

A Little Bit of Cancer is Still Cancer: Is it Time for Lymph Node Micrometastases in Non-small Cell Lung Cancer to Get Their Due?

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In this issue of the *Annals of Surgical Oncology*, Ren and colleagues from Shanghai Pulmonary Hospital use their robust surgical experience to present the original manuscript titled “Lymph Node Micrometastasis Prognosticate Survival in Patients with Stage I Bronchogenic Carcinoma.”¹ The authors evaluated the significance of lymph node micrometastasis (defined as metastases < 2.0 mm in greatest dimension) by examining the nodal specimens of patients with clinical stage 1 and pathologic T1-2aN0-1 adenocarcinoma who underwent surgical resection between January 1, 2009 and December 31, 2013. Their study highlights several important points regarding the modern thinking of the role of lymph node sampling and evaluation in non-small cell lung cancer (NSCLC) and supports in a single-institution coverage of clinical stage I adenocarcinoma the conclusions of other similar studies examining occult and microscopic nodal disease NSCLC.^{2,3}

The study included 589 patients who satisfied the inclusion and exclusion criteria. Using immunohistochemical (IHC) staining for cytokeratin (CK) and TTF-1, the authors found in their cohort 55 patients who would be deemed N0 by conventional lymph node evaluation methods. This group of patients represented 9.3% (55/589) of the total included patient population and 10.8% (55/510) of patients who otherwise would have been considered N0. Quite importantly but perhaps not surprisingly, patients with lymph node micrometastasis (LNMM or Nmic) had

worse recurrence-free survival (RFS) and overall survival (OS) than N0 patients but better RFS and OS than N1 patients. Importantly, multivariate analysis confirmed nodal micrometastasis as an independent prognostic factor, suggesting that a separate nodal stage for LNMM is more than just a pedantic distinction without real world merit.

Another interesting but likely not surprising finding in this study is that patients who were found to have LNMM had a greater number of lymph nodes resected than those patients who were N0 (15.2 ± 6.3 vs. 12.9 ± 6.4). This finding underscores the importance of adequate lymph node sampling for accurate staging.

Ren and colleagues acknowledge some drawbacks and limitations of this current study, most notably its unknown extrapolation and application to NSCLC patients as a whole. They acknowledge that their patient population consisted entirely of adenocarcinoma patients at a single center. However, while common sense may not always reign supreme in medicine, it certainly stands to reason that the findings of this study would be no different for future studies that incorporate larger groups of patients, patients with different demographic profiles, and patients with different clinical stages and histologic subtypes of lung cancer. Subsequent studies on this very topic will no doubt broaden the findings in this manuscript to a wider pool of patients.

Ultimately, this manuscript should charge us on the individual level to stage our patients as accurately as possible through thorough lymph node dissection and on the societal level to continue to refine our ever-improving staging system for non-small cell lung cancer. We should seek to make accurate pathologic assessment of lymph node micrometastases as accessible and economically feasible as possible, because it has been shown that such a distinction has measurable impact. Furthermore, improving

our understanding of the nature of micrometastatic disease will undoubtedly have therapeutic implications in this era of personalized medicine and targeted treatment.

By the same token, this paper should serve to remind us that staging systems work best when they are as easily understood and practical as can reasonably be. The proposed staging system in the manuscript does not seek to be overly detailed, and it does not look to subdivide lymph node staging in myriad new ways; it simply adds a single additional nodal grouping that makes clinical sense and has meaningful prognostic implications.

Nodal micrometastases have already made their way into the stage classification system of breast cancer.⁴ Will they soon get their due in lung cancer?

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