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LETTER – ENDOCRINE TUMORS

Reply to Letter to the Editor Regarding "The Importance of Diagnosing Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) Based on the Defined Criteria"

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Dear Editor,

We thank Dr. Rosario for his letter, which stimulates discussion around this important new diagnostic entity. We agree with Dr. Rosario's point that improvements in methodology would result if there were a secondary review of all pathology specimens in the study;[1] however, this is both not feasible and also not necessary to demonstrate our main conclusion. The added benefit of our current methodology is that it provides a unique dataset with long-term survival that would otherwise not be possible in most retrospective studies. Given the long-term survival and its importance in studying noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), many of the cell blocks and histology slides would realistically no longer be available. The recommendation against the diagnosis being made on the original pathology report by the American Association of Clinical Endocrinologists (AACE) and the American Head and Neck Society (AHNS), quoted by Dr. Rosario, are clinical guidelines not designed for research purposes and therefore do not apply to our study, with its objective to assess the potential impact at a population-based level.[2,3] Health Services Research uses population-based administrative data sources and 'real world' experience to describe outcomes in a population. However, the limitations of this type of research are those that Dr Rosario has pointed out.

Given the poor NIFTP diagnostic *inter-observer reliability*, even among expert endocrine pathologists, found in the data supplement of the original publication, combined with the constantly *changing diagnostic criteria* for NIFTP diagnosis,[4,5] we hypothesize that there will likely be misclassification error at the population-level in groups that have long-term follow up. Most pathologists reviewing thyroidectomy specimens are general pathologists not dedicated to endocrine pathology, likely experiencing challenges with the diagnostic criteria, which Dr. Rosario claims is both 'strict and laborious'. The challenges faced by pathologists are compounded by the fact that a significant volume of thyroid surgery is performed by many surgeons at less-experienced, low-volume hospitals.[6–8] Thus far, the diagnosis has been developed and studied only among tertiary thyroid cancer centers, and its generalizability, particularly at a population-based level, is yet unknown. When new 'guidelines' are published, it takes a significant amount of time for appropriate dissemination and adherence. Specimen handling, sectioning and interpretation may be fraught with error in the earlier years,

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especially for large tumors where assessing the full tumor capsule can be challenging.[5] Therefore, nuances around this challenging diagnosis, especially with changing criteria as previously mentioned, may not be picked up in many specimens, leading to *diagnostic errors*.

Our population-based study therefore adds value to the literature. We suspect our study methodology could very well lead to misclassification (overdiagnosis of NIFTP, leading to a higher adverse event rate), which is an important finding. Future work is required to confirm the impact of the diagnosis, its potential misclassification, and whether this leads to higher than expected 'adverse events' in the NIFTP group using a prospective design. Nonetheless, even if our estimates of adverse events in the NIFTP group are incorrect by tenfold, which would lead to a far lower estimate than that reported in the literature (3–6% metastatic rate),[9–11] an important signal would have still been detected in our study. Dr. Rosario's erroneous interpretation of the three studies reported that demonstrate a *non-zero metastatic rate* is quite different than ours and we will therefore summarize their findings below in more detail.

Aburjania et al.[10] identified a 5% lymph node metastatic rate in an NIFTP population, although none developed distant metastases. Parente et al.[11] identified 6% of patients had metastases, including a single patient with distant metastases, therefore Dr. Rosario's interpretation that no patients had persistent or recurrent disease after surgery is incorrect. It should be noted that in this study, the entire capsule was assessed and that the pathologists reviewing the slides were experts in the field and on the original NIFTP publication. The distant metastasis was detected well after the thyroidectomy and the NIFTP diagnosis. This demonstrates that even with the 'entire' capsule being assessed, small areas of invasion can be missed between slices, which is a limitation related to minimum slice width on histopathology. In a multi-institutional study of NIFTPs, Cho et al.[9] identified a 3% rate of nodal metastases after excluding any tumors with any papillary structures, a stricter criteria than the original NIFTP publication (which allowed $< 1\%$ papillae). In excluding any tumor with papillary structure, they found that none of the NIFTP tumors had $BRAF^{V600E}$ mutations, and recommended that this be incorporated in future diagnostic criteria for NIFTP. They concluded that *NIFTP should not be regarded as a benign thyroid neoplasm as it can present with lymph node metastases.* This confirms and strengthens the American Thyroid Association recommendations to treat NIFTP as a low-risk thyroid cancer.[12] A recent study published after our original work identified micrometastases in patients with NIFTP, all of whom, on pathology re-review had micropapillary cancers.[13] They concluded that micrometastases in NIFTP patients are likely related to missed micropapillary cancers. Therefore, further study, with larger series and greater long-term follow-up is required to mature this literature, given these mixed results.

Dr. Rosario's own work confirms these concerns. In a recent publication, Dr. Rosario confirms that "NIFTP does not represent a benign lesion" and that "outcomes should be confirmed by long-term studies".[14] These were also our conclusions.[1]

In summary, the NIFTP diagnosis is challenging for the pathologist and this may make tumor behavior difficult to predict. Ultimately, molecular testing may be required to differentiate between NIFTP and the follicular variant of papillary thyroid cancer, with higher reliability and accuracy than the current diagnostic criteria. Currently, this would be prohibitively expensive. Until then, careful implementation and follow-up of these low-grade (not benign) tumors in a similar fashion to low-risk, well-differentiated thyroid cancer is warranted, as recommended by the American Thyroid Association.[12]

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