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Commentary: To ignore evil is to become an accomplice to it—predicting malignancy in mediastinal lymph nodes

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CENTRAL MESSAGE

Scores to predict malignancy in mediastinal lymph nodes fall short to justify avoiding a biopsy. In reality, the major problem with invasive mediastinal staging is actually doing it.

The evaluation of mediastinal lymph nodes is perhaps the most critical step in the staging of patients with suspected or confirmed non–small cell lung cancer. Current national practice guidelines published by the National Comprehensive Cancer Network¹ and the American College of Chest Physicians² recommend a noninvasive first step with computed tomography and positron emission tomography for all patients, followed by invasive mediastinal staging in patients with radiographic evidence of hilar or mediastinal lymph node involvement, or those with a radiographically normal mediastinum and central tumors <3 cm or any tumor >3 cm in size. In the absence of metastatic disease, results from mediastinal lymph node assessment directly impact subsequent treatment, which can range from surgery to definitive chemoradiation followed by immune checkpoint inhibition.³ The stakes are high when such different treatment strategies depend on this crucial step. Endobronchial ultrasound (EBUS)-transbronchial needle aspiration has emerged as the preferred first-line method for invasive mediastinal staging, with excellent diagnostic performance and an extremely low complication rate.⁴ Technical recommendations on the methods of EBUS-transbronchial needle aspiration have been published in an attempt to maximize its diagnostic yield.⁵ However, in certain situations, a diagnosis remains elusive and these patients are thus recommended to undergo further tissue sampling.

In their study, Hylton and colleagues⁶ attempt to tackle

this issue by proposing a scoring system to classify lymph nodes according to their predicted risk of harboring malignancy based exclusively on ultrasonographic features obtained by EBUS. Individual lymph nodes were assessed, and results were contrasted to the histopathologic evaluation of biopsies or resection specimens, which served as the gold standard to determine the presence of malignancy. Importantly, the authors identified 4 ultrasonographic features that were strongly associated with the presence of malignancy: size, absence of a central hilar structure, sharpness of the margins, and central necrosis. These features were included in a scoring system that performed fairly when predicting malignancy with a calculated bias-corrected C statistic of 0.66. Hylton and colleagues⁶ concluded that a cutoff of ≥ 3 points (sensitivity: 31.5%, specificity: 96.3%) may be helpful when making decisions about repeated biopsy of a specific lymph node if the initial samples are inconclusive. The authors emphasize that the current standard of care is to biopsy lymph nodes in at least 3 nodal stations but introduce the idea of potentially using the proposed score to determine whether a lymph node should be biopsied at all. In a second part of their study, the authors demonstrated the efficacy of an online education module teaching health care providers how to score lymph nodes according to their ultrasonographic features, although with limited inter-rater agreement.

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There are limitations to this study that deserve mention. First, the ultrasonographic images were obtained by one person only, limiting reproducibility. Second, the authors failed to integrate important factors that are known to affect the probability of a mediastinal lymph node harboring malignancy, such as results from positron emission tomography/computed tomography, primary tumor size, and location. Furthermore, there was no acknowledgment of the conditional change in probability that arises when a lymph node (independent of its ultrasonographic features) is found to be malignant, as the presence of a positive mediastinal lymph node increases the likelihood of the presence of other positive mediastinal lymph nodes.¹ Third, the authors did not apply other previously published methods to their population for a direct comparison to prove the superiority of their proposed method. Finally, and more troublesome, is the fact that the proposed scoring system misclassified 37 of 54 (68.5%) lymph nodes with malignancy as “low risk.” Therefore, the performance of the proposed method is not compelling enough to ignore the gold standard: obtaining a biopsy. Current guidelines recommend that tissue samples should always be obtained, independent of ultrasonographic features, as these are not reliable enough to forgo biopsy.⁵

The authors should be commended on their sound methodology and the precious infrastructure that they assembled to complete this work. This country-wide collaboration will prove fruitful in future studies. They have a strong foundation to build on their results to develop a more accurate and comprehensive prediction model for mediastinal lymph node malignant involvement. Such a score will likely prove useful in the clinic or in the operating room by streamlining the process of obtaining lymph node biopsies or deciding when to quit when the sample is persistently nondiagnostic, therefore, saving time and resources.

However, we strongly believe that the major problem with invasive mediastinal staging is actually doing it. Current recommendations for selection for invasive mediastinal staging have focused on being extremely sensitive to

identify most patients with mediastinal nodal involvement,^{1,2} capturing up to 100% of patients with true mediastinal disease.⁷ However, a recent analysis of the Society of Thoracic Surgeons General Thoracic Surgery Database showed that 57% of patients with non-small cell lung cancer clinical stages IB to IIIA did not undergo invasive mediastinal staging.⁸ Ignoring the potential evil residing in the mediastinal lymph nodes results in suboptimal outcomes. Therefore, the real hurdle is getting surgeons and patients into the room to have the mediastinum sampled. Hopefully, noninvasive methods in the future will accurately predict the presence of malignancy in the mediastinum. Until then, we should enforce a sensitive strategy to select patients for invasive mediastinal staging, always sampling nodes, even if that means sampling several benign lymph nodes.

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