TO THE EDITOR: Deandreis et al. aimed to compare two therapeutic interventions using radioactive iodine therapy in metastatic differentiated thyroid cancer (MDTC): the empiric "standard" activity (3.7 GBq) approach at Gustave Roussy (GR) and the dosimetric approach at Memorial Sloan Kettering Cancer Center (MSKCC) (*1*). Overall survival was selected for the study outcome measure. This was a retrospective investigation that required equal distribution of confounding factors in the cohorts to enable unbiased comparison of the two tested approaches. We would like to highlight several inconspicuous confounders that require the authors' consideration and comment.

The GR cohort comprised mostly French women who, in general, had an approximately 22% lower overall probability of dying per 100,000 than the American women who made up most of the MSKCC cohort—84.92 in 1980, which gradually declined to 53.63 in 2010, as compared with 102.51 declining gradually to 77.16, respectively (*2*). Hence, the GR cohort had an inherent advantage over the MSKCC cohort in overall survival that needs to be recognized and addressed.

The GR cohort was younger than the MSKCC cohort, a difference for which the multivariate analysis attempted to correct. But Table 1 reveals the presence of another important confounder: inclusion of pediatric patients in both cohorts. Published experience from MSKCC shows 100% survival in pediatric patients with MDTC (*3*). This finding agrees with the widely recognized notion that the "biologic behavior of thyroid cancer can differ significantly between adults and children" (*4*). Most experts consider pediatric MDTC to be a different disease from adult MDTC. In survival studies, the two should be investigated separately, and, therefore, inclusion of pediatric patients in this study is a design error. Disappointingly, the exact numbers of pediatric patients per cohort were not disclosed. The younger median age of the GR cohort suggests that it probably had a greater proportion of pediatric patients, which would have guaranteed an overall survival advantage to the GR approach. Multivariate analysis cannot correct for this basic design flaw.

Another confounding variable that cannot be corrected for is the difference in patient preparation. GR used thyroid hormone withdrawal, whereas MSKCC used recombinant human thyroid-stimulating hormone (rhTSH). The authors conceded that "the effect of rhTSH vs [thyroid hormone withdrawal] preparation on [^{131}I] efficacy still remains unknown." However, the available observational evidence shows better radioactive iodine uptake and retention in metastatic lesions with thyroid hormone withdrawal than with rhTSH (*5*–*7*). This difference could also have given an overall survival advantage to the GR approach, if it depends on the effectiveness of radioactive iodine therapy.

Use of rhTSH in MDTC is off-label. The MSKCC practice of incorporating rhTSH into the routine dosimetry protocol is very rare, if not unique, but Deandreis et al. inappropriately extrapolated conclusions to the whole-body (blood clearance) dosimetric approach in general. Furthermore, some of the authors have previously disclosed relationships with the company that manufactures rhTSH (*8*). Off-label rhTSH use in the current report certainly requires at least a similar disclosure.

The above-addressed four deficiencies should be addressed by the authors, but are more than sufficient to show that this work failed to adequately balance confounders in the cohorts in favor of the GR approach. The results from the atypical (i.e., rhTSH stimulated) dosimetry protocol at MSKCC should not be generalized. Practitioners of the standard dosimetry-tailored, maximum-tolerated-activity approach can rest assured that there is still no evidence in the literature to equate the effectiveness of that approach to the one-size-fits-all empiric approach.

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. Population division: world population prospects, the 2015 revision—data query. United Nations, Department of Economic and Social Affairs, website. https://esa.un.org/unpd/wpp/DataQuery/. Data for July 29, 2015, retrieved on January 16, 2017.
3. Balachandar S, La Quaglia M, Tuttle RM, Heller G, Ghossein RA, Sklar CA. Pediatric differentiated thyroid carcinoma of follicular cell origin: prognostic significance of histologic subtypes. *Thyroid.* 2016;26:219–226.
4. Parisi MT, Mankoff D. Differentiated pediatric thyroid cancer: correlates with adult disease, controversies in treatment. *Semin Nucl Med.* 2007;37:340–356.
5. 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.
6. Hung GU, Ho M, Kao CH. Faster radioiodine washout in the treatment of pulmonary metastases of papillary thyroid cancer prepared with recombinant human thyroid-stimulating hormone. *Clin Nucl Med.* 2009;34:316–317.
7. 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.
8. Haugen BR, Alexander EK, Bible KC, et al. American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2016;26:1–133.

Mark Tulchinsky*
Lucas J. Gross
**Penn State University Hospital*
P.O. Box 850, M.C. H066
Hershey, PA 17033
E-mail: mark.tulchinsky@gmail.com

Published online Feb. 23, 2017.
DOI: 10.2967/jnumed.117.190199

REPLY: We agree that several confounding variables may be present in retrospective studies, but available data on thyroid cancer patients are mostly retrospective. Therefore, treatment strategies are based on low-level evidence and always open to challenge. The efficacy of radioactive iodine (RAI) treatment may be related to patient age, histology, lesion size and number, ^{18}F-FDG uptake, treatment preparation (thyroid hormone withdrawal [THW] vs. recombinant human thyroid-stimulating hormone [rhTSH]), administered activity, number of treatments, cumulative activity, radiation dose to tumor foci, and assessment of response. Most of these factors were considered and discussed in our article (*1*).

Tulchinsky et al. point out the difference in mortality rate between French and American women, but this does not apply in our statistical analysis. We agree that patients who have metastatic disease and are younger than 20 y old frequently have an excellent response to RAI treatment, with previous reports showing a 100% 10-y survival rate at both Memorial Sloan Kettering Cancer Center (MSKCC) and

Gustave Roussy (GR) (*2,3*). In our study, such patients represent 9.9% of the GR cohort (23/231) and 7.4% of the MSKCC cohort (9/121). When these patients are excluded from the analysis, the median age at the discovery of distant metastases is still younger for GR patients than for MSKCC patients (45 vs. 54 y, respectively; $P = 0.01$), but in the multivariate analysis, the difference in overall survival remains non–statistically significant ($P = 0.16$). Furthermore, there is still no difference in overall survival between the two centers in predefined matched subgroups of patients less than 40 y old: 5-y overall survival is 94% for both centers for group 1 (vs. 96% reported in our article) and 92% and 87% (with no changes in that reported in our article) for group 2 for GR and MSKCC patients, respectively.

We underlined in our discussion that a limit of the study was the imperfect matching between GR and MSKCC patients: MSKCC patients were older and had more aggressive disease. This is the population for whom it is most critical to define the best approach to improving overall survival, as noted by Flux et al. That is why we performed a separate analysis on predefined matched subgroups based on age and metastasis extent (*3*).

We agree with Tulchinsky et al. about the confounding bias of comparing the MSKCC approach (rhTSH preparation for dosimetry and treatment) with the GR approach (THW preparation for empiric administered activities). rhTSH preparation is not the standard approach in metastatic disease and may induce a lower RAI uptake than THW preparation. However, limited data from retrospective studies comparing RAI efficacy in metastatic cancer after THW or rhTSH did not show THW to have a clinically meaningful advantage over rhTSH in terms of overall survival or response to therapy (*4,5*). In our study, MSKCC patients received at least a 2- to 3-fold higher activity per treatment course after rhTSH-based whole-body/blood clearance (WB/BC) dosimetry than the empiric activities administered to GR patients after THW, and older patients with extensive disease received a 2-fold higher median cumulative activity. We found no benefit to overall survival, even considering the higher administered activities. The only other available retrospective study comparing the empiric versus the WB/BC dosimetry approach was on a smaller number of patients with metastatic disease and was only partially based on rhTSH-aided preparation; that study found no effect on PFS in either group (*6*). Only prospective studies including homogeneous groups of patients may clearly determine whether different preparations or the empiric versus the dosimetry-based approach can affect the efficacy of RAI.

In conclusion, in metastatic thyroid cancer, routine use of a WB/BC dosimetry management approach relying on high administered activities given under rhTSH preparation does not show a significant advantage over an empiric dosing approach using lower administered activities under THW preparation. However, as underlined by Flux et al., WB/BC dosimetry might be used in selected patients to minimize the risk of acute dose-related toxicities or in association with lesional dosimetry to optimize therapeutic efficacy. We strongly support the concept that the lesion-absorbed dose should be a major predictor of the tumoricidal effect of RAI, and in this context the combined use of WB/BC dosimetry and lesional dosimetry is expected to provide the optimally safe and effective individualized RAI activity to administer, as suggested from ^{124}I PET studies (*7*). As underlined by Flux et al., optimal outcomes in patients with metastatic thyroid cancer can be achieved only through an integrated multidisciplinary management approach considering all of the various available treatment modalities (e.g., RAI, surgery, localized therapies, and new drugs, either as specific therapies or as redifferentiation agents to improve the efficacy of RAI).

Finally, to address the concerns of Tulchinsky et al., we would like to declare that there was no financial conflict of interest regarding the publication of our paper.

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. Balachandar S, La Quaglia M, Tuttle RM, Heller G, Ghossein RA, Sklar CA. Pediatric differentiated thyroid carcinoma of follicular cell origin: prognostic significance of histologic subtypes. *Thyroid.* 2016;26:219–226.
3. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab.* 2006;91:2892–2899.
4. Tala H, Robbins R, Fagin JA, Larson SM, Tuttle RM. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. *J Clin Endocrinol Metab.* 2011;96:2105–2111.
5. Klubo-Gwiezdzinska 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. Klubo-Gwiezdzinska J, Van Nostrand D, Atkins F, et al. Efficacy of dosimetric versus empiric prescribed activity of ^{131}I for therapy of differentiated thyroid cancer. *J Clin Endocrinol Metab.* 2011;96:3217–3225.
7. Freudenberg LS, Jentzen W, Görges R, et al. ^{124}I-PET dosimetry in advanced differentiated thyroid cancer: therapeutic impact. *Nuklearmedizin.* 2007;46:121–128.

Désirée Deandreis*
Martin Schlumberger
R. Michael Tuttle
**Gustave Roussy*
114 Rue Edouard Vaillant
Villejuif, 94805, France
E-mail: desiree.deandreis@gustaveroussy.fr

Published online Feb. 23, 2017.
DOI: 10.2967/jnumed.117.190496