic activity was almost 4 times lower (median, 2.8 GBq; range, 1.1–5.5 GBq), and the estimated lesion AD range extended to the lower lesion AD values. As a result, we observed a statistically significant dose–response relationship, confirming a higher calculated lesion AD of completely responding lesions than the incompletely responding lesions. Interestingly, for thyroid rem-

nants we observed a complete lesion response of 89% which is in good agreement with a complete response of 91% found by Jentzen et al. (*17*), whereas for metastases our study showed a complete lesion response of 69% compared with 88%. These findings suggest that an optimized activity approach might be most beneficial in DTC patients presenting with metastatic disease.

Using ROC curve analysis, we showed that for lesions larger than 0.15 mL, pretherapeutic ^{124}I PET/CT lesion dosimetry can be used as a prognostic tool to predict lesion-based ^{131}I therapy response. For these lesions, the optimal threshold value was 90 Gy for thyroid remnants and 40 Gy for metastases. These values are considerably lower than the accepted threshold values of 300 and 85 Gy. However, it is important to note that these optimum lesion AD thresholds are defined as the values that give the maximum correct classification combining both sensitivity and specificity. In DTC patient management, a correct prediction of incompletely responding lesions is important. Consequently, for patient's management decision making, higher AD threshold values may be preferred.

Reliable lesion dosimetry requires accurate radioactivity quantification and volume estimation, which are affected by the finite spatial resolution of current nuclear medicine imaging equipment (*28*), in particular for the small lesion volumes often encountered in DTC patients. In addition, high-spatial-resolution images obtained by ultrasonography or CT are considered unreliable because of a lack of differentiation between thyroid tissue and hematoma on these modalities (*1*). As a result, lesion AD calculations are considered unreliable for small lesions. Using an established PET-based thresholding method yielding reliable volume estimation for lesions larger than 0.80 mL, Jentzen et al. (*17*) were able to accurately calculate lesion AD for 24% and 27% of all analyzed thyroid remnants and metastases, respectively. In our study, we used a more advanced segmentation technique allowing volume estimation down to the ^{124}I PET spatial resolution volume of 0.15 mL. Consequently, reliable lesion AD estimation was obtained in 38% of thyroid remnants and 40% of metastases. Despite the improved volume segmentation technique, for most lesions only the minimum lesion AD could be calculated. In the future, further developments in PET/MRI might contribute to additional improvements of the dosimetry in small-volume disease (*29*).

Using voxel-based 3-dimensional dose distribution calculations, several studies have reported on the AD distribution heterogeneity within lesions (*13,14*). In these studies, substantial variability in intratumoral AD was observed, possibly resulting in underdosing of tumor subregions and ultimately therapy failure (*13*). Although in our study correction for partial-volume effect was performed by means of the recovery coefficient, heterogeneity of the lesion AD distribution was not considered because most lesions included in our study were small compared with the ^{124}I PET spatial resolution.

A limitation of our study was its retrospective nature. However, a high concordance with other studies using ^{124}I likely confirms the validity of our results. In fact, to date, no prospective randomized study addressing the optimal activity approach has been published,

and the optimal therapeutic activity is not established yet ($1,2$). The results of our study indicate that pretherapeutic ^{124}I PET/CT lesion dosimetry can be used as a prognostic tool to predict lesion response. Therefore, we would strongly advocate cooperative efforts to establish a multicenter prospective ^{124}I trial to confirm our findings.

CONCLUSION

This study provides evidence of a statistically significant dose–response relationship assessed by means of pretherapeutic ^{124}I PET/CT dosimetry in both thyroid remnants and metastases. This will be a clinically useful contribution in patient management.

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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