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.

REFERENCES

1. Champion C, Zanotti-Fregonara P, Hindié E. CELLDOSE: a Monte Carlo code to assess electron dose distribution—S values for ^{131}I in spheres of various sizes. *J Nucl Med.* 2008;49:151–157.
2. Eterović D, Antunović Ž, Marković V, Grošev D. Planning of ^{131}I therapy for Graves disease based on the radiation dose to thyroid follicular cells. *J Nucl Med.* 2008;49:2026–2030.
3. Muller HW, Shroder S, Schneider C, Seiffert G. Sonographic tissue characterisation in thyroid gland diagnosis: a correlation between sonography and hystology. *Klin Wochenschr.* 1985;63:706–710.
4. Marković V, Eterović D. Thyroid echogenicity predicts outcome of radioiodine therapy in patients with Graves' disease. *J Clin Endocrinol Metab.* 2007;92:3547–3552.
5. Hindié E, Champion C, Zanotti-Fregonara P, et al. Calculation of electron dose to target cells in a complex environment by Monte Carlo code "CELLDOSE." *Eur J Nucl Med Mol Imaging.* 2009;36:130–136.

Davor Eterović
Vinko Marković
Ante Punda
Željko Antunović
University of Split
Split, Croatia

DOI: 10.2967/jnumed.108.061697

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.

REFERENCES

1. Champion C, Zanotti-Fregonara P, Hindié E. CELLDOSE: a Monte Carlo code to assess electron dose distribution—S values for ^{131}I in spheres of various sizes. *J Nucl Med.* 2008;49:151–157.
2. Hartman T, Lundqvist H, Westlin JE, Carlsson J. Radiation doses to the cell nucleus in single cells and cells in micrometastases in targeted therapy with ^{131}I-labeled ligands or antibodies. *Int J Radiat Oncol Biol Phys.* 2000;46:1025–1036.
3. Neti PV, Howell RW. Isolating effects of microscopic nonuniform distributions of ^{131}I on labeled and unlabeled cells. *J Nucl Med.* 2004;45:1050–1058.
4. Goddu SM, Rao DV, Howell RW. Multicellular dosimetry for micrometastases: dependence of self-dose versus cross-dose to cell nuclei on type and energy of radiation and subcellular distribution of radionuclides. *J Nucl Med.* 1994;35:521–530.
5. Hindié E, Zanotti-Fregonara P, Keller I, et al. Bone metastases of differentiated thyroid cancer: impact of early ^{131}I-based detection on outcome. *Endocr Relat Cancer.* 2007;14:799–807.
6. Chéhadé F, de Labriolle-Vaylet C, Moins N, et al. Secondary ion mass spectrometry as a tool for investigating radiopharmaceutical distribution at the cellular level: the example of I-BZA and ^{14}C-I-BZA. *J Nucl Med.* 2005;46:1701–1706.
7. Hindié E, Champion C, Zanotti-Fregonara P, et al. Calculation of electron dose to target cells in a complex environment by Monte Carlo code "CELLDOSE." *Eur J Nucl Med Mol Imaging.* 2009;36:130–136.

Christophe Champion
Université Paul Verlaine-Metz
Metz, France

Paolo Zanotti-Fregonara
Commissariat à l'Energie Atomique
Orsay, France

Elif Hindié
Assistance Publique-Hôpitaux de Paris
Paris, France

DOI: 10.2967/jnumed.109.061978

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