



A new approach to predicting risk for N2 disease in non-small cell lung cancer

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There is no precedent from which to truly define a ‘central’ lung cancer. Institutional tumor boards are likely to have standardized their own definition, however the lack of uniformity to define ‘centrality’ potentially varies dramatically without direction from consensus guidelines. The definition of ‘centrality’ is critical, given that the diagnosis or even a clinical suspicion of non-small cell lung cancer (NSCLC) mandates accurate mediastinal staging to assign appropriate treatment pathways for patients, particularly for tumors that are close to central structures. Risk for hilar and mediastinal lymph node metastasis is clearly higher in central tumors, owing more to the proximity of those structures to the primary tumor rather than aggressiveness of disease (1). Prior work has explored clinical features thought to impact risk for lymph node involvement, including tumor histology and grade, which have obvious disadvantages given this data may be unknowable prior to surgery (2). Classic imaging features that drive recommendations for mediastinal staging include lymph node size >1 cm in greatest dimension, PET avidity of a lymph node of >2.5 (SUVmax), PET avid or enlarged N1 lymph nodes, or tumor size >3 cm. These findings trigger the need for invasive staging by either endobronchial ultrasound (EBUS) or cervical mediastinoscopy prior to considering any local treatment option. Even with these tools, imaging characteristics may under stage patients in up to 20% of cases (3).

Additionally, given the false negative rate of PET to detect locoregional lymph node involvement, there is risk in relying just on imaging characteristics alone for staging, particularly since the presence of ‘incidental N2’ disease is associated with worse prognosis both for surgical patients and those managed with stereotactic body radiotherapy (SBRT). Therefore, the optimal management of patients with central disease relies on standardizing its definition. Although most clinicians who manage lung cancer have defined triggers for mediastinal staging in suspected cases of NSCLC, a formalized evidence-based definition of a ‘central’ lung cancer is clearly warranted to help triage patients towards pre-treatment assessment for locoregional lymph node involvement.

The authors of “*Which definition of central tumor is more predictive of occult mediastinal metastasis in NSCLC patients with radiologic N0 disease?*” address this question from a novel point of view. This study makes the argument that ‘centrality’ as a predictor for lymph node involvement in NSCLC can be defined based on specific imaging characteristics, particularly to define the risk for occult N2 disease in the setting of radiographically negative disease. As discussed in this manuscript, the definition of ‘centrality’ is highly variable amongst institutions, societies, and within surgical and radiation trials, which the authors correctly attributed to discrepant outcomes associated with the management of these tumors. This is not surprising;

prospectively collected data in both surgical and radiation work have been inconsistent in their definition of ‘centrality’: RTOG 0236 (SBRT for medically inoperable NSCLC) defined a tumor within 2 cm of the proximal bronchial tree (PBT) as central (4), RTOG 0813 (SBRT for medically inoperable NSCLC) within 2 cm of the PBT or touching the mediastinal pleura (5), whereas the International Association for the Study of Lung Cancer (IASLC) considers tumors within 2 cm of any mediastinal structure (not specifically the airway), and the American College of Chest Physicians (ACCP) within the inner one-third of the chest cavity as their definition (6,7).

In this institutional sample of over 1,300 patients, Shin *et al.* explore 7 different definitions of ‘centrality’ to define which is most predictive of lymph node metastasis. The authors appropriately selected patients with tumors <3 cm, which have both a low risk of locoregional lymph node involvement and are the target population from which to consider local treatment options including surgical resection or radiation therapy as the primary treatment. Although the use of a single institutional data set from South Korea has fundamental issues including selection bias and concern for exchangeability to other lung cancer populations around the world, the definitions considered that define radiographically suspicious N2 disease are uniform, and the staging algorithms and treatment plans are consistent with recommendations from major societies including the National Comprehensive Cancer Network (NCCN) and ACCP (8,9). The authors’ inclusion criteria were reasonable considering the study question asked, particularly given that not all patients were required to undergo surgery (patients with EBUS/endoscopic ultrasound (EUS) defining N2 disease treated without surgery were included in this study). In either case, EBUS/EUS negative patients with a high pre-test probability for N2 disease were evaluated with cervical mediastinoscopy prior to surgery, which should minimize the false negative results of staging. It is interesting that none of the patients that underwent mediastinoscopy were found to have occult N2 disease. This speaks to both improvements in imaging technology to define the potential for N2, as well as the impact of EBUS (improved sensitivity compared to historical data) on mediastinal staging in this space.

After adjustment, it is impressive that the authors found only one of their imaging models to be associated with risk for N2 disease in the setting of a radiographically negative mediastinum, results that remained unchanged even when considering tumor density. While the definition

of ‘centrality’ by concentric lines derived radially from the hilum would seem to be the most logical model when surveyed, the results of this study find concentric lines arising from the midline to be most predictive of risk. This finding is unexpected, although the authors’ discussion points are well developed including that the lymphatic drainage of lung cancer, regardless of location, is highly variable and may not follow definable patterns of spread. Whether these results were impacted by definitions of tumor centrality based on the center of the nodule or the edge closest to the inner-third, as discussed in the limitations section, is hard to know although this level of granularity is unlikely to have a significant impact on these results. Additionally, we would not have expected a ground glass nodule (GGN), regardless of centrality, to have a significant association with risk for lymph node metastasis as defined in the multivariate model. The risk of lymph node involvement in GGN’s is dependent on the proportion of pure, heterogeneous, and part solid nodules within a sample, with increasing risk for lymph node spread defined by increased solid component on mediastinal windows (10). Although the proportion of each type of GGN is not well defined in this study, the large sample has sufficient power to define the risk for N2 involvement regardless of tumor density. Future studies should help clarify the risk of ‘incidental N2’ disease with stratification based on well-established classification schemes for GGN’s (10).

In conclusion, Shin *et al.* should be congratulated on their work to help formally define ‘centrality’ for NSCLC. These results have significant clinical implications and will likely be replicated in other larger datasets with a more diverse patient population. In the meantime, any opportunity to improve how the delivery of care for potential Stage IIIA patients will likely have an important impact on how these patients are managed. Future studies aimed at refining the role of mediastinal staging for central GGN’s based on nodule density, particularly for patients that will undergo non-surgical local therapy, might have a significant impact on risk for local recurrence and survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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