Apart from making what might be considered a plea for the systematic use of optimized postoperative metabolic imaging in patients with thyroid carcinoma, I would also raise the problem of the frequent simplification and overgeneralization of WDTC histology. Follicular carcinomas are WDTCs, but their prognosis is different from that of papillary carcinomas, and their hematogenous route of dissemination differs from the lymphogenous route of papillary carcinomas (how do Hay et al. classify follicular carcinomas with histologically demonstrated vascular invasion?). Pure papillary carcinomas (and the so-called macrofollicular variant) are WDTCs with a good prognosis, but when familial their prognosis is reported to be worse, although these carcinomas are usually then small. Furthermore, in the papillary carcinoma family, some variants are more aggressive than others, including the follicular variants, the papillary carcinomas with an insular growth pattern, the tall cell variants (4%–12% of papillary carcinomas), the diffuse sclerosing cases (up to 3% of papillary carcinomas), and the trabecular or solid papillary variants (up to 3% of papillary carcinomas). These aggressive variants represent a substantial group but, unfortunately, in the literature are frequently not distinguished clearly from their pure parents (except for the Hürthle cell cases, which are known to be non-iodine-avid).

Thus, the management of thyroid carcinoma should be based on histologic characteristics as well as, or even instead of, TNM staging. With the introduction of ^{18}F -deoxyglucose and ^{124}I metabolic PET/CT, and new drugs that target precise metastatic pathways (6–8), we must shift from a macroscopic definition of thyroid cancers toward their microscopic, metabolic, histologic, and genetic characterization. With regard to this last point, we would stress that most cases of thyroid cancer express the sodium iodide symporter (9). As with other membranous receptors in other cancers, it would be logical to take into account immunohistologically assessed sodium iodide symporter expression in managing thyroid carcinoma and in deciding on treatment with high-activity ^{131}I .

As a conclusion and in response to the perspective of Hay et al. (1), I would propose the following approach (the cost-effectiveness of which needs to be evaluated). As a first step, patients with stage I pure papillary carcinomas using the TNM system and without antithyroglobulin antibodies (especially postsurgical patients in whom thyroglobulin does not become undetectable on thyroid hormone substitution) would be investigated by ^{123}I or ^{131}I SPECT/CT or by ^{124}I PET/CT if the tumor is sodium iodide symporter-positive, or by ^{18}F -deoxyglucose PET/CT (either after recombinant human thyroid-stimulating hormone stimulation or after thyroid hormone withdrawal) if the tumor is sodium iodide symporter-negative. Whether the patients are treated and the method of treatment would be determined by the results of these investigations.

REFERENCES

- Hay ID, McDougall IR, Sisson JC. Perspective: the case against radioiodine remnant ablation in patients with well-differentiated thyroid carcinoma. *J Nucl Med*. 2008;49:1395–1397.
- Yamamoto Y, Nishiyama Y, Monden T, et al. Clinical usefulness of fusion of ^{131}I SPECT and CT images in patients with differentiated thyroid carcinoma. *J Nucl Med*. 2003;44:1905–1910.
- Freudenberg LS, Antoch G, Frilling A, et al. Combined metabolic and morphologic imaging in thyroid carcinoma patients with elevated serum thyroglobulin and negative cervical ultrasonography: role of ^{124}I -PET/CT and FDG-PET. *Eur J Nucl Med Mol Imaging*. 2008;35:950–957.
- Dewaraja YK, Wilderman SJ, Ljungberg M, et al. Accurate dosimetry in ^{131}I radionuclide therapy using patient-specific, 3-dimensional methods for SPECT reconstruction and absorbed dose calculation. *J Nucl Med*. 2005;46:840–849.
- Kuffner, et al. Micropapillary and “nanopapillary” thyroid carcinomas are not risk free: experience with the 2377 patient Pittsburgh database. *Thyroid*. 2007;17(suppl 1):S-104.
- Henderson YC, Ahn SH, Kang Y, Clayman GL. Sorafenib potentially inhibits papillary thyroid carcinomas harboring RET/PTC1 rearrangement. *Clin Cancer Res*. 2008;14:4908–4914.
- Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol*. June 9, 2008 [Epub ahead of print].
- Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med*. 2008;359:31–42.
- Lee SJ, Choi KC, Han JP, Park YE, Choi MG. Relationship of sodium/iodide symporter expression with I131 whole body scan uptake between primary and metastatic lymph node papillary thyroid carcinomas. *J Endocrinol Invest*. 2007;30:28–34.

Pierre Bourgeois
Institut Jules Bordet
Université Libre de Bruxelles
Brussels, Belgium

DOI: 10.2967/jnumed.108.057141

REPLY: We appreciate Professor Bourgeois’ thoughtful letter. Our perspective (1) was limited to making major points to indict ablation in the management of thyroid carcinomas, and Professor Bourgeois’ questions offer an opportunity to expand on our thesis.

We agree with Professor Bourgeois that refinements in scintigraphic imaging will more accurately define the anatomic sites of residual functioning thyroid tissues. The sensitivity of imaging is also likely to improve over time. We further agree that diagnostic scintigraphic imaging may help to locate residual carcinomas and thereby aid in decisions about therapy (surgical or ^{131}I). Although images made after ablation therapy may be more sensitive than pretherapeutic scans, we do not believe that this observation justifies such management of patients who have stage I carcinomas. If, from data available, there is concern about carcinoma not seen on the diagnostic images, consideration may be given to treatment, not ablation, with ^{131}I . However, long-term benefits from this approach have not been shown. We also agree that if ^{131}I treatments are to be given for carcinomas, the administered dose should be optimal, a goal that often requires dosimetry.

Whereas thyroglobulin antibodies often disappear over time after ^{131}I ablation (2), it is possible that this immune interference may also disappear without radiation treatment. In any case, such antibodies may serve as a surrogate for circulating tumor thyroglobulin (3).

Because papillary microcarcinomas are so frequently present, the numbers of patients are difficult to grasp. From autopsy evidence, such tumors have been found in 1.4%–36% of populations around the world (4–6). In addition, of those afflicted, multifocality was found in 20%–47% and micrometastases to cervical lymph nodes in 3%–18% (4), yet cause-specific mortality was 0%–1% (6). Nevertheless, after surgical therapy, recurrences have been documented. For patients with primary tumors smaller than 5 mm, recurrences appear in about 1% (7). In follow-up, cervical metastases were discovered more frequently if, at the time of the original operation, the lymph nodes contained carcinoma (8,9). Hay et al. found that postoperative ^{131}I treatments were not followed by statistically fewer nodal recurrences (8), but Chow et al. reported that, after ablation, new cervical disease was statistically less common (9). However, overall, recurrences in the absence of ablation therapy were seen in few patients: only 11 (8) and 4 (9).

Some patients with microcarcinomas may require therapy after surgical removal of the tumors; depending on ancillary findings,

treatments will vary (6,10). Still, it is important to remember that the prognosis for most patients with microcarcinomas is excellent. Because of the frequency of this tumor in the population, accepted treatments will have wide applications, and those with unsubstantiated efficacy, including the radiation from ablation, are likely to do much more harm than good.

Therapies for the uncommon variants of papillary carcinoma, such as tall cell or insular, have not been thoroughly studied, but it is difficult to see how ablation would be helpful for patients with these neoplasms. Follicular carcinomas have recently been classified as minimally invasive (capsule only), moderately invasive (angioinvasion), and widely invasive (11), distinctions that appear to be helpful in addition to the prognostic schemes of MACIS (metastases, age, completeness of resection, invasion, size) and TNM (12).

Recently, an editorial created by many contributors discussed and promoted recombinant human thyroid-stimulating hormone for ablation (13). Recombinant thyroid-stimulating hormone has not been approved by the Food and Drug Administration for treatment with ¹³¹I. In the past, ¹³¹I ablations and ¹³¹I treatments of thyroid carcinoma have sometimes been used interchangeably, but the differences must now be addressed. Except when a large amount of residual thyroid tissue inhibits TSH secretion after an incomplete surgical thyroidectomy, ablation has no role. Thyroidectomies should be performed by well-trained surgeons; incomplete thyroidectomies should then be uncommon. We believe that research should focus on how better to treat health-impairing and life-threatening carcinomas for which ¹³¹I is an important therapy.

REFERENCES

1. Hay ID, McDougall IR, Sisson JC. Perspective: the case against radioiodine remnant ablation in patients with well-differentiated thyroid carcinoma. *J Nucl Med*. 2008;49:1395–1397.
2. Chiovato L, Latrofa F, Braverman LE, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. *Ann Intern Med*. 2003;139:346–351.
3. Spencer CA, Bergoglio LM, Kazarosyan M, Fatemi S, LoPresti JS. Clinical impact of thyroglobulin (Tg) and Tg autoantibody method differences on the management

- of patients with differentiated thyroid carcinomas. *J Clin Endocrinol Metab*. 2005;90:5566–5575.
4. Bramley MD, Harrison BJ. Papillary microcarcinoma of the thyroid gland. *Br J Surg*. 1996;83:1674–1683.
5. Kovacs GL, Gonda G, Vadasz G, et al. Epidemiology of thyroid microcarcinoma found in autopsy series conducted in areas of different iodine intake. *Thyroid*. 2005;15:152–157.
6. Pazaitou-Panayiotou K, Capezzone M, Pacini F. Clinical features and therapeutic implication of papillary thyroid microcarcinoma. *Thyroid*. 2007;17:1085–1092.
7. Roti E, Rossi R, Trasforini G, et al. Clinical and histologic characteristics of papillary thyroid microcarcinoma: results of a retrospective study of 243 patients. *J Clin Endocrinol Metab*. 2006;91:2171–2178.
8. Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery*. 1992;112:1139–1146.
9. Chow S-M, Law SKW, Chan JKC, Au S-K, Yau S, Lau W-H. Papillary microcarcinoma of the thyroid: prognostic significance of lymph node metastases and multifocality. *Cancer*. 2003;98:31–40.
10. McDougall IR, Carnargo CA. Treatment of micropapillary carcinoma of the thyroid: where do we draw the line? *Thyroid*. 2007;17:1093–1096.
11. D'Avanzo A, Treseler P, Ituarte PHG, et al. Follicular carcinoma: histology and prognosis. *Cancer*. 2004;100:1123–1129.
12. D'Avanzo A, Ituarte P, Treseler P, et al. Prognostic scoring systems in patients with follicular thyroid cancer: a comparison of different staging systems in predicting the patient outcome. *Thyroid*. 2004;14:453–458.
13. Haugen BR, Emerson C, Pacini F, et al. Expanding indications for recombinant human TSH in thyroid cancer. *Thyroid*. 2008;18:687–694.

Ian D. Hay

Mayo Clinic

Rochester, Minnesota

I. Ross McDougall

Stanford University Hospital and Clinics

Stanford, California

James C. Sisson

University of Michigan Health System

Ann Arbor, Michigan

DOI: 10.2967/jnumed.108.057349