Editorial Commentary

# Intratumoral lymph vessel invasion as a predictive risk factor for nodal metastasis in non-small cell lung cancer: should L-1 status obligate adjuvant chemotherapy?

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The presence of lymph node involvement has long been established as a critical prognostic factor and principal determinant of adjuvant therapy in the treatment of non-small cell lung cancer (NSCLC). In the manuscript "Predictive risk factors for lymph node metastasis in patients with resected non-small cell lung cancer: a case control study", Moulla and colleagues present an analysis of data collected over nearly a decade with the goal of determining both pre- and postoperative predictors for nodal metastasis (1). The authors propose two approaches for predicting nodal involvement: a preoperative model based on radiology and bronchoscopic evaluation, and a post-operative model based on pathologic analysis of the resected specimen.

This retrospective analysis assessed 204 patients with NSCLC who underwent surgical resection at the authors' institution with curative intent and without neoadjuvant therapy. Several preoperative clinical elements were evaluated including endobronchial ultrasound (EBUS) for patients with radiographically suspicious N2 or N3 disease. Most patients (78%) received a lobectomy, with systematic lymph node dissection performed according to a predetermined approach (2). Postoperatively, histopathological elements including pathologic T stage (pT), residual tumor (R-status), lymphatic vessel invasion (L-status), venous invasion (V-status), tumor type, and grading were included in the assessment.

Univariate analysis found the following factors to hold predictive value for both pN1+ or pN(any)+ disease: size >3 cm, central location, pT category, R-status, L-status, V-status, and higher grade. In this study, centrally located tumors were specifically defined as those that were endoscopically visible during bronchoscopy. All factors except pT category and R-status were also significant predictors for pN2+ disease. No significant predictive value was found regarding age, gender, laterality, or histologic tumor type.

Interestingly though not surprisingly, multivariate analysis ultimately found significant predictive value for pN1+, pN2+, or pN(any)+ if the tumor was centrally located or >3 cm. Pretreatment evaluation guidelines presented by the European Society of Thoracic Surgeons (ESTS) (3) have recommended pathological mediastinal lymph node evaluation for tumors of at least 3 cm, and existing studies (4) have shown validity in following these recommendations. Studies have also demonstrated higher rates of occult nodal metastasis with centrally located tumors (5).

When evaluating postoperative histopathological findings, the multivariate analysis found intratumoral lymph vessel invasion (L1-status) to be another significant predictor, which was preserved in the pT1 subgroup as well. Lymphovascular invasion has been associated with

decreased overall and recurrence-free interval, even in early stage tumors (6). Although attempts at developing a risk-prediction model based on lymphovascular invasion have not been able to clearly predict recurrence rates (7), its inclusion into the TNM classification for NSCLC has been proposed (8).

Moulla and colleagues acknowledge some drawbacks of the study, including the lack of data regarding carcinoembryonic antigen (CEA) levels, which have been correlated with mediastinal lymph node metastasis (9). Regardless, the data presented here are valuable, although would be most beneficial alongside further information regarding follow-up and recurrence-free intervals.

Ultimately, this manuscript puts further emphasis on the importance of routine assessment for intratumoral lymph vessel invasion on pathologic specimens, and supports the meticulous nodal staging for larger, centrally located tumors. The importance of multidisciplinary discussion of adjuvant therapy for patients with pN0 but positive L1-status findings should not be overlooked.

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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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