LETTER TO THE EDITOR

In Reply

Dr. Metze is to be commended for his efforts at explaining a possible mechanism whereby lymph node yield (LNY) may be mistakenly identified as a significant prognostic factor at more advanced N stages.¹ The basis for his theory lies in the introduction of bias inherent to pathological analysis (sampling bias). If numerous macroscopic (and likely metastatic) lymph nodes are detectable on cursory examination, Dr. Metze asserts, then why go looking for smaller lymph nodes that are less likely to be involved with metastases? Such bias may artificially increase the significance of LNY as the number of lymph nodes with metastases approaches the total number of lymph nodes excised. Dr. Metze has utilized a test dataset to illustrate his point. In his analysis, if the pathologist fails to remove even a few “negative” lymph nodes, LNY fails to reach statistical significance on univariate analysis.

Dr. Metze’s observations raise several critical points about our and similar studies that utilize registry datasets for lymph node analysis questions. The accurate representation of a patient’s nodal status is dependent upon: (1) patient biology (the true number of lymph nodes—positive and negative—present in a defined anatomic area), (2) surgical technique (the number of lymph nodes excised), and (3) pathological analysis (the number of lymph nodes examined). Items (2) and (3) together represent an approximation of “the truth,” as indicated by item (1). As with most studies employing the Surveillance, Epidemiology, and End Results database of the National Cancer Institute, information is limited regarding the scope of the intended surgical procedure and pathology quality control. While these are indeed major shortcomings, our hope is to offset this by dramatically increasing patient sample size to diminish the effect of random errors.

We agree with Dr. Metze about the potential for bias introduced during pathological analysis, but we have no practical way of proving this, nor of determining if this is a bias introduced at all centers (systematic error) or only at select centers (random error). It is instructive to point out, however, that Dr. Metze’s theory of pathological bias is based on the assumption that the examining pathologist will preferentially harvest macroscopically apparent lymph nodes. Such nodes would seem more likely to harbor metastases than their smaller and more troublesome to identify counterparts. However, there is little information

to suggest that presence on metastatic disease in lymph nodes can be judged on size criteria alone. In fact, the ability to determine the metastatic status of a lymph node basin based on inspection and palpation is little better than a flip of a coin.² Thus, one must assume that pathologists must fail to harvest negative lymph nodes with a similar frequency to positive lymph nodes. Even if we concede the unlikely scenario that only negative lymph nodes will go unharvested, Dr. Metze’s data set aligns with our published results. Although LNY achieved significance as a prognostic factor in the univariate analysis of our patient population as a whole, we were not able to demonstrate an understaging effect in node-negative medullary thyroid cancer patients by univariate or multivariate analysis. As Dr. Metze himself asserts, “the absence of this effect in node-negative patients suggests that nodal understaging is unlikely to be an important problem ... because the relation between LNY and improved survival should not be restricted to the subgroup with metastases.”¹ Indeed, we agree that the only group that we can use to demonstrate nodal understaging is the node-negative population. If we repeat Dr. Metze’s analysis using his test data set, but restrict our observations to the node-negative population ($n = 16$), then both LNpathologist and LNspecimen are no longer prognostic factors ($p > 0.2$ and $p > 0.2$, respectively), as we noted in our study.

Again, we are in agreement with Dr. Metze that pathology sampling bias may exist in our study, but that it is difficult to prove or disprove given the constraints of our registry data. Furthermore, we welcome his call for prospective investigations with standardized histopathology protocols to further assess this important issue.

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Published Online: 24 January 2009

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