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Letter to the Editor: "Medullary Thyroid Carcinoma in MEN2A: ATA Moderate- or High-Risk *RET* Mutations Do Not Predict Disease Aggressiveness"

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We thank Voss *et al.* (1) for their interesting study about the overall outcome of patients with moderate- and high-risk multiple endocrine neoplasia type 2, American Thyroid Association classification A (MEN2A). The authors compared the mortality and time to distant metastases in patients carrying moderate- and high-risk (634 codon) mutations of *RET*, and they did not observe any significant difference. They recommend modifying the schematic of the American Thyroid Association classification by replacing moderate and high risk with "late" and "early disease onset." This is of importance as it is the first time that the idea of parallel survival curves is suggested, the only difference being the time of disease onset. We would like to share two main concerns about this study, and the reasons why we think this new terminology might be premature.

First, in retrospective studies, the mortality is always biased by the management of the patients. Given the fact that the authors initially considered 634 *RET* mutations as high risk, it would be interesting to know whether their management was different between both groups: number of cervical surgeries, radiotherapy, targeted therapy, or chemotherapy. A more aggressive management in patients carrying 634 *RET* mutations would lead to a better outcome, but would also be an evidence in favor of a more aggressive disease. The authors also elegantly showed that the time to the first distant metastasis was comparable; however, isolated slow-growing metastasis does not behave like multiple fast-growing metastases, and this information would also be of importance to better characterize the outcome of the disease, particularly in view of the different age at last follow-up between both groups. Indeed, in the results, it is stated that the median age at diagnosis was 42 and 23 years and the median follow-up time was 6.5 and 11.5 years for moderate- and high-risk groups, respectively. Thus, one-half of the patients with 634 *RET* mutations were censored by age 34.5 vs 48.5 in the moderate-risk group. A longer follow-up is undoubtedly necessary to ascertain that the mortality would be identical at the same final age.

Second, endocrinologists dealing with MEN2A have always noticed the wide phenotypic variability among patients (age at distant metastasis, final outcome). The authors recently reported that a worst outcome or progression differed among 12 families with the same RET mutation; they "recommended counseling patients with codon 634 mutations that their MTC [medullary thyroid carcinoma] disease course cannot be predicted by that of their relatives" (2). This emphasizes the difficulty in predicting the outcome of such patients as a whole. The term "risk" is thus a reminder for the clinicians that MEN2A should lead to appropriate treatment as soon as possible. Replacing the term risk by onset would likely tone down the dramatic outcome of some of the patients carrying 634 *RET* mutations. In the absence of larger-scale studies (as recommended by the authors in their discussion) with long-term follow-up that would confirm the interesting data shown in this study, we thus think that a semantic replacement is premature and would send a wrong message to the clinicians dealing with MEN2A.

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Abbreviation: MEN2, multiple endocrine neoplasia type 2, American Thyroid Association classification A.

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