

## Response to Letter to the Editor: "Time to Separate Persistent From Recurrent Differentiated Thyroid Cancer: Different Conditions With Different Outcomes"

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**W**e believe that Burmeister and Drake agree with our statement that, from a biological point of view, relapse of differentiated thyroid cancer (DTC), whether occurring 1 year or 10 years after initial surgery, always indicates "persistent" disease because it is very unlikely that a second, independent DTC emerges after removal of the thyroid or even only its malignant component.

From a clinical point of view, however, the perspective is different: the disease is considered "persistent" when detected a short time after initial therapy and "recurrent" when detected after a disease-free period of  $\geq 1$  year.

Most published studies have considered persistent and recurrent DTC as a single condition. Conversely, studying retrospectively a large series of 4292 patients with DTC, we demonstrated that these two clinical conditions have important differences in terms of outcome and clinical implications (1).

Burmeister and Drake question that the clinical criteria for defining the two conditions are insufficiently indicated in our study because the disease-free status is not defined (which is incorrect; please see page 260, second paragraph) and that in our series most patients with "recurrence" did not received initial radioiodine (which is correct; radioiodine is recommended only in high-risk patients or in certain intermediate-risk patients) (2). They also mention that "true recurrence" definition requires a period with no detectable thyroid cancer (which is correct, as indicated in our study) but that full clinical confidence for the absence of residual disease

after surgery requires that the patient has been treated with radioiodine. Although this may be correct under previous definitions of absence of disease, more recent published criteria indicate that disease-free status is suggested by undetectable or stable serum thyroglobulin (even without TSH stimulation when third-generation assays are used) (2) in the absence of antithyroglobulin antibodies and negative ultrasound examination. These criteria are valid regardless of radioiodine treatment (3).

Therefore, we agree with Bates *et al.* (4) that recurrent DTC represents persistent disease, undetected during the early postsurgery follow-up. In addition, we demonstrate that clinical "persistence" has a worse outcome because a larger, more diffuse, or more aggressive cancer, easily identifiable at early follow-up, is present. In contrast, "recurrence" after a disease-free period indicates that a minimal, stationary, and not easily detectable malignant residue was present. As a consequence, these patients will have a more favorable outcome. Thus, based on our data in this large case series, we believe that from a clinical perspective the separation between persistent and recurrent disease, as defined, separates patients in higher- and lower-risk categories.

### Additional Information

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## References and Notes

1. Sapuppo G, Tavarelli M, Belfiore A, Vigneri R, Pellegriti G. Time to separate persistent from recurrent differentiated thyroid cancer: different conditions with different outcomes. *J Clin Endocrinol Metab.* 2019;**104**(2):258–265.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 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):1–133.
3. Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. *Endocrinol Metab Clin North Am.* 2014;**43**(2): 401–421.
4. Bates MF, Lamas MR, Randle RW, Long KL, Pitt SC, Schneider DF, Sippel RS. Back so soon? Is early recurrence of papillary thyroid cancer really just persistent disease? *Surgery.* 2018;**163**(1):118–123.