4,033-MBq [109-mCi] median for rhTSH, $P = 0.01$) were statistically significant, we do not consider these to be clinically significant differences. It seems unlikely that these small differences, although statistically significant, would have a meaningful impact on the clinical outcomes. Oftentimes in clinical studies we detect differences that are statistically significant that have little if any clinical meaning. Therefore, it is important to put statistically significant differences in a proper clinical context.

Following standard practice, we reported the overall *P* values for the contingency tables presented in the article (Tables 5 and 6). Although it is certainly possible to calculate specific *P* values for each category, these individual values still need to be interpreted in light of the overall contingency analysis. For example, in Table 5, although there were no significant differences overall between rhTSH and thyroid hormone withdrawal with respect to the clinical outcomes, analysis of the individual category described as "no clinical evidence of disease" (vs. all other outcomes) does demonstrate a statistical significance ($P = 0.02$) between thyroid hormone withdrawal and rhTSH preparation, whereas each of the other individual categories demonstrates no significant individual differences (vs. all other outcomes). In our opinion, one must be careful in attributing significance to individual categories when the overall contingency analysis does not find significant differences. Therefore, we chose not to emphasize the individual category analysis and simply reported the overall *P* value for the contingency table.

We have similar concerns about reporting specific categoric *P* values for Table 6, although in this case the overall *P* value for the contingency analysis is significant and therefore individual category analysis seems more reasonable. To that end, comparing the category of "no clinical evidence of disease" with all other outcomes demonstrates a *P* value of 0.002, and comparing the category of "persistent disease" with all other outcomes reveals a *P* value of 0.02, indicating a statistically significant difference within each of those categories when thyroid hormone withdrawal is compared with rhTSH. Therefore, based on both the initial contingency table analysis and this additional individual-category analysis, we continue to conclude that "when the definition of no clinical evidence of disease included a suppressed thyroglobulin level of less than 1 ng/mL and a stimulated thyroglobulin level of less than 2 ng/mL, rhTSH-assisted [radioiodine remnant ablation] was associated with significantly higher rates of no clinical evidence of disease. . .and significantly lower rates of persistent disease. . .than was [radioiodine remnant ablation] after [thyroid hormone withdrawal]" (*1*).

We thank the reader for pointing out the typographic error in Table 7: the total excluding distant metastases at diagnosis should be 371 (rather than 394). The remainder of the data in this table are correct.

In both Table 5 and Table 6, we included as a specific category "thyroid bed uptake only," defined as persistent uptake in the thyroid bed with no structural evidence of persistent disease and stimulated thyroglobulin values less than 10 ng/mL. This is always a difficult group to categorize. Some of these patients probably have persistent disease, whereas others likely have just normal thyroid remnants. Therefore, we could not with confidence classify them as either no clinical evidence of disease or persistent disease. Since it did not seem reasonable to exclude this group from analysis, we included them as a separate clinical endpoint as we have done in our previous studies (*2,3*). As with any retrospective study, not all patients received identical follow-up (neck ultrasound, CT scans, MRI scans, ^{18}F-FDG PET scans, or radioactive iodine scans); therefore, we included all patients regardless of the extent of follow-up studies to provide our best disease status classification for each individual patient.

In conclusion, we view rhTSH stimulation as a safe and effective alternative to traditional thyroid hormone withdrawal preparation for routine radioactive iodine remnant ablation. Additional studies are needed to define the minimal administered activity of radioactive iodine that can achieve both successful remnant ablation and acceptable long-term clinical outcomes.

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^{131}I Radiation Dose Distribution in Metastases of Thyroid Carcinoma

TO THE EDITOR: We would like to comment on the article of Champion et al. (*1*), who applied the Monte Carlo method to assess electron dose distributions both inside and outside small water spheres uniformly filled with ^{131}I. Although others have done the same before, Champion et al. emphasized the important issue of the decaying radial gradient of electron dose inside the spheres of sizes comparable to the ranges of ^{131}I β-radiation. This prompts us to conclude that cancer cells at the periphery of small metastases would receive less radiation than would cells near the center.

We accept this conclusion but emphasize that iodine is not distributed uniformly within the thyroid tissue or, probably, within the metastases of thyroid carcinoma either. Iodine spends most of its intrathyroidal life bound to thyroglobulin molecules, segregated in the colloidal lumina of thyroid follicles—that is, extracellularly. The self-absorption of β-radiation in colloidal lumina decreases the radiation dose to thyroid cells. Our simulation showed that thyroid cells comprising a colloidal sphere 250 μm in radius would receive about 85% of an average electron radiation dose to the thyroid (*2*). This effect does not depend on the size of a metastasis but on whether it has a follicular structure and how large the follicles are. Bearing in mind that a thyroid ultrasound image reflects the follicular structure (*3*), the histology-specific inhomogeneity of intrathyroidal electron dose distribution may be, at least in part, responsible for the greater radiosensitivity of hypoechogenic thyroids (small follicles) than of the normoechogenic thyroids (large follicles) of patients with Graves disease (*4*).

More recently, Champion et al. have also capitalized on the issue of thyroid microstructure but obtained results that differ from our results (*5*), which we will comment on separately.

We conclude that, beyond the radioiodine uptake and its effective half-life, both the size of a metastasis and its structure determine the ^{131}I radiation dose to target cells.

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REPLY: We thank Dr. Eterović and colleagues for their interest in our work. Our study on the distribution of the electron dose of ^{131}I in isolated spheres of various sizes was not specifically referring to micrometastases of thyroid cancer and was not referring at all to normal thyroid tissue (*1*). ^{131}I can be used for targeted radiotherapy using a variety of ligands (*2*), such as ^{131}I-metaiodobenzylguanidine and ^{131}I-labeled anti-CD20 antibody. We showed that, even in cases of homogeneous ^{131}I distribution, the dose received by tumor cells within micrometastases will depend on a number of variables. For example, in a micrometastasis of 500-μm radius, the outermost shell layer would receive only two thirds of the average dose, and half that at the center (*1*). Also, as micrometastases become smaller, a higher radioactive concentration is necessary to achieve the same dose, because a larger part of the energy escapes from the metastases. A radioiodine concentration that delivers a dose of 100 Gy to a micrometastasis of 2,500-μm radius would deliver only 10 Gy in a cluster of 50-μm radius (*1*). These data, as we explained, assume a homogeneous distribution of ^{131}I, and of course, heterogeneity in isotope distribution would affect dose distribution. Even for a long-range isotope such as ^{131}I, the dose to a specific cell in small clusters can vary depending on whether this cell has retained the radioligand and on the subcellular distribution of ^{131}I (*3,4*).

^{131}I has an important role in the treatment of metastatic differentiated thyroid cancer and should indeed be applied early, before major heterogeneity in ^{131}I uptake and distribution occurs (*5*).

Within micrometastases from thyroid cancer, the distribution of ^{131}I should be variable depending on histology (papillary vs. follicular vs. Hürthle cell cancer) and also probably on the location (lymph node, lung, bone). For the most common variety, papillary thyroid cancer, the distribution of iodine should also be very variable depending on the subtype. Although iodine is bound to thyroglobulin and localized mostly in the extracellular compartment, its distribution is rather disorganized. Most often, there is no clear evidence that micrometastases of papillary cancer show a colloidal follicular structure as is present in normal tissue. It would be interesting to use microautoradiography or secondary ion mass spectrometry to assess the distribution of radioiodine or of stable iodine, as we showed for other models (*6*).

In conclusion, although our findings relating to the impact of the size of micrometastases and cell position would probably also apply to micrometastases of thyroid cancer; modeling the precise dose distribution in this situation would need knowledge of the heterogeneity using information from microscopic imaging studies.

We appreciate that the authors will comment on another work we recently published (*7*), and we would be pleased to answer those comments.

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Software Fusion: An Option Never Fully Explored

TO THE EDITOR: In a recent PET/CT article, Dr. David Townsend concludes with the opinion that software fusion as a