



Emphysema as a Structural Barrier Against Lymphatic and Hematogenous Tumor Dissemination in NSCLC



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INTRODUCTION

Pulmonary emphysema induces profound architectural remodeling of lung parenchyma, including destruction of alveolar walls, reduction in lymphatic and vascular rarefaction. These changes fundamentally alter the biomechanic and biological properties of the pulmonary microenvironment. While emphysema is traditionally regarded as a risk factor for lung carcinogenesis, its potential role as a modifier of tumor dissemination biology has not been systematically investigated. We hypothesized that emphysematous parenchyma — by virtue of its structural disorganization and reduced vascular-lymphatic infrastructure — constitutes a hostile microenvironment for tumor spread via both lymphatic and hematogenous routes.

METHODS

Two independent cohorts were analyzed. Cohort 1 comprised 327 patients who underwent curative-intent surgical resection for NSCLC at a single center. CT-based emphysema assessment was performed according to Fleischner Society criteria, with classification into centrilobular, paraseptal, and panlobular subtypes. The primary outcome was pathological nodal status (N0 vs. N+). Univariate and multivariate logistic regression analyses were conducted adjusting for age, sex, histological subtype, and tumor density. Cohort 2 comprised 101 patients who underwent pulmonary metastasectomy for extrapulmonary primary malignancies, including colorectal, breast, renal cell, and other non-thoracic primaries. In addition to emphysema characterization, CT-measured tumor-to-emphysema distance (TM-AMF, in centimeters) was recorded for each case to assess the spatial relationship between the metastatic deposit and the nearest emphysematous parenchymal zone. Given that emphysema represents the structural pulmonary sequela of cumulative tobacco exposure, smoking pack-years were not entered as a covariate in multivariate models to avoid collinearity — emphysema was instead treated as an independent biological variable capturing the net structural effect of chronic parenchymal injury.

DISCUSSION AND CONCLUSION

Pulmonary emphysema appears to confer structural resistance against tumor dissemination via both lymphatic and hematogenous pathways, with consistent findings across two independent cohorts. The spatial segregation of metastatic deposits from emphysematous zones further supports the concept of emphysema as a mechanical barrier, potentially mediated by vascular rarefaction, reduced lymphatic density, and altered interstitial pressure dynamics. These findings suggest that emphysematous remodeling creates a microenvironment inhospitable to metastatic seeding and nodal invasion, and may represent an underrecognized determinant of tumor dissemination biology in thoracic oncology. Prospective controlled studies are warranted to confirm this hypothesis.

REFERENCES & ACKNOWLEDGEMENTS

Artificial Intelligence (AI) Use Disclaimer

Artificial intelligence (ChatGPT, OpenAI) was used for language editing. All scientific content, analyses, interpretations, and final presentation were reviewed and approved by the author.

RESULTS

In Cohort 1 (n=327; emphysema present: n=220, 67.3%), emphysema was significantly associated with N0 nodal status (68.6% vs. 53.3% in emphysema-absent patients; OR=1.92, 95% CI 1.19-3.09, p=0.010). The positive predictive value of emphysema for N0 nodal status was 68.6%. On multivariate analysis, emphysema remained an independent predictor of nodal negativity after adjustment for age, sex, and histological subtype. In Cohort 2 (n=101; emphysema present: n=18, 17.8%), emphysema prevalence was markedly lower than in the NSCLC resection cohort (17.8% vs. 67.3%; OR=9.48, 95% CI 5.42-16.59, p<0.001), consistent with the hypothesis that emphysematous lungs are less receptive to hematogenous metastatic seeding from extrapulmonary primaries. Spatial analysis of tumor-to-emphysema distance revealed that 12 of 18 emphysema-positive patients (66.7%) had metastatic deposits located at a measurable distance from emphysematous zones (median TM-AMF: 3.9 cm), with only 2 patients demonstrating tumor localization within emphysematous parenchyma itself. This spatial segregation pattern is consistent with emphysema functioning as a physical deterrent to metastatic implantation.