E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.02.842

Research Article

Clinicopathological Predictors of Lymph Node Metastasis in Resected Non-Small Cell Lung Cancer

Imran Tahir[1], Khalil Ahmed Shaikh[2], Khalid Ali[3], Ali Sufian Ahmad[4], Mobeen ud Din[5], Muhammad Shoaib Hanif[6]

1. Assistant Professor, Department of Thoracic Surgery, Hayatabad Medical Complex, Peshawar, Pakistan.

2. Assistant Professor, Department of Cardiothoracic Surgery, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan.

3. Assistant Professor, Department of Thoracic Surgery, Al-Aleem Medical College, Lahore, Pakistan.

4. Registrar, Department of Thoracic Surgery, Hayatabad Medical Complex Hospital, Peshawar, Pakistan.

5. Assistant Professor, Department of Oncology, Allama Iqbal Medical College, Lahore, Pakistan.

6. Professor of Surgery, Rehmat-ul-Lil-Alameen Postgraduate Institute of Cardiology, Lahore, Pakistan.

Imran Tahir: Corresponding author

Abstract

Background:
Accurate evaluation of nodal status is critical for staging, prognostic assessment, and determining adjuvant therapy in non-small cell lung cancer (NSCLC). While radical surgical resection with systematic lymph node dissection remains the primary curative approach for resectable NSCLC, occult or unsuspected lymph node metastasis (LNM) frequently leads to post-surgical disease recurrence.

Objective:
To identify independent clinicopathological and histopathological predictors of N1 and N2 lymph node metastasis in patients undergoing surgical resection for NSCLC.

Methods:
A hospital-based cross-sectional observational study was conducted evaluating 160 patients with histologically confirmed NSCLC who underwent complete surgical resection (lobectomy or sublobar resection) with systematic hilar and mediastinal lymphadenectomy at Hayatabad Medical Complex. Preoperative demographics, serum carcinoembryonic antigen (CEA) levels, radiologic tumor features (tumor size, consolidation-to-tumor ratio [CTR], central vs. peripheral location), and postoperative pathological characteristics (histological subtype, visceral pleural invasion [VPI], lymphovascular invasion [LVI], and spread through air spaces [STAS]) were systematically evaluated. Univariate and multivariable logistic regression analyses were performed to

identify independent predictors of overall and N2-specific nodal metastasis.

Results:
Pathological lymph node metastasis was identified in 26.3% (n = 42) of the 160 patients, with 11.9% (n = 19) having N1 disease and 14.4% (n = 23) demonstrating N2 mediastinal nodal involvement. Patients with nodal metastasis exhibited significantly larger radiological invasive tumor size (3.2 ± 1.1 vs. 2.1 ± 0.8 cm, $p < 0.001$), higher frequency of elevated serum CEA (> 5 ng/mL; 45.2% vs. 16.1%, $p < 0.001$), higher rates of solid CTR ($p < 0.001$), and greater prevalence of LVI (52.4% vs. 11.9%, $p < 0.001$) and VPI (40.5% vs. 14.4%, $p = 0.001$) compared to node-negative patients. Multivariable logistic regression revealed that invasive tumor size > 2 cm (adjusted OR = 3.24, 95% CI: 1.48–7.11, $p = 0.003$), elevated serum CEA level (adjusted OR = 2.86, 95% CI: 1.25–6.54, $p = 0.013$), lymphovascular invasion (adjusted OR = 4.15, 95% CI: 1.78–9.68, $p = 0.001$), and micropapillary/solid predominant histological subtype (adjusted OR = 3.52, 95% CI: 1.51–8.20, $p = 0.003$) were independent predictors of nodal metastasis.

Conclusion:
Tumor size > 2 cm, elevated preoperative serum CEA, lymphovascular invasion, and micropapillary/solid histological predominant patterns are major independent predictors of lymph node metastasis in resected NSCLC. Integrating these clinicopathological biomarkers allows for improved risk stratification, guiding decisions regarding the extent of intraoperative lymph node dissection and the administration of adjuvant systemic therapies.

Keywords: Non-small cell lung cancer; Lymph node metastasis; Clinicopathological predictors; Lymphovascular invasion; Carcinoembryonic antigen; Thoracic surgery; N2 disease.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all primary lung malignancies and remains a leading cause of cancer-related mortality globally. For patients with early and locally resectable disease (Stages I–III), radical anatomical surgical resection (lobectomy, segmentectomy) accompanied by systematic hilar and mediastinal lymph node dissection (LND) offers the highest likelihood of long-term cure. Pathological evaluation of lymph node status is the primary determinant of post-resection staging (TNM classification), directly informing patient prognosis and guiding decisions regarding adjuvant chemotherapy, targeted therapies, or immunotherapy. [1-3]

Despite complete macroscopic resection (R0), a significant proportion of patients with clinically node-negative disease (cN0) harbor occult or unsuspected pathologically positive hilar (pN1) or mediastinal (pN2) lymph node metastases. Unsuspected N2 nodal spread is associated with elevated rates of regional and systemic recurrence. While non-invasive staging modalities—such as contrast-enhanced chest computed tomography (CT) and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT)—have improved preoperative evaluation, their diagnostic sensitivity for detecting microscopic nodal deposits remains suboptimal, with reported false-negative rates ranging between 10% and 20%.[4-6]

Consequently, identifying robust clinical, radiological, serum, and histopathological predictors associated with nodal spread is

necessary. Primary tumor features—including radiological maximum invasive diameter, consolidation-to-tumor ratio (CTR), central anatomical location, and serum carcinoembryonic antigen (CEA) levels—have been implicated in nodal dissemination. Furthermore, pathological invasive biomarkers—such as lymphovascular invasion (LVI), visceral pleural invasion (VPI), spread through air spaces (STAS), and high-grade histological patterns (micropapillary and solid predominant subtypes in adenocarcinoma)—are increasingly recognized as key drivers of nodal metastasization.

Unraveling the combined predictive capacity of these clinicopathological parameters can assist thoracic surgeons in tailoring intraoperative lymph node dissection strategies (e.g., systematic mediastinal dissection versus lobe-specific nodal sampling) and identifying high-risk patients who require intensive postoperative surveillance or adjuvant systemic treatment. [7-10]

Therefore, this cross-sectional observational study was undertaken to evaluate the clinicopathological predictors of lymph node metastasis in patients undergoing surgical resection for NSCLC.

2. Rationale of the Study

Preoperative staging techniques frequently underestimate hilar and mediastinal nodal involvement in NSCLC, leading to unexpected pathological N1 or N2 diagnoses following surgical resection. While systematic lymph node dissection remains the gold standard, sublobar resections and selective nodal sampling are increasingly used for early-stage lesions. Identifying clinical, biochemical, radiological, and histopathological predictors associated with nodal dissemination provides thoracic surgeons and oncologists with an evidence-based tool to optimize surgical staging completeness, refine adjuvant therapy selection, and improve oncological outcomes.

3. Objectives

Primary Objective

- To evaluate the prevalence and independent clinicopathological predictors of hilar (N1) and mediastinal (N2) lymph node metastasis in patients undergoing anatomical surgical resection for NSCLC.

Secondary Objectives

1. To determine the association between preoperative serum biomarkers (CEA) and pathological nodal involvement.

2. To assess the predictive value of radiologic parameters (tumor diameter, CTR, tumor location) for nodal spread.

3. To examine the correlation between adverse histopathological features (LVI, VPI, STAS, histological subtype) and N1/N2 nodal status.

4. To establish a multivariable risk prediction model for identifying occult mediastinal nodal metastasis.

4. Materials and Methods

4.1 Study Design and Setting

A hospital-based cross-sectional observational study was conducted at the Department of Thoracic Surgery at Hayatabad Medical Complex.

4.2 Study Duration

The study was conducted over an eight-month period, encompassing patient identification, medical record review, standardization of pathology specimens, whole-slide histology re-evaluation, and statistical modeling.

4.3 Study Population

Adult patients with histologically confirmed primary NSCLC who underwent complete curative-intent anatomical surgical resection (lobectomy, sleeve lobectomy, or segmentectomy) with systematic lymph node dissection.

4.4 Sample Size

A sample size of 160 surgical cases was included. The sample size was calculated based on expecting a pathological nodal metastasis prevalence of 20–25% in resected NSCLC, maintaining an alpha error level of 0.05 and a statistical power of 80% to detect significant odds ratios (OR $\geq$ 2.5) for primary clinical predictors.

4.5 Inclusion Criteria

1. Age $\geq$ 18 years.
2. Histologically proven primary NSCLC (adenocarcinoma, squamous cell carcinoma, or large cell neuroendocrine carcinoma).
3. Complete macroscopic surgical resection (R0) accompanied by systematic hilar (N1) and mediastinal (N2) lymph node dissection (minimum of 3 mediastinal nodal stations harvested).
4. Complete preoperative thin-section CT imaging and baseline clinical biomarker records.
5. Availability of FFPE tissue blocks for detailed pathomorphological review.

4.6 Exclusion Criteria

1. Prior neoadjuvant chemotherapy, immunotherapy, or thoracic radiotherapy.
2. Preoperative evidence of distant metastatic disease (Stage IV).
3. Synchronous or metachronous primary lung tumors or history of extrapulmonary malignancy within 5 years.
4. Incomplete nodal dissection or missing pathological data regarding harvested lymph node stations.

4.7 Preoperative Clinical and Radiological Evaluation

Demographic parameters (age, sex, smoking history), clinical symptoms, and preoperative serum tumor markers (CEA) were systematically recorded. Thin-section contrast-enhanced chest CT images were analyzed to determine:

- **Maximal Tumor Diameter (cm):** Measured on lung window settings.
- **Consolidation-to-Tumor Ratio (CTR):** Ratio of maximal solid component diameter to maximal total lesion diameter (classified as pure GGO [CTR = 0], part-solid [0 < CTR < 1.0], or pure solid [CTR = 1.0]).

- **Tumor Location:** Central (inner one-third of the lung parenchyma adjacent to bronchial tree) versus peripheral (outer two-thirds).

- **Lobe Distribution:** Upper lobe versus non-upper lobe (middle/lower lobes).

4.8 Histopathological Evaluation

Resected surgical specimens were processed according to standard thoracic pathology guidelines. Pathological evaluation determined:

- **Histological Subtype:** Classified according to WHO criteria into Adenocarcinoma, Squamous Cell Carcinoma, and others. Adenocarcinomas were subtyped by predominant pattern (lepidic, acinar, papillary, micropapillary, solid).

- **Lymphovascular Invasion (LVI):** Defined as the presence of tumor emboli within endothelia-lined vascular or lymphatic channels confirmed by CD31/D2-40 IHC when equivocal.

- **Visceral Pleural Invasion (VPI):** Graded as PL0 (no invasion), PL1 (invasion beyond elastic lamina), PL2 (invasion to visceral pleural surface), or PL3 (parietal pleural involvement).

- **Spread Through Air Spaces (STAS):** Defined as tumor cells within air spaces beyond the main tumor edge.

- **Pathological Nodal Status:** Total harvested lymph nodes were evaluated; nodal stations were mapped according to IASLC recommendations into N0 (no nodal spread), N1 (ipsilateral peribronchial/hilar nodes), and N2 (ipsilateral mediastinal/subcarinal nodes).

4.9 Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and expressed as mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were presented as absolute numbers and percentages (n, %).

Comparisons between node-negative (pN0) and node-positive (pN1/pN2) groups were performed using Student's t-test or Mann-Whitney U test for continuous parameters, and Pearson's Chi-square or Fisher's exact test for categorical parameters. Univariate logistic regression identified potential factors associated with nodal metastasis. Variables with $p < 0.10$ in univariate analysis were entered into multivariable binary logistic regression models to identify independent predictors. Odds ratios (OR) with 95% confidence intervals (CI) were derived. Statistical significance was set at a two-sided p-value < 0.05.

5. Results

5.1 Patient Demographics and Clinical Characteristics

The study included 160 patients (mean age 60.4 ± 9.8 years; 58.8% male). Pathological examination confirmed lymph node metastasis in 42 patients (26.3%), comprising 19 cases (11.9%) of pN1 disease and 23 cases (14.4%) of pN2 mediastinal disease. Baseline clinical characteristics stratified by pathological lymph node status are shown in Table 1.

Variable	Pathological N0 (n = 118)	Pathological N1/N2 (n = 42)	Total Cohort (n = 160)	p-value
Age, years	61.2 ± 9.5	58.2 ± 10.2	60.4 ± 9.8	0.091
Male sex, n (%)	68 (57.6)	26 (61.9)	94 (58.8)	0.628
Female sex, n (%)	50 (42.4)	16 (38.1)	66 (41.2)	0.628
Smoking history (Ever-smoker), n (%)	62 (52.5)	27 (64.3)	89 (55.6)	0.188
Preoperative Serum CEA > 5 ng/mL, n (%)	19 (16.1)	19 (45.2)	38 (23.8)	<0.001
Surgical Resection Type, n (%)				0.312
- Lobectomy	98 (83.1)	38 (90.5)	136 (85.0)	
- Sublobar Resection (Segmentectomy)	20 (16.9)	4 (9.5)	24 (15.0)	
Mean Total Harvested Lymph Nodes	16.4 ± 4.8	18.2 ± 5.6	16.9 ± 5.1	0.048

Table 1: Baseline demographic and clinical parameters stratified by nodal status.

5.2 Radiological and Histopathological Characteristics

Pathological nodal involvement was significantly higher in patients with larger invasive CT tumor size (3.2 ± 1.1 vs. 2.1 ± 0.8 cm, $p < 0.001$), solid CTR ($p < 0.001$), central tumor location ($p =$

0.002), non-upper lobe location ($p = 0.012$), presence of LVI (52.4% vs. 11.9%, $p < 0.001$), VPI (40.5% vs. 14.4%, $p = 0.001$), and micropapillary/solid predominant adenocarcinoma subtype ($p < 0.001$).

Feature	**Pathological N0 (n = 118)**	**Pathological N1/N2 (n = 42)**	**p-value**
Radiological Features			
CT Invasive Tumor Size, cm	2.1 ± 0.8	3.2 ± 1.1	<0.001
Consolidation-to-Tumor Ratio (CTR)			<0.001
- Part-solid (CTR < 1.0)	42 (35.6)	4 (9.5)	
- Pure solid (CTR = 1.0)	76 (64.4)	38 (90.5)	
Central Tumor Location, n (%)	14 (11.9)	14 (33.3)	0.002
Non-Upper Lobe Location, n (%)	41 (34.7)	24 (57.1)	0.012
Histopathological Features			
Histology Type, n (%)			0.142
- Adenocarcinoma	88 (74.6)	35 (83.3)	
- Squamous Cell Carcinoma	24 (20.3)	5 (11.9)	
- Others	6 (5.1)	2 (4.8)	

Feature	Pathological N0 (n = 118)	Pathological N1/N2 (n = 42)	p-value
High-Grade Subtype (Micropapillary/Solid), n (%)	12 (10.2)	18 (42.9)	<0.001
Lymphovascular Invasion (LVI), n (%)	14 (11.9)	22 (52.4)	<0.001
Visceral Pleural Invasion (VPI), n (%)	17 (14.4)	17 (40.5)	0.001
Spread Through Air Spaces (STAS), n (%)	19 (16.1)	16 (38.1)	0.003

Table 2: Comparison of radiological and histopathological tumor features between groups.

5.3 Univariate and Multivariable Logistic Regression Analysis

In multivariable logistic regression analysis, CT invasive tumor size $>$ 2 cm (adjusted OR = 3.24, 95% CI: 1.48–7.11, $p = 0.003$), preoperative serum CEA $>$ 5 ng/mL (adjusted OR = 2.86, 95% CI: 1.25–6.54, $p = 0.013$), lymphovascular invasion (adjusted OR = 4.15, 95% CI: 1.78–9.68, $p = 0.001$), and micropapillary/solid predominant adenocarcinoma subtype (adjusted OR = 3.52, 95% CI: 1.51–8.20, $p = 0.003$) remained significant independent predictors of lymph node metastasis.

Variable	Univariate OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
CT Tumor Size $>$ 2 cm	**4.25 (1.98–9.12)**	**<0.001**	**3.24 (1.48–7.11)**	**0.003**

Variable	Univariate OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Serum CEA > 5 ng/mL	**4.30 (1.98–9.35)**	**<0.001**	**2.86 (1.25–6.54)**	**0.013**
Lymphovascular Invasion (LVI)	**8.17 (3.54–18.88)**	**<0.001**	**4.15 (1.78–9.68)**	**0.001**
Micropapillary/Solid Subtype	**6.63 (2.81–15.62)**	**<0.001**	**3.52 (1.51–8.20)**	**0.003**
Visceral Pleural Invasion (VPI)	3.98 (1.76–9.02)	0.001	2.08 (0.84–5.15)	0.112
Central Tumor Location	3.71 (1.56–8.84)	0.003	1.94 (0.72–5.21)	0.191
Non-Upper Lobe Location	2.51 (1.21–5.18)	0.013	1.82 (0.81–4.10)	0.148

Table 3: Univariate and multivariable logistic regression analysis for lymph node metastasis.

5.4 Subgroup Analysis: Independent Predictors of Occult N2 Mediastinal Metastasis

Analysis restricted to the 23 cases of pathological N2 mediastinal node metastasis demonstrated that lymphovascular invasion (adjusted OR = 5.22, 95% CI: 2.01–13.56, $p < 0.001$), micropapillary/solid histological pattern (adjusted OR = 4.18, 95% CI: 1.58–11.04, $p = 0.004$), and preoperative CEA > 5 ng/mL (adjusted OR = 3.12, 95% CI: 1.21–8.05, $p = 0.018$) were independent risk factors specifically associated with mediastinal nodal involvement.

Predictor Variable for N2 Disease	Adjusted OR	95% Confidence Interval	p-value
Lymphovascular Invasion (LVI)	5.22	2.01 to 13.56	<0.001
Micropapillary / Solid Predominant Subtype	4.18	1.58 to 11.04	0.004
Preoperative Serum CEA > 5 ng/mL	3.12	1.21 to 8.05	0.018
CT Invasive Tumor Size > 2 cm	2.78	1.08 to 7.15	0.034

Table 4: Multivariable logistic regression predicting pathological N2 mediastinal metastasis.

6. Discussion

Accurate assessment of lymph node status is a fundamental prerequisite for effective surgical staging and clinical management in resectable non-small cell lung cancer. In this prospective cross-sectional study, pathological lymph node metastasis was identified in 26.3% of patients, with 14.4% harboring N2 mediastinal disease. Multivariable analysis identified tumor size > 2 cm, elevated preoperative serum CEA, lymphovascular invasion, and micropapillary/solid predominant histological subtypes as independent predictors of nodal dissemination. [11-13]

6.1 Clinical and Biochemical Predictors (Tumor Size and Serum CEA)

Primary tumor size reflects overall neoplastic burden and biological invasiveness. Larger invasive tumor diameters facilitate increased vascular access and regional lymphatic permeation. In line with major clinical trials, our study demonstrated that tumors > 2 cm carry more than a 3-fold higher odds of harboring nodal metastasis. Furthermore, elevated preoperative serum CEA (> 5 ng/mL) served as a key biochemical marker for occult nodal spread. Elevated CEA reflects advanced biological aggressiveness and higher cellular turnover, aiding in the preoperative identification of patients at risk for occult N2 disease. [14-17]

6.2 Histopathological Predictors (LVI and Subtype Heterogeneity)

Among pathological metrics, lymphovascular invasion (LVI) emerged as the strongest independent risk factor for nodal dissemination (adjusted OR = 4.15). Penetration of tumor emboli into lymphatic channels is the direct anatomical precursor to regional nodal seeding. Tumor histology also plays a critical role: lung adenocarcinomas displaying micropapillary or solid predominant growth patterns showed a

higher rate of nodal involvement. These aggressive patterns exhibit reduced cell-cell adhesion and heightened invasive capacity, promoting early metastatic detachment into lymphatic spaces. [18]

6.3 Clinical Implications for Surgical and Oncological Management

These findings have direct implications for surgical planning and postoperative management. For patients undergoing sublobar resections or minimally invasive lobectomies, the presence of high-risk features (such as solid CTR, elevated CEA, or intraoperative frozen-section confirmation of high-grade histological patterns) indicates the need for thorough systematic mediastinal lymphadenectomy rather than limited nodal sampling. Postoperatively, identifying pN0 patients who possess multiple high-risk invasive features (LVI, VPI, micropapillary pattern) can guide decisions regarding closer surveillance imaging or enrollment in adjuvant systemic therapy trials. [19-20]

6.4 Limitations

Several study limitations should be noted. First, the cross-sectional study design evaluated pathological nodal status at resection without prospective long-term disease-free survival follow-up. Second, molecular driver mutation profiles (e.g., EGFR, ALK, KRAS) were not systematically available for all cases to assess genomic correlates of nodal spread. Third, radiomics and deep-learning machine analysis of CT images were not incorporated into this clinical model.

7. Conclusion

Preoperative radiological tumor size > 2 cm, elevated serum CEA (> 5 ng/mL), presence of lymphovascular invasion, and micropapillary or solid predominant histological patterns are major independent clinicopathological predictors of lymph node metastasis in resected non-small cell lung cancer. Preoperative and intraoperative integration of these predictive biomarkers can assist thoracic surgeons in tailoring the extent of lymph node dissection and refining postoperative adjuvant treatment strategies.

8. Recommendations

1. Perform systematic mediastinal lymph node dissection in all patients presenting with tumors > 2 cm, solid CTR, or elevated preoperative serum CEA levels.

2. Routinely evaluate and report lymphovascular invasion (LVI), visceral pleural invasion (VPI), and detailed adenocarcinoma histological predominant subtypes in pathology reports.

3. Utilize frozen-section intraoperative histopathological assessment of primary tumor architecture to guide decisions regarding the completeness of nodal dissection during sublobar resections.

4. Consider high-risk pN0 patients with multiple adverse features (LVI, elevated CEA, high-grade histology) for closer postoperative surveillance protocols or adjuvant systemic therapy.

5. Conduct multi-center prospective studies integrating radiomics, CT deep learning, and circulating tumor DNA (ctDNA) liquid biopsies with clinicopathological parameters to refine preoperative nodal staging accuracy.

9. References

1. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth)

Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39–51. doi:10.1016/j.jtho.2015.09.009.

2. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10(12):1675–1684. doi:10.1097/JTO.0000000000000678.

3. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Pathological Ontologies Since the 2011 Classification. J Thorac Oncol. 2015;10(9):1243–1260. doi:10.1097/JTO.0000000000000630.

4. Zhang L, Zhang FF, Li G, Xiang X, Liang H, Zhang Y. Predicting lymph node metastasis of clinical T1 non-small cell lung cancer: a brief review of possible methodologies and controversies. Front Oncol. 2024;14:1422623. doi:10.3389/fonc.2024.1422623.

5. Yu X, Li Y, Shi C, et al. Clinicopathological models for predicting lymph node metastasis in early-stage lung adenocarcinoma. J Thorac Dis. 2021;13(8):4832–4842. doi:10.21037/jtd-21-610.

6. Chen CY, Liu YH, Chen KC, et al. Prognostic Value of Tumor Size in Resected Stage IIIA-N2 Non-Small-Cell Lung Cancer. J Clin Med. 2020;9(5):1321. doi:10.3390/jcm9051321.

7. Takamori S, Shimokawa M, Fayyaz F, et al. The Clinical Role of Adjuvant Chemotherapy after Sublobar Resection for Non-Small-Cell Lung Cancer ≤ 20 mm with Lymph Node Metastases: A Propensity-Matched Analysis. Cancers (Basel). 2024;16(12):2184. doi:10.3390/cancers16122184.

8. Zeynelgil E, Yilmaz A, Turgut B, et al. Prognostic Value of STAS, Lymph Node Metastasis, and VPI in NSCLC ≤ 4 cm Treated with Lobectomy. J Clin Med. 2025;14(1):102. doi:10.3390/jcm14010102.

9. Chien JC, Hu YC, Tsai YJ, Chien YT, Feng IJ, Shiue YL. Predictive Value of Clinicopathological Factors to Guide Post-Operative Radiotherapy in Completely Resected pN2-Stage III Non-Small Cell Lung Cancer. Diagnostics (Basel). 2023;13(19):3095. doi:10.3390/diagnostics13193095.

10. Ye B, Cheng M, Li W, et al. Predictive risk factors for lymph node metastasis in clinical T1aN0 non-small cell lung cancer patients. J Thorac Dis. 2014;6(10):1423–1430. doi:10.3978/j.issn.2072-1439.2014.08.33.

11. Sung SY, Kwak YK, Lee SW, et al. Lymphovascular Invasion Increases the Risk of Nodal and Distant Recurrence in Node-Negative Stage I-IIA Non-Small-Cell Lung Cancer. Oncology. 2018;95(3):156–162. doi:10.1159/000488858.

12. Moon Y, Park JK, Lee KY, et al. Consolidation-to-tumor ratio on computed tomography as a predictor of lymph node metastasis in clinical stage IA lung adenocarcinoma. World J Surg. 2018;42(8):2492–2498. doi:10.1007/s00268-018-4508-2.

13. Dai J, Yu B, Zhang C, et al. Predictors of occult lymph node metastasis in clinical T1 lung adenocarcinoma. BMC Pulm Med. 2024;24(1):312. doi:10.1186/s12890-024-03120-x.

14. Seok Y, Yang HC, Kim TJ, et al. Frequency of lymph node metastasis according to histological subtype in clinical stage IA lung adenocarcinoma. Thorac Cancer. 2020;11(3):612–619. doi:10.1111/1759-7714.13302.

15. Qu X, Wang K, Lin Y, et al. Micropapillary and solid growth patterns are independent risk factors for lymph node metastasis in small-sized lung adenocarcinoma. J Surg Oncol. 2019;120(4):681–689. doi:10.1002/jso.25621.

16. Bera K, Schalper KA, Rimm DL, et al. Artificial intelligence in digital pathology: new tools for diagnosis and precision oncology. Nat Rev Clin Oncol. 2019;16(11):703–715. doi:10.1038/s41571-019-0252-y.

17. Niazi AK, Mahmood H, Awan KH. Digital pathology and artificial intelligence applications in thoracic oncology: A systematic review. J Pathol Inform. 2023;14:100312. doi:10.1016/j.jpi.2023.100312.

18. Bankhead P, Loughrey MB, Fernández JA, et al. QuPath: Open source software for digital pathology image analysis. Sci Rep. 2017;7(1):16878. doi:10.1038/s41598-017-17204-5.

19. Pani E, Kennedy G, Amini A, et al. Histologic subtypes as predictive factors for lymph node metastasis in clinical stage IA lung adenocarcinoma. Ann Thorac Surg. 2021;112(2):415–422. doi:10.1016/j.athoracsur.2020.08.035.

20. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding Multiple Pulmonary Sites of Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification. J Thorac Oncol. 2016;11(5):636–652. doi:10.1016/j.jtho.2016.03.006