determined. As stated, a dynamic design may be particularly suitable when assessing the role of statistical noise on variability of individual PET/CT systems. Yet, we would like to emphasize that a test–retest study is needed for the assessment of repeatability in a response evaluation setting in which patients are scanned at different occasions. A true test–retest design is the closest approximation of the clinical conditions met during response assessment and includes all sources of variability encountered in clinical practice, such as variability in injected activity, uptake time, physiologic status, patient repositioning, and breathing-induced artifacts. These results can be used to determine thresholds that are able to differentiate metabolic response and progression from intrinsic measurement variability of quantitative uptake metrics after the start of treatment.

We also want to point out that differences in ^{18}F-FDG uptake measures due to variation in uptake time are caused by differences in ^{18}F-FDG kinetics at 60 and 90 min after injection and not physical decay of ^{18}F (*2*). Omitting physical decay correction to correct for differences in uptake time between 2 scans falsely assumes that ^{18}F decay and ^{18}F-FDG kinetics are proportional. This uptake time correction method should therefore not be used in a longitudinal setting because of physiologic variations in ^{18}F-FDG kinetics.

In addition, we assessed the effect of several ^{18}F-FDG uptake normalization methods, including one for glucose correction, on repeatability. In the current cohort, all plasma glucose levels (4.5–7.1 mmol/L) were well within the recommended range and showed a low interscan variability (≤2.2 mmol/L) (*3*). The influence of competing endogenous glucose on ^{18}F-FDG uptake metrics was thus likely to be limited. However, by correcting tumor uptake for glucose correction a potential source of measurement variability is also introduced. This is supported by the finding that the median difference of repeated glucose level measurements in the same patient, using a calibrated device, was 0.2 mmol/L (0–0.8 mmol/L) in this study. We would therefore suggest that glucose correction should not be performed if glucose levels are within the reference range, as also noted by Dr. Thie in his letter. We would like to encourage Dr. Thie and colleagues to study the influence of other (more complex) glucose-correction methods on the repeatability of ^{18}F-FDG uptake metrics in a cohort with a higher variability in plasma glucose levels. This is of particular interest for metastatic diseases because a wide variety of tissues can be affected.

REFERENCES

1. Kramer GM, Frings V, Hoetjes N, et al. Repeatability of quantitative whole-body ^{18}F-FDG PET/CT uptake measures as function of uptake interval and lesion selection in non-small cell lung cancer patients. *J Nucl Med.* 2016;57:1343–1349.
2. Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* 2010;37:181–200.
3. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging.* 2015; 42:328–354.

Gerbrand Maria Kramer*
Otto S. Hoekstra
Ronald Boellaard
**VU University Medical Center*
P.O. Box 7057
1007 MB Amsterdam, The Netherlands
E-mail: ge.kramer@vumc.nl

Published online Jun. 15, 2017.
DOI: 10.2967/jnumed.117.195461

Regarding "Subjecting Radiologic Imaging to the Linear No-Threshold Hypothesis: A Non Sequitur of Non-Trivial Proportion"

TO THE EDITOR: I applaud the authors of the recent article by Siegel et al., "Subjecting Radiologic Imaging to the Linear No-Threshold Hypothesis: A Non Sequitur of Non-Trivial Proportion" (*1*), and *The Journal of Nuclear Medicine* for publishing this important review in such a prominent journal. The authors condense an enormous amount of scientific data and rigorous interpretation into a relatively small space. I hope this paper will help slow the disheartening impact of radiophobia that is sweeping our country and reducing the quality and use of radiologic imaging and consequently of medical care, as described so clearly in the article. The authors have raised the level of scientific discussion regarding the health effects of radiation. Any rebuttal to their cogent arguments needs to be on that same high scientific level. I think part of the wide acceptance of the linear, no-threshold theory is the unfamiliarity of most people with the widespread biologic phenomenon of the J-shaped curve, namely, that many things that are harmful at high doses are harmless, or even helpful, at low doses. The classic and best-studied example is that of alcohol on all-cause human mortality, nicely summarized in Figure 1 modified from Di Castelnuovo et al. (2), a metaanalysis involving more than 1 million subjects. The data in the red circle in Figure 1A are shown larger in Figure 1B, and clearly demonstrate the strikingly nonlinear relationship between alcohol and mortality at low doses. This corresponds to the area of contention in the radiation–cancer relationship (equivalent to several whole-body CT scans), for which there are no data—or rather, the data at such low radiation doses are so noisy that no reliable signal can be discerned above background. The data are much better for alcohol and show a relationship that could never be predicted from the high-dose data.

REFERENCES

1. Siegel JA, Pennington CW, Sacks B. Subjecting radiologic imaging to the linear no-threshold hypothesis: a non sequitur of non-trivial proportion. *J Nucl Med.* 2017;58:1–6.
2. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med.* 2006;166:2437–2445.

Ronald E. Fisher
Houston Methodist Hospital
6565 Fannin St.
Houston, Texas 77030
E-mail: rfisher@bcm.edu

Published online Apr. 27, 2017.
DOI: 10.2967/jnumed.117.193920

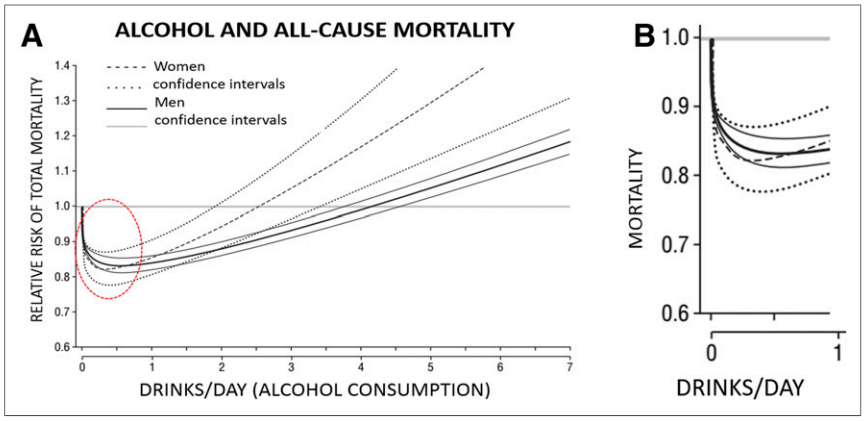

FIGURE 1. Relative risk of mortality with increasing alcohol consumption. Note that the relationship is nonlinear at low doses, and that alcohol is beneficial at low doses, while harmful at high doses. (Reprinted with permission of (*2*)).

Fixed 3.7-GBq ^{131}I Activity for Metastatic Thyroid Cancer Therapy Ignores Science and History

TO THE EDITOR: Deandreis et al. (*1*) compared the overall survival (OS) of 2 patient groups with metastatic differentiated thyroid cancer (mDTC). One group of patients underwent multiple ^{131}I treatments using a standard administered activity (AA) of 3.7 GBq (100 mCi) at Gustave Roussy (GR), whereas the other group received individualized maximal tolerated activity (MTA) therapy at the Memorial Sloan Kettering Cancer Center (MSKCC). Finding no differences in OS between the approaches of GR and MSKCC, the authors generalized their findings to conclude that therapy using MTAs is no better than multiple standard AAs. We concur with previously expressed concerns regarding the study design (*2,3*) and would like to offer additional comments.

The MTA formalism at MSKCC is not adequately described in the provided references. The individual calculated MTAs at MSKCC were not reported (*1*), but the AAs were lower than in our experience (*4*). This raises concern that AAs differ from calculated MTAs. The authors should report MTAs along with AAs, explaining any differences between the two.

In the 1950s, Benua and Leeper (*5*) observed that "metastases treated with either small repeated doses of ^{131}I or with external irradiation seemed to lose the ability to function [that is, accumulate iodine] but continued to grow." That was their reason for developing the MTA-based approach at MSKCC that permitted administration of much higher AAs. They also observed that thyroid hormone withdrawal was the most effective stimulation for iodine uptake in mDTC, which their successors substituted by recombinant human thyroid-stimulating hormone (rhTSH) without proof of equivalence, as conceded by the authors ("the effect of rhTSH versus THW preparation on ^{131}I efficacy still remains unknown") (*1*). Importantly, rhTSH as the preferred stimulation for dosimetry and therapy is highly unusual in global practice. Hence, any conclusion from this study would apply only to MSKCC practice of MTA-guided therapy, and maybe to a few other centers.

We are particularly perplexed by the assumption at GR in support of standard activity, which is that "any increase in lesional radiation dose achieved with larger administered activities is unlikely to confer therapeutic benefit." We administer up to 5 times the GR standard activity under MTA guidance; radiobiologically this is expected to significantly increase the probability of tumor control. What is the radiobiologic basis for the GR assumption?

We know that mDTC consists of clonogens with interpatient and intrapatient heterogeneity in radiosensitivity and iodine avidity (*6*). Standard activity may kill radiosensitive and iodine-avid clones, leaving non–iodine-avid and more radio-resistant ones viable in some patients, who later may develop recurrence. Indeed, in the study designed in part by the senior GR investigator, patients with progressive mDTC were recruited into a novel chemotherapy trial (*7*). Most of those patients had 2 or more standard ^{131}I therapies, which is expectedly similar to Benua's observation in the 1950s.

Clinically, patients with mDTC have excellent OS, which makes this metric not ideal. Optimizing quality of life and minimizing the side effects are no less important, but not addressed in this work; therefore, applied AAs should be reasonable. In addition, dosimetry does not always result in only increased AA but also quite frequently in a change in therapeutic concept.

REFERENCES

1. Deandreis D, Rubino C, Tala H, et al. Comparison of empiric versus whole-body/-blood clearance dosimetry-based approach to radioactive iodine treatment in patients with metastases from differentiated thyroid cancer. *J Nucl Med.* 2017;58:717–722.
2. Flux GD, Verburg FA, Chiesa C, et al. Comparison of empiric versus dosimetry-guided radioiodine therapy: the devil is in the details [letter]. *J Nucl Med.* 2017;58:862.
3. Tulchinsky M, Gross LJ. Comparison of empiric versus dosimetry-guided radioiodine therapy: the devil is in the details. *J Nucl Med.* 2017;58:863.
4. Jentzen W, Bockisch A, Ruhlmann M. Assessment of simplified blood dose protocols for the estimation of the maximum tolerable activity in thyroid cancer patients undergoing radioiodine therapy using ^{124}I. *J Nucl Med.* 2015;56:832–838.
5. Benua RS, Leeper RD. A method and rationale for treating metastatic thyroid carcinoma with the largest safe dose of I-131. In: Medeiros-Neto G, Gaitan E, eds. *Frontiers in Thyroidology.* New York, NY: Plenum Medical Book Co; 1986:1317–1321.
6. Nahum AE. Microdosimetry and radiocurability: modelling targeted therapy with beta-emitters. *Phys Med Biol.* 1996;41:1957–1972.
7. Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med.* 2008;359:31–42.

Walter Jentzen*
Alan E. Nahum
Andreas Bockisch
Ina Binse
Mark Tulchinsky
**Klinik für Nuklearmedizin*
Hufelandstrasse 55
D-45122 Essen, Germany
E-mail: walter.jentzen@uni-duisburg-essen.de

Published online Apr. 6, 2017.
DOI: 10.2967/jnumed.117.192872