

8. Haugen BR, Pacini F, Reiners C, et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab*. 1999;84:3877–3885.

Frederik A. Verburg*

Markus Dietlein

Lutz Freudenberg

Sophie Leboulleux

Fabian Pitoia

Christoph Reiners

Marcel Stokkel

Markus Luster

**University Hospital Aachen*

Pauwelsstrasse 30

52074 Aachen, Germany

E-mail: fverburg@ukaachen.de

Published online Aug. 30, 2012.
DOI: 10.2967/jnumed.112.108738

REPLY: We always welcome a professional dialogue from esteemed colleagues in regard to studies that we have published, and we believe that such a dialogue helps us all move forward to a more accurate understanding of the world about us. Continuing in that spirit, I would like to address the various comments in the letter to the editor from Verburg et al. regarding our report comparing the number of metastatic lesions of differentiated thyroid cancer (DTC) detected after preparation with thyroid hormone withdrawal (THW) versus injections of recombinant thyroid-stimulating hormone (rhTSH) (1).

Our understanding of the main point of their letter is that they believe that our recommendation regarding selective use of rhTSH is too strong and that they would like to see a more “nuanced” view on the data presented. Our recommendation was that, until more data become available, physicians should be cautious in using rhTSH for patient preparation before diagnostic scanning for the detection of DTC or treatment of distant metastases secondary to DTC with ^{131}I . Insofar as the data support this recommendation, it would not appear appropriate to characterize the recommendation as being too strong. When data are clear-cut, there is less accommodation for “nuance.”

With regard to the observation of Verburg et al. that our entire study appeared methodologically geared toward comparing ^{131}I with ^{124}I —indeed, the data were obtained from our previously published original study (2) comparing ^{131}I planar imaging with ^{124}I PET, with 16 additional patients studied and included. However, whether the data were derived from a study comparing lesion detection of ^{131}I planar imaging with ^{124}I PET is not in and of itself a limitation. Although there were limitations to our study that we recognized and discussed in the publication, we do not believe this is one of them.

With regard to the interest of Verburg et al. in seeing further statistical analyses comparing the 2 radioisotopes, especially if we additionally had acquired and evaluated ^{131}I SPECT/CT, we noted in our original publication (2) that a comparison of ^{131}I SPECT/CT with ^{124}I PET would have been valuable for that study. However, such a comparison was not critical to the present study (1) because we were comparing planar imaging with planar imaging and PET with PET. To address Verburg et al.’s further opinion that we analyzed differences between rhTSH and THW instead of comparing lesion detection on ^{131}I planar imaging versus ^{124}I PET, we did not perform evaluations after rhTSH and THW *instead of* lesion detection but *in addition to* lesion detection.

Verburg et al. subsequently state that they were surprised we did not use ^{124}I -PET to perform dosimetry for our patients. They believe

this would have been clinically relevant, especially in patients with metastatic lesions, because visualization of metastases does not automatically indicate the possibility of an effective ^{131}I treatment. Several important facts will help clarify this issue. First, the calculated radiation absorbed dose to a focal lesion or organ as determined by the various methods of ^{124}I dosimetry does not necessarily correlate with clinical outcomes or side effects (3,4). However, we do agree that lesional dosimetry should be performed—not necessarily to indicate clinical relevance based on a calculated radiation absorbed dose but rather to indicate clinical relevance based on a comparison of relative lesional radiopharmacokinetics. We have such a study already under way, as well as another study comparing ^{124}I dosimetry after preparation with THW and rhTSH injections in patients serving as their own controls. Nevertheless, because clinical outcomes are more important as an endpoint than the calculated radiation absorbed dose by ^{124}I dosimetry, our paper (1) referred to work from our institution by Klubo-Gwiedzinska et al., who demonstrated no difference in outcomes when patients with metastatic DTC were prepared for ^{131}I treatment with either rhTSH or THW (5). Although THW scans may allow better detection of metastatic lesions than do rhTSH scans, preparation with THW may not necessarily result in significantly more radiation absorbed dose to the metastases than does preparation with rhTSH, thereby not improving outcomes. Thus, the caveat implied by Verburg et al. in regard to the lack of lesional dosimetry using ^{124}I does not mitigate the fact that more lesions were detected after preparation with THW versus rhTSH injections and that—as concluded in our paper—until more data become available, physicians should be cautious in using rhTSH for patient preparation before diagnostic scanning for the detection of DTC or treatment of distant metastases secondary to DTC with ^{131}I .

In drawing attention to methodology-based drawbacks in our interpretation of the presented data, Verburg et al. are simply repeating limitations of our study that we already noted in our discussion.

Next, Verburg et al. note that our statement that our result was most consistent with the data of Freudenberg et al. did not reflect the fact that the conclusion of Freudenberg et al. was more cautious. Our actual statement was, “In comparing our data with other reports that evaluated preparation with THW and rhTSH, our data are most consistent with those of Freudenberg et al. (6). . . In the study of Freudenberg et al. (6), their endpoint was the estimation of the radiation absorbed dose to the metastatic foci after THW and rhTSH preparation. They reported that the mean radiation absorbed dose for the lesions identified in a group of patients ($n = 27$) prepared with rhTSH was only 60% of the radiation absorbed dose to lesions in another group of patients ($n = 36$) prepared with THW. However, this difference was not statistically different.” I will leave the judgment to the reader regarding whether our statement reflected the data and conclusion of Freudenberg et al. and whether our data are most consistent with their data.

Interestingly, Verburg et al. reference an article by Haugen et al. (7) as evidence that patient preparation with rhTSH injections has already been shown to be equivalent to patient preparation with THW. However, Verburg et al. do not point out the limitations of the study by Haugen et al. Notably, Haugen et al. reported that THW scans were superior to rhTSH scans in 16% (8/49) of patients, albeit not to a statistically significant extent ($P = 0.109$). Second, although Verburg et al. state that this information was crucial for the approval of rhTSH (Thyrogen; Genzyme Corp.) by the Food and Drug Administration, it has not approved Thyrogen for use in metastatic DTC in the United States, which is stated in the drug insert. Third, the order of THW and rhTSH scans was not randomized; all rhTSH scans were performed first. Although Haugen et al. recog-

nized this limitation and their reason for not randomizing these scans, the performance of an rhTSH scan first may result in a potential bias in favor of rhTSH scans relative to THW scans. This is so because the approximately 144 MBq (~4 mCi) of ^{131}I administered for the rhTSH scan may have stunned the uptake of metastases on the THW scan. The controversies involving stunning have been extensively discussed (8), and although the THW scans were performed at least 2 wk after the rhTSH scan, this interval does not necessarily eliminate potential stunning effects, which may result in a bias favoring the rhTSH scan. Nevertheless, Haugen et al. dismissed stunning as a potentially significant bias with their statement that 96% of the scans in their study were either equivalent or superior after THW, suggesting that any contribution of stunning may have been small. Of those 96% of scans, 80% were concordant, and we would submit that the mere fact that they were concordant (e.g., both scans showing no areas of uptake or both scans showing the same number and areas of uptake) does not rule out stunning. Stunning depends on many factors, and there may be metastatic sites that are not visually affected and other sites of metastatic disease that are stunned and hence potentially not visualized. If the THW scan had been performed first, the potential exists that more THW scans may have been superior to rhTSH scans, and if these are added to the other 8 THW scans that had already been demonstrated to be superior to rhTSH scans, statistical significance might have been achieved. Another limitation of the study by Haugen et al. was the lack of urinary iodine measurements. Although Haugen et al. stated that the use of a low-iodine diet was specifically recommended, that most investigators followed a low-iodine protocol, and that patients received the same dietary instructions for both scans, lower iodine intake before the rhTSH scan relative to the level of iodine intake before the THW scan could bias the scan results. Finally, an important limitation of the study of Haugen et al. is the imaging parameters used for the THW scans and rhTSH scans. The image parameters selected by Haugen et al. to help ensure that the THW scans had no unfair advantage relative to the rhTSH scans may in fact have given the rhTSH scans an unfair advantage relative to the THW scans. Haugen et al. stated that one of the purposes of their study was to address a significantly lower whole-body retention of radioiodine after rhTSH stimulation compared with THW. To compensate for this difference, they used a slower scanning speed or a minimum total-count number for each image rather than scanning for a defined period, thereby minimizing potential count-poor scans after rhTSH administration. Although the intent of compensating for poorer counting statistics is certainly reasonable, this method may have unfairly benefited the rhTSH scans. When one uses a slower scanning speed or a minimum total number of counts that must be obtained before the image is completed, one is obviously increasing total imaging time. In the situation where both the background activity and the lesional activity have decreased equally with rhTSH preparation relative to THW preparation, it may be arguably fair to increase the imaging time. However, in the situation where the background activity has decreased more rapidly than the activity in the lesion with rhTSH preparation, then the target-to-background ratio for a lesion could be higher for rhTSH. This, of course, would favor the rhTSH and is again arguably fair for rhTSH and an advantage for rhTSH. However, increasing the imaging time not only will increase the background and total counts in the image obtained after preparation with rhTSH but also will result in relatively more counts obtained from the target than from the background, in turn improving the counting statistics of the target and potentially building a bias into the study

favoring rhTSH scans over THW scans. Verburg et al. overlook these inherent potential limitations of the report by Haugen et al. and simply accept the study as showing that the 2 modalities were comparable in their diagnostic yield.

In summary, we thank Verburg et al. for their thought-provoking letter. However, we believe that the results of our study remain important observations and that our original recommendation is appropriate—specifically that until more data become available, physicians should be cautious in using rhTSH for patient preparation before diagnostic scanning for the detection of DTC or treatment of distant metastases secondary to DTC with ^{131}I . Of course, both physicians and patients would like preparation by rhTSH injections to be as effective as THW in the management of patients with metastatic DTC, but convincing data free of the limitations inherent in prior studies will be required before we can be fully assured of that efficacy.

REFERENCES

1. Van Nostrand D, Khorjekar GR, O'Neil J, et al. Recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal in the identification of metastasis in differentiated thyroid cancer with ^{131}I planar whole-body imaging and ^{124}I PET. *J Nucl Med*. 2012;53:359–362.
2. Van Nostrand D, Moreau S, Bandaru VV, et al. ^{124}I positron emission tomography versus ^{131}I planar imaging in the identification of residual thyroid tissue and/or metastasis in patients who have well-differentiated thyroid cancer. *Thyroid*. 2010;20:879–883.
3. Jentzen W, Schneider E, Freudenberg L, et al. Relationship between cumulative radiation dose and salivary gland uptake associated with radioiodine therapy of thyroid cancer. *Nucl Med Commun*. 2006;27:669–676.
4. Sgouros G, Hobbs RF, Atkins FB, Van Nostrand D, Ladenson PW, Wahl RL. Three-dimensional radiobiological dosimetry (3D-RD) with ^{124}I PET for ^{131}I therapy of thyroid cancer. *Eur J Nucl Med Mol Imaging*. 2011;38(suppl 1):S41–S47.
5. Klubo-Gwiezdzińska J, Burman KD, Van Nostrand D, Mete M, Jonklaas J, Wartofsky L. Radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. *Thyroid*. 2012;22:310–317.
6. Freudenberg LS, Jentzen W, Petrich T, et al. Lesion dose in differentiated thyroid carcinoma metastases after rhTSH or thyroid hormone withdrawal: ^{124}I PET/CT dosimetric comparisons. *Eur J Nucl Med Mol Imaging*. 2010;37:2267–2276.
7. Haugen BR, Pacini F, Reiners C, et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab*. 1999;84:3877–3885.
8. Wartofsky L, Van Nostrand D, eds. *Thyroid Cancer: A Comprehensive Guide to Clinical Management*. 2nd ed. Totowa, NJ: Humana Press; 2006.

Douglas Van Nostrand*

Leonard Wartofsky

Frank Atkins

**Washington Hospital Center*

110 Irving St., N.W.

Washington, DC 20012

E-mail: douglas.van.nostrand@medstar.net

Published online Sep. 17, 2012.

DOI: 10.2967/jnumed.112.112094

Radiation Exposure Should Not Limit Bone Scintigraphy with ^{18}F -NaF

TO THE EDITOR: The article by Kurdziel et al. (1) focused mainly on the kinetics of ^{18}F -NaF and reproducibility of studies using PET scanners. In addition, the authors presented a dosimetric result that should be emphasized, in our opinion.

Based on the measured biodistribution of ^{18}F -NaF, the authors calculated organ doses using OLINDA. With the highest organ dose