Response Assessment of Bone Metastases from Differentiated Thyroid Cancer Patients in the Initial Radioiodine Treatment Using Iodine-124 PET Imaging

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ABSTRACT

Iodine-positive bone metastases (BMs) are often resistant after initial radioiodine therapy applying the standard activity approach. A comprehensive lesion-based response study for BMs has not yet been performed. Pre-therapy and follow-up $^{124}$I PET/CT data on BMs from differentiated thyroid cancer patients were retrospectively analyzed to assess the relationship between absorbed radiation dose (AD) and response after initial radioiodine treatment.

Methods: Before and after initial radioiodine therapy, patients received serial PET/CT scans after administration of 20–40 MBq $^{124}$I. The pre-therapy PET data were used to segment BM volumes and to predict the average ADs after administrations of dosimetry-guided $^{131}$I activities. The lower volume limit of determinability of the applied segmentation method was a sphere volume of 0.16 mL. This volume limit classified the BMs into known-volume and fixed-volume groups with their respective average and minimum ADs. Follow-up $^{124}$I and $^{18}$F-FDG PET/CT data after treatment were analyzed to assess lesion-based therapy response. Response rates at different AD thresholds were calculated and were expressed as the percentage of completely responding BMs above the respective AD threshold. BMs with maximum extensions greater than twice the PET spatial resolution were visually scored for nonuniformity.

Results: A total of 61 BMs in 10 patients were included, of which 46 and 15 comprised the known-volume group and the fixed-volume group, respectively. The median follow-up time was 5.7 mo (range, 3.7–23.2 mo). The median average and median minimum ADs in therapy were 183 Gy (range, 39–3,600 Gy) and 270 Gy (range, 63–1,300 Gy), respectively. A range of response rate of 70-80% was achieved at an AD threshold range of 350–650 Gy. There were 26 BMs that were amenable to visual assessment of nonuniformity, of which two-thirds (17/26) were scored as clearly nonuniform, and the majority (11/17) of these nonuniform BMs responded incompletely.

Conclusion: Both the high AD threshold associated with high response rates and the low median AD per unit $^{131}$I activity elucidate the difficulty in achieving a therapeutic efficacy for BMs when administering a single standard activity. The relatively high AD threshold range is possibly a result of distinct levels of spatial nonuniformity of ADs.
INTRODUCTION

Radioiodine therapy following total thyroidectomy has been established in the management of patients with differentiated thyroid cancer (1,2). Radioiodine therapy is used to ablate thyroid remnants and, primarily, to eliminate lymph node metastases (LMs) and distant metastases, most commonly pulmonary (PMs) and bone metastases (BMs).

In performing radioiodine treatment, most institutions apply the standard-activity approach. In contrast, we perform an individual pre-therapy dosimetry for high-risk patients using the positron-emitting tracer $^{124}$I-Nal ($^{124}$I). In this dosimetry approach, the lesion absorbed radiation dose (AD) per unit $^{131}$I activity is estimated using $^{124}$I positron emission tomography/computed tomography ($^{124}$I PET/CT) and the “maximum tolerable activity” is derived from blood sample and whole body retention data (3,4). The maximum tolerable activity is defined to be the maximum therapeutic activity that can be administered without producing severe bone marrow or lung toxicities (≥ grade 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0). The dosimetry data are used to calculate an individual therapeutic activity that results in ADs higher than the accepted AD thresholds without exceeding the maximum tolerable therapeutic activity.

The widely accepted AD thresholds are approximately 85 Gy for metastatic tissue and 300 Gy for thyroid remnant tissue. These key quantities were derived more than two decades ago by Maxon et al. (5), who demonstrated a response rate of approximately 80-90%. However, the historical data by Maxon et al. (5) included cervical LMs but not distant metastases. Thus, pre-therapy dosimetry studies implicitly assume that the widely accepted AD threshold is also valid for distant metastases, such as PMs and BMs. A recent lesion-based dose response study (3) using $^{124}$I PET/CT demonstrated that the 85-Gy AD threshold value may be valid for LMs and also for PMs as a high response rate of >80% was observed. In contrast, after single standard $^{131}$I activities, multiple studies (6–8) reported that iodine-positive BMs are often resistant after
initial radioiodine therapy. There are only two studies (3,9) that assessed a lesion-based therapy response of BMs with a total of 6 BMs exceeding the AD threshold of 85 Gy. Consequently, a comprehensive lesion-based response study for BMs has not yet been performed.

Since 2003, we have been routinely conducting pre-therapy $^{124}$I PET/CT dosimetries for high-risk thyroid cancer patients, a few of whom have received a second $^{124}$I PET/CT dosimetry after radioiodine treatment as part of the follow-up examination. Thus, the aim of this retrospective $^{124}$I PET/CT study was to assess the relationship between ADs to BMs and response after initial radioiodine treatment.

**MATERIALS AND METHODS**

**Patient and Bone Metastases Inclusion Criteria and Patient Preparation**

The patients provided written informed consent to perform the examination and the study has been approved by the local ethics committee. Patients who had received $^{124}$I PET/CT dosimetry prior to their first radioiodine therapy were included. After radioiodine treatment, the patients underwent follow-up examinations, at least a post-therapy $^{124}$I PET/CT scan and a $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET/CT scan. Patients were excluded if they had received any treatments, such as surgery, between pre-therapy and follow-up scans. BMs were included if they were unambiguously assigned as BMs. The BM had to be sufficiently separated from radioiodine accumulating tissues to minimize spill-in of external activity into the BM.

Patient preparation was similar for the pre-therapy and follow-up $^{124}$I PET/CT. All patients had undergone total thyroidectomy. The patients were either under endogenous thyroid-stimulating hormone (TSH) stimulation (by levothyroxine withdrawal for 4 weeks) or under exogenous TSH stimulation (by use of recombinant human TSH), with TSH levels $\geq 30$ mIU/L. Exogenous TSH stimulation was performed if exacerbation of concomitant disease was expected. Recombinant human TSH administration was required for the pre-therapy dosimetry
and again for radioiodine therapy. The patients were instructed to be on a low iodine diet for 4 weeks prior to the $^{124}$I PET/CT scans. Iodine contamination was excluded by urine testing. The single therapeutic $^{131}$I activity was individually assessed by an expert team that considered the pre-therapy results of all lesions as well as the results of the toxicity levels of the activity-limiting organs (10). The treatment activity was administered 1 to 2 days after the last pre-therapy scan.

The $^{18}$F-FDG PET/CT scans are performed to identify initially iodine-positive BMs that changed to vital $^{18}$F-FDG-positive ones after radioiodine therapy. Patients fasted for at least 4 h before $^{18}$F-FDG PET/CT scans. The measured blood glucose level at the time of tracer injection was below 150 mg/dL.

**Image Acquisition and Image Reconstruction**

The images were acquired on a BIOGRAPH Duo PET/CT scanner (Siemens Medical Solutions; Illinois, USA). Two PET/CT scans (24 h and $\geq$96 h) were acquired after administration of 20–40 MBq $^{124}$I for the pre-therapy and follow-up investigations. $^{18}$F-FDG scans were acquired 55–70 min after injection of 300 MBq $^{18}$F-FDG. The examinations included whole-body PET/CT scans from head to thigh using 5–8 bed positions. PET/CT started with a spiral CT in low-dose technique (tube voltage of 110 kVp, tube current time product of 15 mAs, a pitch of 1.6, and slice width of 5 mm). No CT contrast agent was applied. The $^{124}$I and $^{18}$F-FDG PET emission time was 3–5 min per bed position.

The PET images were reconstructed after Fourier rebinning using the iterative attenuation-weighted ordered-subset expectation maximization algorithm with 4 iterations and 16 subsets. A relatively small post-reconstruction Gaussian smoothing filter of 1 mm was applied to obtain a high reconstructed PET spatial resolution of 6.7 mm. Standard scatter, attenuation, and dead-time corrections provided by the manufacturer were used. The reconstructed transverse emission images had a voxel size of 1.7x1.7x2.4 mm$^3$. Filtered backprojection using a reconstruction kernel B40s was used for the CT images (voxel size of 1.0x1.0x2.4 mm$^3$).
Volumetry and Categorization into Three Volume Groups

The low-dose CT images for BM volume segmentation could have been used; however, discerning the BM was often difficult or not possible. To include all the BMs observed on pre-therapy $^{124}$I PET images and to use a consistent methodology, an improved PET-based iterative thresholding method was applied to pre-therapy 24-h $^{124}$I PET image (11). The volume segmentation algorithm used the enclosed delineation-averaged activity concentration instead of the commonly used maximum signal. This volume segmentation method has been shown to segment tumors more reliably in the presence of nonuniform uptake than the maximum-based approach. The lower volume limit of determinability was a sphere-equivalent diameter equaling the PET spatial resolution (6.7 mm or 0.16 mL).

Three groups of BMs were considered in this study. The first group contained BMs that were amenable to reliable volume estimations (>0.16 mL) and termed known-volume group. The second group included BMs with volumes ≤0.16 mL, which was termed fixed-volume group. Note that the second group was referred to as small-volume group in a previous study (3). The third group was a subgroup of the first group and was termed large-volume group. It comprised of BMs that were "large" enough to assess their nonuniformity visually. A BM was considered “large” if its maximum three-dimensional extension was greater than twice the PET spatial resolution; the maximum extension was obtained by measuring distances within the segmented BM image (11).

Absorbed Dose Calculations

The AD calculations involved different steps, which have been described in previous studies (12,13). Average $^{124}$I activity concentrations were evaluated for BMs in the known-volume group. In the fixed-volume group, average $^{124}$I activity concentration was ascertained using a spherical volume of interest with a fixed volume of 0.16 mL (3). In follow-up images, often the volume decreased below 0.16 mL; in this case, the fixed-volume activity concentration was used to
obtain an uptake estimation.

Two corrections, partial-volume effect and half-life corrections, were necessary to obtain the (projected) $^{131}$I activity concentrations and their uptake values, which were used to estimate the $^{131}$I residence time. Using the $^{131}$I uptake values at 24 h and $\geq 96$ h, either a bi- or a triphasic model was used to estimate the residence time. When the effective $^{131}$I half-life was less than or equal to the physical $^{131}$I half-life, the residence time was estimated using the adapted 2-point approach (14). In this approach, the uptake curve was biphasic and was parameterized using a combination of a linear function and a mono-exponential function. The uptake curve was parameterized with a triphasic model when the effective $^{131}$I half-life was greater than the physical $^{131}$I half-life. The residence time arising from the first and second phase was the time integral from zero to the last measured point using the functions based on the biphasic model. The contribution resulting from the third phase was calculated assuming physical decay after the last imaging time point.

The above procedures yielded average and minimum ADs per unit $^{131}$I activity for the known-volume and fixed-volume groups, respectively; a common osseous tissue density of 1.3 g/mL was used for all BMs. The (predicted) average and minimum ADs in therapy were calculated using the single therapeutic activity administered to the patient.

Of note, the present dosimetry calculations assume a uniform AD distribution within the BM, which is often not true in reality. Moreover, the PET-based ADs were slightly higher than the actually delivered ADs as a more rapid $^{131}$I release is expected during therapy. In addition, stunning effect, which may diminish the ADs in therapy, was not likely to have a significant impact on therapeutic efficacy as low $^{124}$I activities were used (15).

Therapy Response Assessment and Response Rate

Each individual BM was either defined as completely or incompletely responding. A completely responding BM was negative on both $^{124}$I PET/CT and $^{18}$F-FDG PET/CT follow-up images. An
incompletely responding BM showed conspicuous focal $^{124}$I or $^{18}$F-FDG uptake. Following a previous study (3), for $^{18}$F-FDG-negative BMs only, the percentage decrease in 24-h $^{124}$I uptake between pre-therapy and follow-up PET was used as a quantitative measure of therapeutic efficacy and is referred to as the response index. A response index of 100% denotes a completely responding BM, whereas a value of less than 100% was an incompletely responding BM. The response rate at different AD thresholds starting at 85 Gy was determined and was expressed as the percentage of completely responding BMs above the respective AD threshold.

Visual Assessment of Nonuniformity

For the large-volume group, five nuclear medicine specialists visually assessed the nonuniform radioiodine activity distribution within the segmented BM volume of interest. A three-point scale was applied: score 0, none; score 1, uncertain; score 2, substantial. The individual scores of each observer were summed and divided (or normalized) by the highest achievable score (of 10). A BM was assigned to be clearly “nonuniform” or “uniform” if the normalized score threshold was ≥0.8 or ≤0.2, respectively. The normalized score thresholds were derived by statistical simulation, representing a probability of about 9% to obtain the respective values by chance.

Statistics

The descriptive statistics included the mean, median, standard deviation (SD), minimum, and maximum. Differences between 2 groups were evaluated by the Mann-Whitney $U$ test. A significance level of $P<0.05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

Ten patients (8 females, 2 males) met the patient inclusion criteria. There were 5
patients, each with papillary and follicular differentiated thyroid cancer. Stimulation of TSH (≥30 mIU/mL) was achieved endogenously in 9 patients (pre-therapy) and 7 patients (follow-up) or exogenously in 1 patient (pre-therapy) and 3 patients (follow-up). Therapeutic activities greater than 11 GBq were administered in 2 patients. The descriptive statistics yielded the following values: age, 63±13 y (median, 64 y; range, 42–78 y); pre-therapy and post-therapy 124I activity, 25±5 MBq (median, 23 MBq; range, 22–43 MBq); single therapeutic 131I activity, 8±5 GBq (median, 7 GBq; range, 1–20 GBq); and follow-up time, 8.0±5.9 mo (median, 5.9 mo, range, 3.7–23.2 mo).

Characteristics of the Bone Metastases

A total of 61 BMs in 10 patients were included, of which 46 (three-quarters) and 15 (one-quarter) comprised the known-volume group and the fixed-volume group, respectively. They were located in the following body regions (number within parentheses): vertebra (22), rib (19), skull (7), pelvis (6), femur (2), sternum (2), and 1 in each clavicle, humerus, and scapula. For the known-volume group, the statistics of the volume and the average AD per 131I activity are illustrated in Figure 1. The descriptive statistics yielded the following values: volume, 4.93±13.0 mL (median, 1.46 mL; range, 0.20–85.3 mL); the average AD per unit 131I activity, 76±103 Gy/GBq (median, 36 Gy/GBq; range, 5–577 Gy/GBq); and the average AD, 388±586 Gy (median, 183 Gy; range, 39–3,560 Gy). For the fixed-volume group, the minimum AD per unit 131I activity was 94±85 Gy/GBq (median, 63 Gy/GBq; range, 21–270 Gy/GBq), and the minimum AD in therapy was 489±423 Gy (median, 270 Gy; range, 63–1,270 Gy).

For comparison purposes, the respective statistics of 20 LMs and 10 PMs (all known-volumes) that were taken from a previous study (3) are illustrated in Figures 1 and 2. BM volumes were, on average, larger than other metastatic tissue types but statistically not significantly greater (Fig. 1A). The median AD per unit 131I activity for BMs was significantly lower, almost by a factor of 5 (36 Gy/GBq vs. 165 Gy/GBq), than for LMs (Fig. 1B, P=0.002). A
significantly smaller median AD per unit $^{131}$I activity was found for PMs (13 Gy/GBq) relative to BMs ($P<0.001$). The half-lives are illustrated in Figure 2A. The median half-life tended to be higher in BMs (6.2 d) compared to LMs (4.1 d) or PMs (3.6 d), but the difference was not statistically significant. The lowest median 24-h $^{131}$I uptake/mL (Fig. 2B) was observed for BMs (0.24%/mL) and PMs (0.07%/mL). The highest median 24-h $^{131}$I uptake/mL was found for LMs (1.16%/mL) and was five times higher than that of BMs ($P<0.001$).

**Dose Response and Response Rate**

Figure 3A illustrates the dose-response diagram of the known-volume and fixed-volume groups. Of the 61 BMs, more than half (35) responded incompletely (31 out of the known-volume and 4 out of the fixed-volume group). The percentage of incompletely responding BMs with response indices greater than 90% was 17% (6/35). More than one-third (14/35) of the incompletely responding BMs had negative response indices, indicating higher $^{124}$I uptake in follow-up than in pre-therapy PET. In a patient-based assessment, a complete BM response was observed in 3 patients, each had only one BM. None of the BMs showed a significant $^{18}$F-FDG uptake on follow-up imaging, thus excluding iodine-negative tumor progress (due to dedifferentiation).

The response rates at different AD thresholds are illustrated in Figure 3B. They were calculated by including both the known-volume and the fixed-volume groups. An AD threshold of 85 Gy resulted in a response rate of 46%. This value was obtained from a total number of 54 BMs, of which 40 belong to the known-volume and 14 to the fixed-volume group. A response rate of 82% was ascertained at an AD threshold of 650 Gy, which was obtained from 11 BMs (6 known-volume BMs, 5 fixed-volume BMs). A slightly lower response rate of 67% derived from 18 BMs (12 known-volume BMs, 6 fixed-volume BMs) was obtained at an AD threshold of approximately 350 Gy. A range of response rate of 70-80% was achieved at an AD threshold range of 350–650 Gy. The percentage of completely responding BMs within 4 groups of ADs defined by <85 Gy, 85 to 350 Gy, 350 to 650 Gy, and >650 Gy were 14% (1/7), 36%(13/36),
43% (3/7), and 82% (9/11), respectively.

The follow-up time statistics yielded 7.3±5.3 mo (median, 5.6 mo; range, 3.7–23.2 mo) for the group of incompletely and 6.3±3.8 mo (median, 5.6 mo; range, 3.7–23.2 mo) for the group of completely responding BMs. No statistically significant difference in the median follow-up time between the group of incompletely and completely responding BMs was found ($P=0.40$). Two-third of BMs (39/61) in 7 patients were assessed after a follow-up time greater than 5 mo; the follow-up time was below 4 mo in only 1 patient with a total of 8 BMs, of which 5 responded completely and 3 responded incompletely (range of response indices, 84–99%).

Nonuniformity

There were 26 BMs that were amenable to visual assessment of nonuniformity (Fig. 4). Only one-quarters (7/26) responded completely and almost three-quarters (17/26) were scored as clearly nonuniform. Of these clearly nonuniform BMs, two-thirds (11/17) responded incompletely. If the large BMs received less than 650 Gy, only one-fifths (5/23) responded completely. Three clearly nonuniform BMs showed complete (2 BMs) and very high response (1 BM, response index of 99%) if they received an AD above 900 Gy. Note that 6 BMs were scored clearly uniform, of which 5 BMs responded incompletely.

DISCUSSION

After application of dosimetry-guided $^{131}$I activities, more than half of the BMs (35/61) were still evident on follow-up $^{124}$I PET. Approximately one-third (14 BMs) of the 35 incompletely responding BMs showed an increased radioiodine uptake after treatment, indicating progressive or at least stable disease. Such an insufficient patient-basis response of BMs on was also observed in the standard-activity approach (6–8). One study (6), however, reported complete disease remission following single standard $^{131}$I activities of 3.7-11.1 GBq in 3 patients, each of whom had 3 or fewer BMs. Likewise, in the present study, BMs were not evident in 3 patients each bearing one small BM (volume $\leq$0.3 mL) after administration of 6-8 GBq. The observed
incomplete lesion-based response of BMs is in contrast to the high therapeutic efficacy in other sites. A recent dosimetry-guided $^{124}$I PET response study (3) of our group using a patient cohort, other than the one in the present study, demonstrated that more than three quarter of LMs (66/84) and almost all PMs (33/34) were not evident on follow-up $^{124}$I PET images after single $^{131}$I administration.

Hence, both the standard-activity approach and even the dosimetry-guided approach often fail to obtain a high therapeutic efficacy for patients with BMs when administering a single therapeutic activity. In a framework of a lesion-based response analysis, there are two main reasons that may elucidate the findings.

First, the (average) AD threshold of approximately 85 Gy – deemed to be sufficient for achieving a high response for soft tissue and metastatic tissue – appears to be too low for BMs. As illustrated in Figure 3A, with an AD threshold of 85 Gy less than half of the BMs responded completely. This provides evidence that the AD threshold of 85 Gy for BM is too low for achieving a high therapeutic efficacy. From Figure 3B, it can be derived that a range of response rate of 70-80% was achieved at an AD threshold range of 350–650 Gy; a value which is almost 4-8 times higher than that of LMs.

We surmise that such a high AD threshold range is not caused, for instance, by a difference in radiosensitivity between BM and LM tissues, but rather is primarily a result of distinct levels of spatial nonuniformity of ADs, indicating that the average AD may not be a suitable response quantity (16). This hypothesis is substantiated by several observations. There is a great variation in the individual BM response in an AD range between 85 and 650 Gy (Fig. 3A) that may be partly explained by distinct levels of nonuniform uptake (17). In addition, BMs are generally larger than LMs or PMs (Fig. 1A) and, therefore, a nonuniform uptake is likely to occur more frequently in BMs, producing a spatial nonuniformity of ADs. In this study, 26 BMs amenable to visual assessment of nonuniformity were included (large-volume group). Of these,
almost three-quarters were scored as clearly nonuniform and the majority of these nonuniform BMs responded incompletely (Fig. 4). This demonstrates that the majority of the “large” BMs are indeed nonuniform and are therefore difficult to treat effectively, unless the average AD is considerably high. For example, the response rate of clearly nonuniform BMs with AD less than 650 Gy was approximately 30% (4/14) (Fig. 4). When the average AD was sufficiently high, 2 clearly nonuniform BMs with an average AD above 1,200 Gy responded completely. Of note, the present study did not provide conclusive evidence that nonuniformity at macroscopic level is the main reason for the insufficient BM response because 5 out of 6 BMs scored visually uniform also responded incompletely (Fig. 4). Finally, compared to soft tissue, osseous tissue has a higher tissue density and therefore has a higher attenuation for β-particles, the dominant radiation mediating the therapeutic response. As a result, the average β-particle range is reduced and the cross-firing contribution is less in osseous than in soft tissue, making BM response more sensitive against nonuniform uptake than in soft tissue. Further studies are warranted to assess the spatial nonuniformity of ADs at microscopic and macroscopic levels using sophisticated approaches (18–20).

The second key factor making radioiodine therapy less effective is the finding that BMs have, on average, a significantly lower AD per unit $^{131}$I activity than LMs (Fig. 1B, $P<0.002$). An approximately 5 times higher amount of $^{131}$I activity is required to achieve an equivalent median AD for BMs. A closer inspection revealed that the difference in AD per unit $^{131}$I activity was primarily caused by a significantly lower 24-h uptake per milliliter for BMs relative to LMs (Fig. 2, $P<0.001$), rather than their effective $^{131}$I half-lives. For PMs, a significantly lower median AD per unit $^{131}$I activity relative to BMs was observed; however, the comparison is hampered because of the low number of PMs included and, in particular, because of respiratory motion, resulting in seemingly lower ADs per unit $^{131}$I activity for PMs (3,21). Consequently, the significant difference in the AD per unit $^{131}$I activity (and the 24-h $^{131}$I uptake) between BMs and PMs is probably only
apparent; further studies using respiratory gating techniques are warranted (22).

Several limitations are worth noting. The AD threshold range of 350–650 Gy relied on 18 BMs, and therefore, a validation study is necessary (Fig. 3B). Moreover, due to the in- and exclusion criteria for patients and for BMs, only 10 patients were included. In addition, one-third (20/61) of the BMs showed slow kinetics; their projected effective $^{131}$I half-lives were greater than the physical $^{131}$I half-life, and therefore, their ADs may be somewhat overestimated as physical $^{131}$I decay was assumed after the last measured uptake point. Furthermore, the ADs for rib metastases (approximately one-third of the total BMs) may be underestimated because of respiratory motion (3,21). Finally, we cannot rule out that in case of thyroid hormone withdrawal a further increasing TSH level after the $\geq 96$ h period of pre-therapy imaging may have modified the predicted AD in therapy. In consequence, the predicted AD may be underestimated if radioiodine therapy is performed after pre-therapy dosimetry. However, this effect may be marginal because a pre-therapy TSH stimulation level of $\geq 30$ mIU/L, which is considered adequate, was achieved in all patients.

CONCLUSION

Both the high AD threshold associated with high response rates and the low median AD per unit $^{131}$I activity contribute to the difficulty in achieving a therapeutic efficacy for BMs when administering a single standard activity. This finding is in accordance to the clinically well-established experience. The relatively high AD threshold range is most likely a result of distinct levels of spatial nonuniformity of ADs. Further studies are warranted to assess the spatial nonuniformity of ADs at microscopic level. For patients suffering from differentiated thyroid cancer patients with potential BMs, individual patient $^{124}$I dosimetry may be especially important to increase therapeutic efficacy and to predict therapy failure.
DISCLOSURE

The authors declare that they have no conflict of interest.
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FIGURE 1.  Box-plots of the volumes (A) and average ADs per unit $^{131}$I activity (B) of the known-volume (first) group. Insert (panel A) is an enlarged view of PM volumes. Significant differences were characterized by a $P$ value below 0.05. Number shown close to the whiskers is the number of lesions. Data for LMs and PMs were retrieved from reference (3). Solid and dashed lines indicate median and mean values, respectively.
FIGURE 2.  Box-plots of the projected $^{131}$I half-lives (A) and projected $^{131}$I 24-h uptake values per mL (B) of the known-volume (first) group. Insert (panel B) is an enlarged view of PM uptake values/mL. For further details, see the caption of Fig. 1.
FIGURE 3. Response-dose diagram of the known-volume and fixed-volume groups (A) and the resulting response rate as a function of the AD threshold (B). Insert is an enlarged view of a region with a high data-point density. Vertical dashed lines indicate the AD threshold value for LMs (85 Gy) and the AD threshold range for BMs (350–650 Gy). Number within parentheses is the number of BMs included.
FIGURE 4. Relationship between normalized nonuniformity score and average therapy-delivered AD for incompletely (A) and completely responding BMs (B) of the large-volume group. For further details, see caption of Fig. 3.
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