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Micropapillary and Solid Histologic Patterns in N1 and N2 Lymph Node Metastases Are Independent Factors of Poor Prognosis in Patients with Stage II-III Lung Adenocarcinoma

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Abstract

Introduction: High-grade histologic patterns are associated with poor prognosis in patients with primary nonmucinous lung adenocarcinoma (ADC). We investigated whether the presence of micropapillary and/or solid patterns (MIP/SOL) in lymph node (LN) metastases has prognostic value.

Methods: Patients who underwent lobectomy for pathologic stage II-III lung ADC with N1 or N2 LN metastases (n=360; 2000–2012) were analyzed. We assessed overall survival (OS), lung cancer–specific cumulative incidence of death (LC-CID), and cumulative incidence of recurrence (CIR) between patients with and without MIP/SOL patterns in LN metastases. Multivariable Cox regression analysis was used to quantify the association between MIP/SOL patterns and outcomes.

Results: Micropapillary and solid patterns in LN metastases were associated with a higher incidence of smoking history ($p=0.004$), tumor necrosis ($p=0.013$), and spread of tumor through air spaces ($p<0.0001$), a higher prevalence of micropapillary or solid pattern in the primary tumor ($p<0.0001$), shorter OS (5-year OS, 40% [95% CI, 29%–56%] vs. 63% [48–83%] for no MIP/SOL in LNs; $p=0.03$), higher LC-CID (5-year, 43% [29%–56%] vs. 14% [4–29%]; $p=0.013$), and higher CIR (5-year, 65% [50%–77%] vs. 43% [25–60%]; $p=0.057$). Micropapillary and solid patterns in LN metastases were independently associated with poor outcomes: OS (hazard ratio [HR], 1.81 [95% CI, 1.00–3.29]; $p=0.05$), LC-CID (HR, 3.10 [1.30–7.37]; $p=0.01$), and CIR (HR, 2.06 [1.09–3.90]; $p=0.026$).

Conclusion: MIP/SOL histological patterns in N1 or N2 LN metastases are associated with worse outcomes in patients with stage II-III lung ADC. MIP/SOL histological patterns in LN metastases can stratify patients with high-risk stage II-III lung ADC.

Keywords

Nodal metastasis; Non-small cell lung cancer; N classification; Micropapillary adenocarcinoma; Solid adenocarcinoma

INTRODUCTION

In the International Association for the Study of Lung Cancer 8th edition of the staging system, metastatic lymph nodal (N) descriptors are recommended to indicate the anatomical location of the metastasis (N1, N2, and N3), the number of lymph node (LN) stations involved (single vs. multiple), and the absence or presence of skip metastasis (N2 with or without N1 involvement), resulting in the stratification of the N category into N1a, N1b, N2a1, N2a2, N2b, and N3.¹ The overlapping survival curves for N1b (multiple N1 stations), N2a1 (single N2 station with skip N1 metastasis), and N2a2 (single N2 station with N1 involvement) provide a rationale to investigate prognostic factors beyond the location and the number of LN metastases.^{2–5}

In addition to primary tumor (T) size, predominant histologic patterns of nonmucinous lung adenocarcinoma (ADC)^{6, 7} are associated with prognosis and can be used to stratify lung ADC into three prognostic groups: low grade (lepidic [LEP] predominant), intermediate grade (acinar [ACI] or papillary [PAP] predominant), and high grade (micropapillary [MIP] or solid [SOL] predominant)—the latter of which is associated with the worst prognosis.^{7–9} We have shown that the SOL-predominant histologic subtype in patients with resected stage I lung ADC is an independent predictor of early, extrathoracic, multisite recurrence and of poor postrecurrence survival.¹⁰ We and others have shown that the presence of “nonpredominant” MIP pattern is associated with high rates of locoregional recurrence after limited resection, a high rate of occult LN metastases, and poor prognosis.^{11–14} Both MIP and SOL histologic patterns are associated with spread of tumor through air spaces (STAS), which is a form of invasion that has been shown to be correlated with poor prognosis.^{15–17} MIP/SOL tumors had higher tumor mutational burden, fraction of genome altered, copy number amplifications, rate of whole-genome doubling, and number of oncogenic pathways altered as compared with LEP and ACI/PAP tumors.¹⁸ Although the observations mentioned above lend further evidence that MIP and/or SOL histologic patterns in the primary tumor are associated with a poor prognosis, the prognostic value of histologic patterns in LN metastases remains unexplored.

Herein, we investigate the prognostic value of histologic patterns in LN metastases by use of a consecutive cohort of patients with primary nonmucinous lung ADC with LN metastases who underwent anatomic resection for pathologic stage II-III lung ADC.

MATERIALS AND METHODS

Study Population

In this retrospective study, we identified patients with pathologic stage II-III lung ADC who underwent curative-intent resection at Memorial Sloan Kettering Cancer Center (MSK) from 2000 to 2012 (n=1169). Pathologic stage was based on the eighth edition of the *American Joint Committee on Cancer Staging Manual*.¹⁹ Patients were excluded if they had received any induction therapy, had multiple nodules, underwent treatment for another type of lung cancer within the previous 2 years, had positive margins (R1 or R2 resection), had concurrent progressive disease other than lung cancer, or had undergone segmentectomy or wedge resection. After histologic evaluation, patients were excluded if they were diagnosed with invasive mucinous ADC or colloid-predominant ADC, had no LN metastasis, or had inadequate LN tissue for analysis (Figure 1). Of the 1169 patients identified, 360 were analyzed in this study. Clinical data were collected from MSK’s prospectively maintained Thoracic Surgery Lung Cancer database. The institutional review board at MSK approved this study.

Histologic Evaluation

By the use of a multi-head Olympus BX51 microscope (Olympus, Tokyo, Japan) with a standard 22-mm diameter eyepiece, all available hematoxylin and eosin–stained tumor and LN slides were reviewed by three pathologists (Y.L., S.H.L., and W.D.T.), who were blinded to patient clinical outcomes. Any discrepancies in histologic evaluation among the

pathologists were later resolved by consensus meeting. The percentage of each histologic pattern in primary tumors and LN metastases was recorded in 5% increments, and tumors were classified by the predominant pattern in accordance with the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society and WHO (2021) classifications: ADC in situ; minimally invasive ADC; LEP, ACI, PAP, MIP, and SOL invasive ADC; invasive mucinous ADC; and colloid ADC.^{6, 7, 20} We also investigated lymphatic, vascular, and pleural invasions, tumor necrosis, and the presence of STAS. STAS was defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor.^{15, 21} Pathologic invasive tumor size was determined as the size of the invasive components, excluding LEP component, on microscopic examination.²² The location, number,¹ and histologic patterns (only ACI, PAP, MIP, and SOL) of LN metastases were recorded.

Statistical Analysis

Patient demographic and clinical characteristics were summarized using frequency (percentage) or median (interquartile range, IQR) and compared between groups using chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables. The primary endpoint was overall survival (OS; duration from surgery to death). The secondary endpoints were lung cancer-specific cumulative incidence of death (LC-CID), and cumulative incidence of recurrence (CIR). OS was estimated using the Kaplan-Meier approach from the time of surgery to death of any cause and compared between groups using log-rank tests. Patients were otherwise censored on the date of last follow-up. Relationships between groups and OS were quantified using Cox proportional hazards analyses.²³ As a secondary endpoint, lung cancer-specific survival was evaluated using a competing-risk approach from the time of surgery to the time of death from lung cancer.²⁴ Non-lung cancer death was considered a competing-risk event. LC-CID was compared between groups using Gray's test, and association between variables and lung cancer-specific deaths was quantified using Fine and Gray competing-risk regression. As in the analysis for LC-CID, CIR was analyzed in the competing-risk analysis framework. CIR was used to estimate the probability of recurrence after surgical resection with curative intent.²⁴ Death without recurrence was treated as a competing event. Patients were otherwise censored at the time of the last available follow-up (assessed in September 2016). Multivariable models for each outcome included a set of clinically important factors define *a priori*: all models included STAS, invasive tumor size, location of involved LN (N1 or N2), number of involved stations (single or multiple); the models for OS and LC-CID included age at surgery.

All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$. Statistical analyses were performed using R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria); the "survival" and "cmprsk" software packages were used for the analyses.

RESULTS

Patient Clinicopathologic Characteristics

Patient clinicopathologic characteristics are presented on Table 1. The median age of all patients was 68.3 years (interquartile range, 61.0–74.8 years), 68% of patients (n=244) were women, and 82% of patients (n=294) had a history of smoking. Involved LNs were p-N2 in 51% of patients (n=182); 34% of patients (n=122) had a single involved LN station, and 66% (n=238) had multiple involved LN stations. We stratified all patients by the presence or absence of a high-grade pattern (MIP and/or SOL) in LN metastases as follows: no MIP or SOL (neither), MIP but not SOL (MIP [no SOL] in LN), SOL but not MIP (SOL [no MIP] in LN), and both MIP and SOL (both in LN) in LN metastases. Patients with MIP and/or SOL patterns in LN metastases were more likely to have a history of smoking ($p=0.004$) and have necrosis ($p=0.013$) and had a higher incidence of STAS in primary tumors ($p<0.0001$). Patients with MIP only or SOL only in LN metastases had a higher incidence of MIP-predominant (21/75 [28%]) or SOL-predominant (91/197 [46%]) primary tumors, respectively ($p<0.0001$). Representative images of each histologic pattern observed in LN metastases are shown in Figure, Supplemental Data 1.

Prevalence of MIP and SOL Patterns in LN Metastases and Primary Tumors

The distributions of MIP and SOL patterns in LN metastases, stratified by the location of the involved LN (N1 vs. N2) or the number of involved LN stations (single vs. multiple), are shown in Figures 2A and 2B, respectively. The percentage of MIP pattern in LN metastases increased as N stage increased ($p=0.02$); this relationship was not observed for SOL ($p=0.40$; Figure 2A). There were no significant differences in the percentages of MIP or SOL pattern between single and multiple involved LN stations (Figure 2B).

The distribution of MIP and SOL pattern in primary tumors, stratified by the presence of MIP and/or SOL - in LN metastases, is shown in Figures 2C. The percentage of MIP pattern in primary tumors was highest in patients with only MIP in LN metastases (median [25th-75th percentile]: 20% [10%–40%]; $p<0.0001$; Figure 2C). As with MIP, the percentage of SOL pattern in primary tumors was highest in patients with only SOL in LN metastases (30% [10%–80%]; $p<0.0001$; Figure 2C).

Similar observations were made in patients with MIP-predominant and SOL-predominant LN metastases (Figure 2D). The percentage of MIP or SOL pattern in primary tumors was highest in patients with MIP-predominant or SOL-predominant LN metastases, respectively ($p<0.0001$; Figure 2D). Of note, 51% of patients with MIP-predominant LN metastases (36/70) and 36% of patients with SOL-predominant LN metastases (71/196) had <25% MIP or SOL pattern in their primary tumor, respectively.

Comparison of Histologic Patterns Between Primary Tumors and LN Metastases

The distribution of predominant patterns between primary tumors and LN metastases is shown in Figure 2E. The most common predominant pattern in LN metastases was SOL (n=196 [54%]), followed by ACI (n=77 [21%]), MIP (n=70 [19%]), and PAP (n=17 [4.7%]). The most common predominant pattern in primary tumors was ACI (n=155 [43%]),

followed by SOL (n=110 [30.6%]), MIP (n=49 [13.7%]), PAP (n=39 [10.8%]), and LEP (n=7 [1.9%]).

The percentage of each histologic pattern in LN metastases in relation to the percentage of that pattern in the primary tumor is shown in Figure 2F. Across each histologic pattern, there is a positive correlation between the percent of histological pattern in LN metastases and the percent of the same pattern in the primary tumor. The average percentage of SOL pattern in LN metastases was high even when the percentage of SOL pattern in the primary tumor was low: the average percentage of SOL pattern in LN metastases was 24% when the percentage of SOL pattern in the primary tumor was 0% to 4% and 50% when the percentage of SOL pattern in the primary tumor was 5% to 24%. A similar relationship was observed for MIP pattern.

The Prognostic Value of Histologic Pattern in LN Metastases

Of the 360 patients analyzed, 186 had a recurrence, 222 died during follow-up, and 136 died from lung cancer. The median follow-up was 6.8 years (interquartile range, 4.6 to 9.7 years). When patients were stratified by N1 versus N2 status, patients with N1 status (compared with N2) had better OS ($p=0.021$; Figure 3D) but not LC-CID ($p=0.513$; Figure 3E) or CIR ($p=0.335$; Figure 3F).

When patients were stratified by the presence or absence of each histologic pattern in LN metastases (Figure, Supplemental Data 2), only absence of MIP (compared with presence of MIP) was associated with significantly better OS, LC-CID, and CIR. The presence of ACI or PAP pattern in LN metastases (compared with absence of each) was not associated with significant differences in OS. Although absence of SOL (compared with presence of SOL) was associated with slightly better OS, LC-CID, and CIR, the difference was not statistically significant.

When patients were stratified by predominance or lack of predominance of MIP (Figure, Supplemental Data 3A–C) or SOL (Figure, Supplemental Data 3D–F) in LN metastases, lack of MIP predominance (compared with MIP predominance) was associated with significantly better OS, LC-CID, and CIR; whereas no differences were observed with lack of SOL predominance (compared with SOL predominance).

Since both MIP and SOL are known high-grade patterns, we next aimed to determine whether the absence of the combination of MIP and SOL in LN metastases was associated with a better prognosis. Absence of both MIP and SOL in LN metastases (compared with presence of either or both) was associated with significantly better OS, LC-CID, and CIR (5-year OS, 40% [95% CI, 29%–56%]; $p=0.03$; LC-CID, 43% [95% CI, 29%–56%]; $p=0.013$; and CIR, 65% [95% CI, 50%–77%]; $p=0.057$) (Figure 3A–C). Subset analysis by pN1 only and pN2 only confirmed our observations in the pN1 cohort. Subset analysis in pN2 only did not reproduce the overall observations, likely due to limited sample size (Figure, Supplemental Data 4A–B).

Multivariable Competing-Risks Regression Analysis for OS, LC-CID, and CIR

After adjusting for clinical factors such as age, STAS, invasive tumor size, location of the LNs (N1 or N2), number of involved LN stations (single or multiple), the presence of both MIP and SOL in LN metastases was statistically significantly associated with worse OS (vs neither: hazard ratio [HR], 1.81 [95% CI, 1.00–3.29]; $p=0.05$) (Table 2). Similar relationships were observed for lung cancer specific death (adjusted HR, 3.10 [95% CI, 1.30–7.37]; $p=0.01$) and recurrence (adjusted HR 2.06 [95% CI, 1.09–3.90]; $p=0.026$). Subset analysis of patients stratified by treatment with adjuvant chemotherapy shows that patients with high-grade histological component in the LNs demonstrate improved outcomes with adjuvant chemotherapy compared to patients with high-grade histological component that did not receive adjuvant chemotherapy, particularly those with both SOL and MIP in the LNs (Figure, Supplemental Data 5A–B; Table, Supplemental Data 1).

DISCUSSION

This study demonstrates the prognostic significance of high-grade histologic patterns in LN metastases. The presence of both MIP and SOL patterns in LN metastases is an independent, poor prognostic factor of OS, LC-CID, and CIR in patients with stage II-III lung ADC.

The primary strength of our study is its comprehensive assessment of histologic patterns in both primary tumors and LN metastases in a cohort of 360 patients with a median follow-up of 6.8 years. Most importantly, although the location, size, and number of LN metastases are presently considered in the nodal staging of solid tumors (head and neck, breast, esophagus, gastric, pancreas, colorectal, kidney, ovarian, uterine, or cervical, and prostate), we have demonstrated herein, for the first time in solid tumors, the significance of evaluating clinically important histologic patterns in LN metastases.

Whereas the prognostic significance of N1 and N2 LN metastases was established by the International Association for the Study of Lung Cancer,¹ the results of the multivariable analysis in the present study showed that beyond N1 and N2 status, the presence of both MIP and SOL is a significant factor providing insight into high-risk factors in patients with stage II-III lung ADC. Patients who had no MIP pattern in LN metastases or whose LN metastases were not MIP predominant had significantly better OS, LC-CID, and CIR, compared with those who did. In addition, patients with neither MIP nor SOL pattern in LN metastases had better survival than patients with both patterns in LN metastases.

The inclusion of nodal metastases in the staging of lung ADC is not only prognostic, but it can also serve as an indicator of occult metastases prompting consideration of adjuvant therapy. Adjuvant chemotherapy, administered as the standard of care for patients with resected stage II-III lung ADC to target the premetastatic niche, is associated with a benefit in 5-year OS of only 4% to 15%.^{25–28} Biomarkers are desperately needed to identify patients with stage II-III lung ADC who may benefit from adjuvant chemotherapy—thereby avoiding the side effects of treatment in patients who are unlikely to benefit from it—N1 and N2 status alone cannot differentiate patients in this manner. Our comprehensive analysis demonstrated that the absence of any high-grade component (i.e., absence of both MIP and SOL) in LN metastases offers more prognostic information than the anatomic location (N1

vs. N2) or the number (single vs. multiple stations) of LN metastases. This observation provides a strong rationale to conduct a prospective investigation to determine the prognostic and predictive value of histologic patterns in LN metastases. The necessity of such a study is even more apparent when considered in the context of the current era of induction immunotherapy and the fact that the immune microenvironment can differ by histologic pattern.^{29, 30} In addition, our subset analysis by adjuvant chemotherapy shows that patients with high-grade histological component in the LNs demonstrate improved outcomes with adjuvant chemotherapy compared to patients with high-grade histological component that did not receive adjuvant chemotherapy, particularly those with both SOL and MIP in the LNs (Table, Supplemental Data 1). Our study raises awareness for the consideration of the histological component in the regional LNs while evaluating the efficacy in future clinical trials of adjuvant chemotherapy, immunotherapy, or combination therapies.

Several studies have investigated histologic patterns in primary lung ADC tumors.^{7, 31, 32} The few studies that investigated histologic pattern in LN metastases included relatively small cohorts (<100 patients).^{33, 34} For instance, Russell et al. compared predominant histologic patterns in primary tumors and corresponding N2 metastases in 69 patients with stage III lung ADC.³³ In that study, the predominant pattern in MIP- and SOL-predominant primary tumors was most often observed in the N2 metastases. Survival was not observed to be significantly different by the predominant histologic pattern in N2 metastases. Suda et al. analyzed 24 patients with surgically treated lung ADC with LN metastases and found similar results.³⁴ Given their findings, both groups concluded that the predominant pattern in the primary tumor was the main determinant of outcomes in patients with lung ADC with LN metastasis; however, the small number of patients in each study limits the solidity of these observations. In our study, we showed that predominant histological subtypes in primary tumor were not statistically significant in any of the outcomes; hence, they were not included in the multivariable analysis. Sensitivity analyses, with the inclusion of the primary tumor histological patterns as a variable in all three multivariable models, did not change our observation that high-grade histological components in LNs are independently prognostic (Table 3).

Even when present in only small percentages in the primary tumor, both MIP and SOL were more likely to be present in LN metastases: 51% of patients with MIP-predominant LN metastases (36/70) and 36% of patients with SOL-predominant LN metastases (71/196) had only a small percentage (25%) of MIP or SOL, respectively, in the primary tumor. A higher percentage of either pattern in LN metastases was associated with a higher percentage of that pattern in the primary tumor. Of note, the average percentage of SOL in LN metastases was high even when the percentage of SOL in the primary tumor was low, which echoes previous findings that solid and micro-papillary patterns are tightly linked to the risk of developing nodal metastases.^{35–37} Yamada et al. also found that SOL was often present in LN metastases ≥ 2 mm, even if it was not predominant in the synchronous primary tumor.³⁸ Yu et al. observed that, in lung tumors ≥ 3 cm, the presence of MIP or SOL was associated with a higher percentage of LN metastases.³⁶ Dai et al. also reported that LN micrometastasis was more frequently observed in patients with lung ADC with MIP pattern present.³⁹ These observations are highly clinically significant—in particular, they underline the importance of LN staging (even in the presence, and not necessarily the predominance,

of MIP or SOL pattern in the primary tumor) before treatment by resection or stereotactic body radiation therapy. Furthermore, it could be speculated that MIP and SOL patterns can reflect the presence of metastasis-initiating cancer cells.⁴⁰

Our data suggest there may be clinical value if pathologists can record the histologic patterns of nonmucinous lung adenocarcinoma in LN metastases in their routine clinical work. This approach is currently not standard practice and has not been recommended by the IASLC or WHO. However, this may be considered in the future, given the accumulating data, including our own, demonstrating prognostic significance to even small amounts of the micropapillary and solid patterns in LN metastases. The feasibility of including histological subtypes of each LN in resection samples may not be practical and can only be considered with validation of our data in other cohorts as well as the significance confirmed in prospective studies. However, it is our pathologist's experience that identification of high-grade histological components in LNs is relatively easier in the background of LN architecture than in the primary tumor.

The observations from our study should be interpreted with acknowledgment of the inherent limitations of a retrospective study from a single-institution database with N1 and N2 status combined for analysis. In the current study, our observations were limited to patients with nonmucinous lung ADC; this therefore limits the application of our findings to the tumor-node-metastasis classification for nonmucinous lung ADC.

In conclusion, the co-presence of high-grade histologic patterns in LN metastases has a strong influence on patient survival, and the use of information on histologic patterns in LN metastases can achieve a better prognosis than the current pN classification in this study cohort. This observation raises the question whether recording of histologic patterns of nonmucinous lung adenocarcinoma in LN metastases should be performed in prospective clinical trials and/or in routine clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACI	acinar
ADC	adenocarcinoma
CI	confidence interval
CIR	cumulative incidence of recurrence
HR	hazard ratio
IQR	Interquartile range
LC-CID	lung cancer-specific cumulative incidence of death
LEP	lepidic
LN	lymph node
MIP	micropapillary
N	nodal
OS	overall survival
PAP	papillary
SOL	solid
STAS	spread of tumor through air spaces
T	tumor

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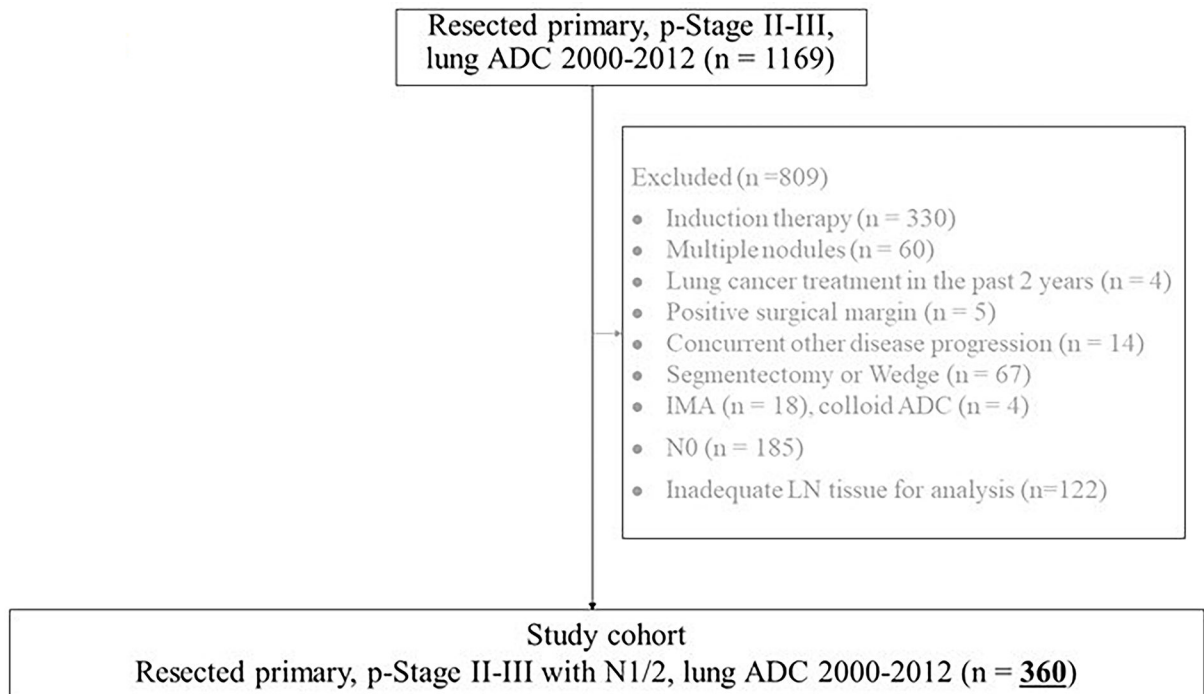


Figure 1. Patient flowchart. ADC, adenocarcinoma; IMA, invasive mucinous adenocarcinoma; LN, lymph node.

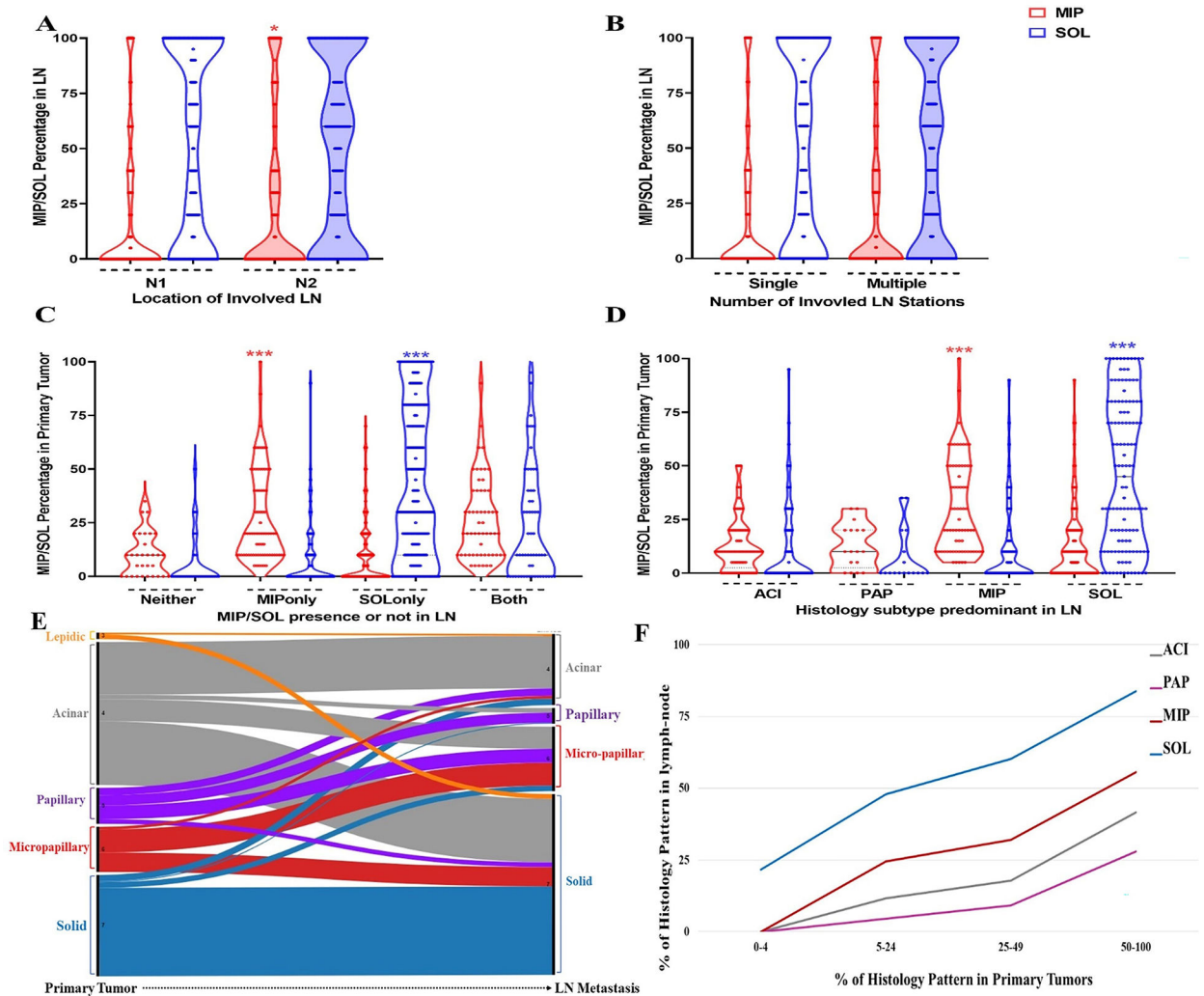


Figure 2. Prevalence of micropapillary (MIP) and solid (SOL) pattern in lymph nodes (LNs) and primary tumors. (A) Violin plot describing the distribution of MIP and SOL pattern in LN from patients with N1 versus N2 staging. (B) Violin plot describing the distribution of MIP and SOL pattern in LN from patients with single versus multiple involved LNs. (C) Violin plot describing the distribution of MIP and SOL pattern in primary tumors of which corresponding LNs had MIP and/or SOL pattern present. (D) Violin plot describing the distribution of MIP and SOL pattern in primary tumors of which corresponding LNs were either acinar (ACI), papillary (PAP), MIP, or SOL predominant. (E) Alluvial plot describing the proportion of patients with each predominant histologic subtype in the primary tumor and in the corresponding LNs. (F) Correlation of the percentage of histologic patterns between primary tumors and LNs. For each histological subtype (ACI, PAP, MIP and SOL), the mean percentage of the pattern in the LN across patients is calculated within four groups of increasing percentages (0–4%, 5–24%, 25–49%, 50–100%) of the pattern in the primary tumor. #, $p > 0.05$; * $p < 0.05$; *** $p < 0.0001$.

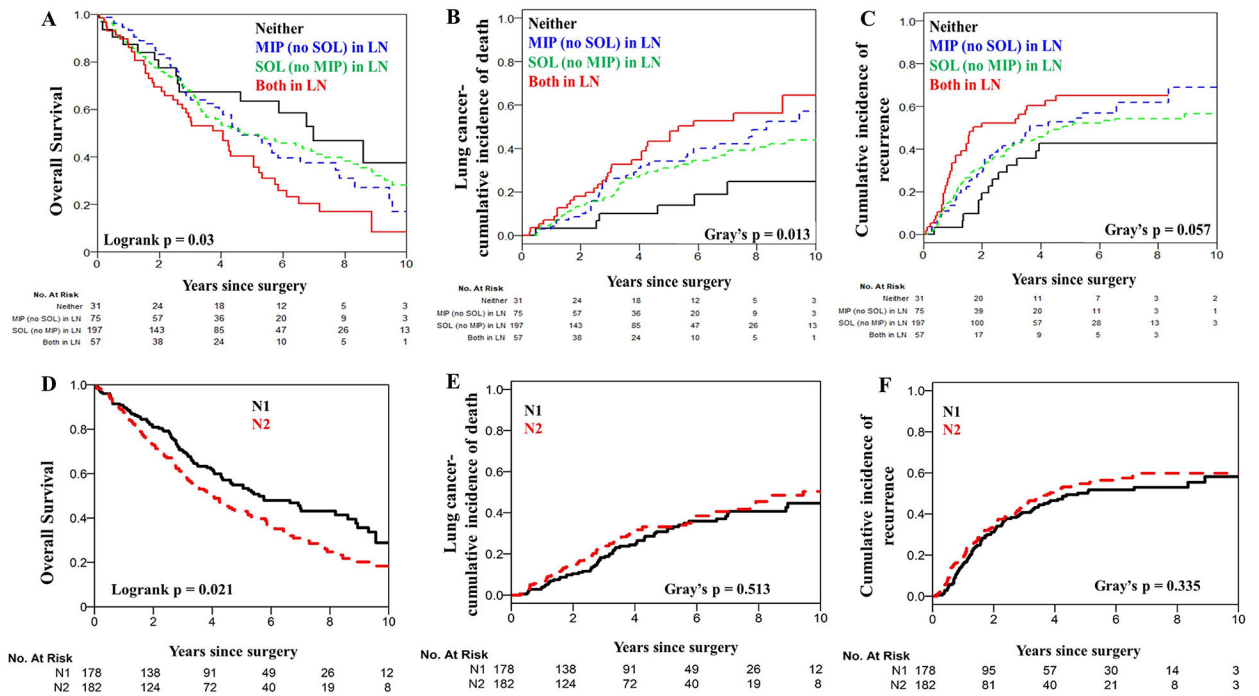


Figure 3. Overall survival, lung cancer-specific cumulative incidence of death, and cumulative incidence of recurrence for patients stratified by N1 versus N2 staging (A-C) or micropapillary (MIP) and/or solid (SOL) patterns in lymph nodes (LN) (D-F).

Table 1.

Clinicopathologic characteristics of patients with stage II-III lung adenocarcinoma

Characteristic	All patients (N=360)	Neither MIP nor SOL in LN (n=31; 8.6%)	MIP (no SOL) in LN (n=75; 21%)	SOL (no MIP) in LN (n=197; 55%)	Both MIP and SOL in LN (n=57; 16%)	P
Age, years	68.3 (61.0–74.8)	72.2 (63.4–78.7)	68.2 (60.4–74.0)	67.7 (59.8–74.3)	70.0 (64.2–75.1)	0.2
Sex						0.7
Female	244 (68)	21 (68)	47 (63)	135 (69)	41 (72)	
Male	116 (32)	10 (32)	28 (37)	62 (31)	16 (28)	
Smoking ever						0.004
Absence	66 (18)	12 (39)	18 (24)	27 (14)	9 (16)	
Presence	294 (82)	19 (61)	57 (76)	170 (86)	48 (84)	
Primary tumor						
LYI						
Absence	66 (18)	8 (26)	11 (15)	37 (19)	10 (18)	0.6
Presence	294 (82)	23 (74)	64 (85)	160 (81)	47 (82)	
Necrosis (N=329)						0.013
Absence	263 (71)	26 (87)	53 (79)	113 (63)	40 (74)	
Presence	97 (29)	4 (13)	14 (21)	65 (37)	14 (26)	
STAS (N=352)						
Absence	123 (33)	17 (55)	12 (17)	79 (41)	7 (12)	<0.0001
Presence	237 (67)	14 (45)	60 (83)	113 (59)	50 (88)	
Invasive tumor size, cm	2.7 (1.9–3.8)	3.1 (2.3–4.0)	2.3 (1.8–3.2)	2.7 (2.0–3.9)	3.1 (2.0–3.8)	0.088
IASLC8						<0.0001
Lepidic	7 (1.9)	0 (0)	0 (0)	5 (2.5)	2 (3.5)	
Acinar	155 (43)	23 (74)	30 (40)	80 (41)	22 (39)	
Papillary	39 (11)	7 (23)	21 (28)	7 (3.6)	4 (7.0)	
MIP	49 (14)	0 (0)	21 (28)	14 (7.1)	14 (25)	
SOL	110 (31)	1 (3.2)	3 (4.0)	91 (46)	15 (26)	
MIP or SOL status						<0.0001
No MIP or SOL	15 (4.2)	8 (26)	0 (0)	7 (3.6)	0 (0)	
Either MIP or SOL presence	71 (20)	9 (29)	27 (36)	24 (12)	11 (19)	

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Characteristic	All patients (N=360)	Neither MIP nor SOL in LN (n=31; 8.6%)	MIP (no SOL) in LN (n=75; 21%)	SOL (no MIP) in LN (n=197; 55%)	Both MIP and SOL in LN (n=57; 16%)	P
Either MIP or SOL secondary predominant	115 (32)	13 (42)	24 (32)	61 (31)	17 (30)	
Either MIP or SOL predominant LN	159 (44)	1 (3.2)	24 (32)	105 (53)	29 (51)	
Location of involved LN						0.13
N1	178 (49)	18 (58)	35 (47)	104 (53)	21 (37)	
N2	182 (51)	13 (42)	40 (53)	93 (47)	36 (63)	
No. of involved LN stations						0.5
Single	122 (34)	13 (42)	25 (33)	69 (35)	15 (26)	
Multiple	238 (66)	18 (58)	50 (67)	128 (65)	42 (74)	
Predominant histologic pattern in LN						<0.0001
Acinar	77 (21)	24 (77)	20 (27)	28 (14)	5 (8.8)	
Papillary	17 (4.7)	7 (23)	5 (6.7)	3 (1.5)	2 (3.5)	
MIP	70 (19)	0 (0)	50 (67)	0 (0)	20 (35)	
SOL	196 (54)	0 (0)	0 (0)	166 (84)	30 (53)	
Adjuvant chemotherapy status (N=323)						
No adjuvant chemotherapy	135 (42)	17 (57)	25 (38)	73 (42)	20 (38)	0.3
Adjuvant chemotherapy	188 (58)	13 (43)	41 (62)	102 (58)	32 (62)	
Outcomes, %						
5-year OS (95% CI)	49 (44-55)	63 (48-83)	49 (38-63)	49 (42-57)	40 (29-56)	0.03
5-year LC-CID (95% CI)	32 (27-37)	14 (4-29)	34 (23-46)	31 (24-38)	43 (29-56)	0.013
5-year CIR (95% CI)	53 (47-58)	43 (25-60)	53 (40-64)	51 (43-58)	65 (50-77)	0.057

Data are presented as no. (%) or median (interquartile range), unless otherwise noted. P values were calculated using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. ACI, acinar; CI, confidence interval; CIR, cumulative incidence of recurrence; IASLC9, International Association for the Study of Lung Cancer classification, 9th edition; LC-CID, lung cancer-specific cumulative incidence of death; LN, lymph node; LVI, lymphovascular invasion; MIP, micropapillary; OS, overall survival; STAS, spread of tumor through air spaces; SOL, solid. Bold type indicates statistical significance.

Table 2.

Multivariable analysis of Cox proportional hazards regression model for overall survival, lung cancer–specific cumulative incidence of death, and cumulative incidence of recurrence

Variable	OS			LC-CID			CIR		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age, years	1.02	1.00–1.03	0.023	1.00	0.98–1.02	0.9			
STAS	1.24	0.90–1.71	0.2	1.26	0.84–1.91	0.3	1.06	0.75–1.50	0.7
Invasive tumor size, cm	1.06	0.98–1.14	0.2	1.09	0.99–1.21	0.093	1.08	0.98–1.18	0.11
Location of involved LN, N2 vs. N1	1.22	0.91–1.62	0.2	0.91	0.63–1.33	0.6	0.93	0.67–1.29	0.7
Number of involved stations, multiple vs. single	1.22	0.89–1.67	0.2	1.35	0.89–2.03	0.2	1.50	1.05–2.14	0.025
MIP or SOL status in LN									
MIP only vs. neither	1.37	0.76–2.48	0.3	2.51	1.05–6.00	0.039	1.53	0.84–2.78	0.2
SOL only vs. neither	1.46	0.86–2.48	0.2	2.12	0.92–4.88	0.078	1.41	0.81–2.45	0.2
MIP and SOL, both vs. neither	1.81	1.00–3.29	0.05	3.10	1.30–7.37	0.010	2.06	1.09–3.90	0.026

CI, confidence interval; CIR, cumulative incidence of recurrence; HR, hazard ratio; LN, lymph node; LC-CID, lung cancer–specific cumulative incidence of death; MIP, micropapillary; OS, overall survival; STAS, spread of tumor through air spaces; SOL, solid. Bold type indicates statistical significance.

Table 3.

Multivariable analysis of Cox proportional hazards regression model for overall survival, lung cancer–specific cumulative incidence of death, and cumulative incidence of recurrence with primary tumor patterns

Outcome 1. Overall survival

Variable	No IASLC9 primary tumor			IASLC9 primary tumor		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age, years	1.02	1.00, 1.03	0.023	1.02	1.00, 1.03	0.019
STAS	1.24	0.90, 1.71	0.2	1.26	0.91, 1.74	0.2
Invasive tumor size, cm	1.06	0.98, 1.14	0.2	1.06	0.98, 1.15	0.2
Location of involved LN, N2 vs. N1	1.22	0.91, 1.62	0.2	1.24	0.93, 1.66	0.14
Number of involved stations, multiple vs. single	1.22	0.89, 1.67	0.2	1.20	0.88, 1.64	0.3
MIP only vs. neither	1.37	0.76, 2.48	0.3	1.46	0.80, 2.68	0.2
SOL only vs. neither	1.46	0.86, 2.48	0.2	1.36	0.78, 2.37	0.3
MIP and SOL, both vs. neither	1.81	1.00, 3.29	0.050	1.83	1.00, 3.37	0.051
IASLC9 primary MIP vs. low/int				0.83	0.54, 1.25	0.4
IASLC9 primary SOL vs. low/int				1.22	0.87, 1.70	0.2

Outcome 2. Cumulative incidence of lung cancer–specific death

Variable	No IASLC9 primary tumor			IASLC9 primary tumor		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age, years	1.01	0.99, 1.03	0.4	1.01	0.99, 1.03	0.3
STAS	1.31	0.86, 1.99	0.2	1.34	0.88, 2.05	0.2
Invasive tumor size, cm	1.09	0.99, 1.20	0.067	1.09	1.00, 1.20	0.060
Location of involved LN, N2 vs. N1	1.03	0.72, 1.49	0.9	1.06	0.73, 1.53	0.8
Number of involved stations, multiple vs. single	1.37	0.91, 2.07	0.13	1.35	0.90, 2.03	0.2
MIP only vs. neither	2.36	0.97, 5.77	0.059	2.55	1.03, 6.30	0.043
SOL only vs. neither	2.13	0.92, 4.94	0.077	1.94	0.82, 4.62	0.13
MIP and SOL, both vs. neither	3.08	1.25, 7.57	0.014	3.11	1.25, 7.73	0.015
IASLC9 primary MIP vs. low/int				0.78	0.47, 1.32	0.4
IASLC9 primary SOL vs. low/int				1.28	0.84, 1.96	0.3

Outcome 3. Cumulative incidence of recurrence

Variable	No IASLC9 primary tumor			IASLC9 primary tumor		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age, years	1.01	0.99, 1.03	0.2	1.01	0.99, 1.03	0.2
STAS	1.10	0.78, 1.55	0.6	1.11	0.78, 1.57	0.6
Invasive tumor size, cm	1.07	0.98, 1.15	0.11	1.07	0.98, 1.16	0.12
Location of involved LN, N2 vs. N1	0.99	0.72, 1.36	0.9	0.99	0.72, 1.37	1
Number of involved stations, multiple vs. single	1.63	1.15, 2.32	0.006	1.62	1.14, 2.31	0.007

MIP only vs. neither	1.51	0.79, 2.89	0.2	1.54	0.79, 2.98	0.2
SOL only vs. neither	1.50	0.83, 2.69	0.2	1.44	0.78, 2.66	0.2
MIP and SOL, both vs. neither	2.28	1.18, 4.41	0.015	2.27	1.16, 4.47	0.017
IASLC9 primary MIP vs. low/int				0.94	0.59, 1.48	0.8
IASLC9 primary SOL vs. low/int				1.09	0.76, 1.57	0.6

CI, confidence interval; HR, hazard ratio; IASLC9, International Association for the Study of Lung Cancer classification, 9th edition; LN, lymph node; MIP, micropapillary; SOL, solid; STAS, spread of tumor through air spaces.

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