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ARTICLE

# Impact of Micropapillary Histologic Subtype in Selecting Limited Resection vs Lobectomy for Lung Adenocarcinoma of 2 cm or Smaller

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**Background** We sought to analyze the prognostic significance of the new International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) lung adenocarcinoma (ADC) classification for patients undergoing resection for small (≤2 cm) lung ADC and to investigate whether histologic subtyping can predict recurrence after limited resection (LR) vs lobectomy (LO).

**Methods** Comprehensive histologic subtyping was performed according to the IASLC/ATS/ERS classification on all consecutive patients who underwent LR or LO for small lung ADC between 1995 and 2009 at Memorial Sloan-Kettering Cancer Center. Clinical characteristics and pathologic data were retrospectively evaluated for 734 consecutive patients (LR: 258; LO: 476). Cumulative incidence of recurrence (CIR) was calculated using competing risks analysis and compared across groups using Grey's test. All statistical tests were two-sided.

**Results** Application of IASLC/ATS/ERS lung ADC histologic subtyping to predict recurrence demonstrates that, in the LR group but not in the LO group, micropapillary (MIP) component of 5% or greater was associated with an increased risk of recurrence, compared with MIP component of less than 5% (LR: 5-year CIR = 34.2%, 95% confidence interval [CI] = 23.5% to 49.7% vs 5-year CIR = 12.4%, 95% CI = 6.9% to 22.1%, $P < .001$; LO: 5-year CIR = 19.1%, 95% CI = 12.0% to 30.5% vs 15-year CIR = 12.9%, 95% CI = 7.6% to 21.9%, $P = .13$). In the LR group, among patients with tumors with an MIP component of 5% or greater, most recurrences (63.4%) were locoregional; MIP component of 5% or greater was statistically significantly associated with increased risk of local recurrence when the surgical margin was less than 1 cm (5-year CIR = 32.0%, 95% CI = 18.6% to 46.0% for MIP ≥ 5% vs 5-year CIR = 7.6%, 95% CI = 2.3% to 15.6% for MIP < 5%; $P = .007$) but not when surgical margin was 1 cm or greater (5-year CIR = 13.0%, 95% CI = 4.1% to 22.1% for MIP ≥ 5% vs 5-year CIR = 3.4%, 95% CI = 0% to 7.7% for MIP < 5%; $P = .10$).

**Conclusions** Application of the IASLC/ATS/ERS classification identifies the presence of an MIP component of 5% or greater as independently associated with the risk of recurrence in patients treated with LR.

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Lobectomy (LO) with hilar and mediastinal lymph node dissection is the current gold standard for resection of early-stage lung cancer (1,2). Approximately 80% of patients with lung cancer are diagnosed with primary non–small cell lung cancer, the most common histologic type of which is adenocarcinoma (ADC) (3,4). Recent advances in imaging technology and the widespread use of computed tomography screening have increased the probability of detecting small early-stage lung ADCs, which usually present in the periphery of the lung (5). Some surgeons have suggested that peripheral lung ADC is treatable by limited resection (LR) and that LR is as effective as LO, with the added advantage of preserving lung function (6–11). However, the ideal type of resection for peripheral early-stage lung ADC remains a matter of controversy and is the focus of several ongoing clinical trials (Cancer and Leukemia Group B [140503] and Japan Clinical Oncology Group [0802, 0804]). To date, there are no evidence-based criteria for choosing LR over LO for the treatment of peripheral early-stage lung ADC, and the only proposed criterion for choosing LR is tumor size (ie, ≤2 cm) (12,13).

The recent classification of lung ADC proposed by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) emphasizes the importance of histologic subtyping (14). The prognostic significance of the new IASLC/ATS/ERS histologic subtypes originally proposed by our group has been validated by use of independent datasets

on lung ADC from the United States (15), Japan (16), Germany (17), and China (18). However, no study to date has investigated the prognostic utility of the new classification for patients with small (≤2 cm) early-stage lung ADC. Here, we analyze and confirm the prognostic significance of the IASLC/ATS/ERS classification for patients with small early-stage lung ADC, and we further identify the presence of micropapillary (MIP) morphologic pattern as a strong predictor of the risk of recurrence after LR. With the expected increase in the detection of small lung ADC by screening computed tomography scans as a result of a recent National Cancer Institute clinical trial (5), our results have immediate implications for the management of these patients.

## Methods

### Patient Selection

This study was approved by the institutional review board at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, New York. From the MSKCC Thoracic Service database we retrospectively identified 1421 consecutive patients who had been surgically treated for small lung ADC between January 1995 and December 2009. Medical records and the prospectively maintained database were reviewed to determine the clinical variables and the rationale for the type of resection performed. Exclusion criteria are listed in Figure 1. A total of 734 patients met our inclusion criteria: 258 underwent LR (wedge resection or segmentectomy), and 476 underwent LO. The reasons for the selection of LR are listed in Supplementary Table 1 (available online). Written informed consent was obtained from all patients before proposed surgical resection.

### Histologic Evaluation

Histologic diagnoses were based on the 2004 World Health Organization (WHO) criteria for lung ADC (19). Pathologic stage (as defined in the seventh edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM classification) (20) and the distance between the surgical staple margin and the resected tumor surface were determined by reviewing the pathology reports. All available hematoxylin and eosin–stained slides were reviewed by two pathologists (K. Kadota and W.D. Travis). A minimum of two hematoxylin and eosin–stained slides were reviewed per patient (median = 4; range = 2 to 10 slides/patient). Each tumor was evaluated by comprehensive histologic subtyping, and the percentage of each histologic component was recorded in 5% increments. In accordance with the IASLC/ATS/ERS classification for lung ADC (14), we classified tumors by their predominant morphologic pattern, which was defined by the histologic subtype found in the greatest proportion: 1) lepidic, including ADC in situ and minimally invasive ADC; 2) acinar; 3) papillary; 4) MIP; and 5) solid. Other predominant histologic subtypes included invasive mucinous ADC and colloid-predominant ADC. Visceral-pleural invasion was reported as either absent (PL0) or present (PL1, PL2) (21,22), and lymphatic and vascular invasion were considered to be present if at least one tumor cell cluster was visible in a lymphatic vessel or a vein, respectively.

### Recurrence and Follow-Up

All recurrences were confirmed by cytologic or histologic evaluation after clinical and/or radiologic suspicion. Recurrences were classified in accordance with the Society of Thoracic Surgeons Workforce recommendations (23). Local recurrence was defined by evidence of a tumor in the same lobe or at the surgical margin of the original tumor. Regional recurrence was defined by evidence of a tumor in a second ipsilateral lobe, in the ipsilateral hilar lymph nodes (N1), or in the ipsilateral mediastinal lymph nodes (N2). Distant recurrence was defined by evidence of a tumor in the contralateral lung, in the contralateral mediastinal or ipsilateral supraclavicular lymph nodes (N3), or elsewhere outside the hemithorax. All patients were evaluated postoperatively with chest x-ray, chest computed tomography scan, and positron emission tomography scan, when clinically indicated, in addition to periodic clinical follow-up, in accordance with National Comprehensive Cancer Network guidelines (24).

### Statistical Analysis

Statistical analyses were performed using IASLC/ATS/ERS subtype classifications, as well as data from comprehensive histologic subtyping. In addition, the percentage of MIP component was analyzed as a continuous variable and was also categorized as low vs high, on the basis of the results of a classification and regression tree analysis. For the purpose of this categorization, the cohort was split into a training set and a validation set (random 2:1 split, stratified by temporal interval of surgery). Classification and regression tree analysis was performed in the training set; the association between the resulting MIP high/low categories and patient outcomes was confirmed in the validation set. All remaining analyses were performed in the entire cohort. The results reported were generated by averaging 500 resamples of the original data.

Time-to-event endpoints were analyzed using competing risks analysis. For this analysis, censoring patients at the time of death would lead to a biased probability of recurrence, as estimated by the Kaplan–Meier method. Instead, the risk of recurrence (defined as the cumulative incidence of recurrence [CIR]) was estimated using a cumulative incidence function, which accounted for death without recurrence as a competing event (25). In addition, in analyses of time to local recurrence, nonlocal (distant and regional) recurrences were treated as a second type of competing risk. Patients were censored if they were alive and without a documented recurrence at the time of the most recent follow-up. Differences in CIR between groups were assessed using the methods of Gray (26) (in univariate nonparametric analyses) and Gray and Fine (27) (in analyses adjusted for other clinical or pathologic factors). All statistical tests were two-sided, and all used a 5% level of statistical significance. Statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC) and R (version 2.14.1; R Development Core Team), including the "survival" and "cmprsk" packages. Data were analyzed by sex but not by major racial/ethnic group.

## Results

### Clinicopathologic Variables

A total of 734 patients were included in the study: 176 and 82 patients in the training and validation sets, respectively, in the LR

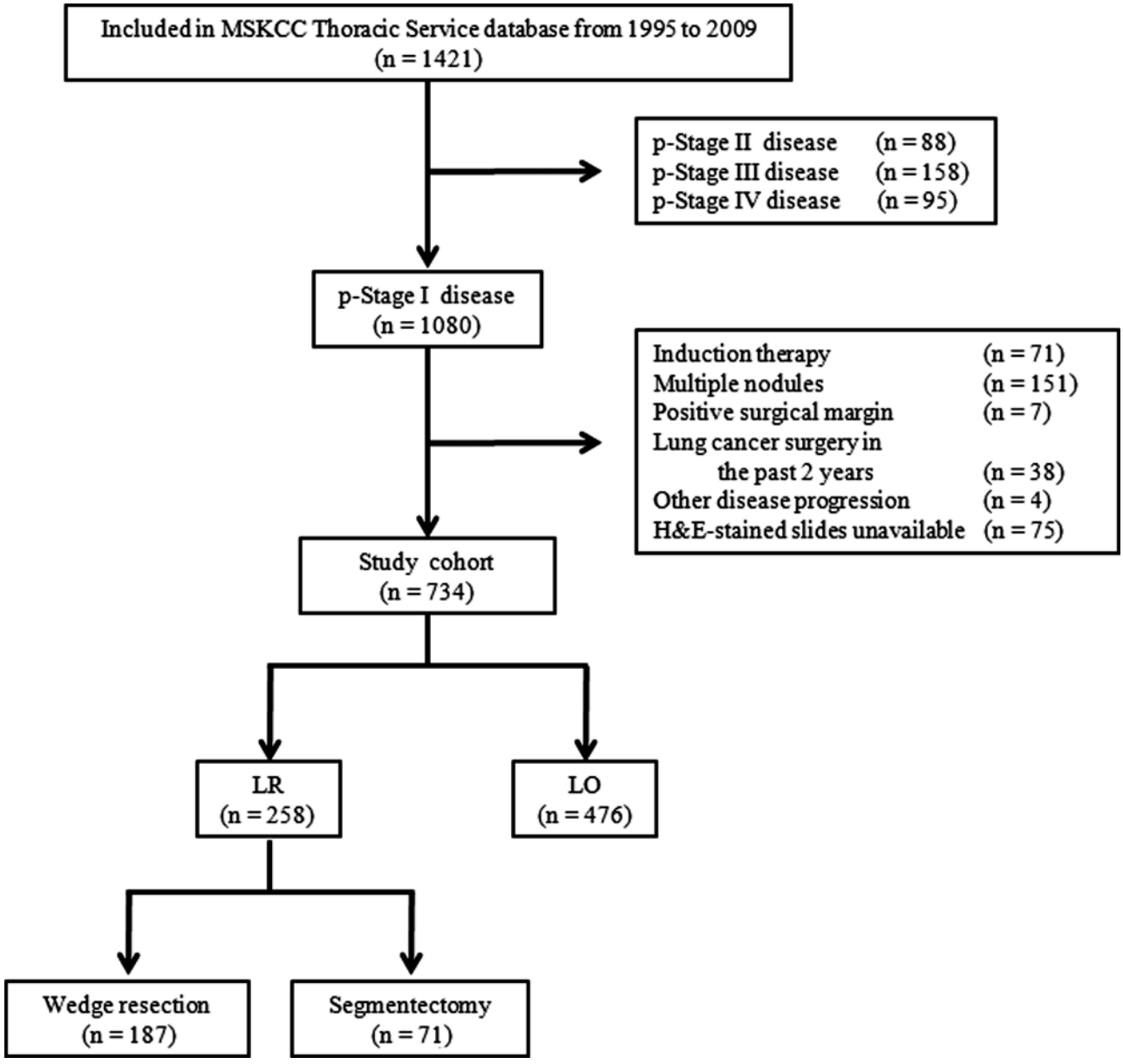



**Figure 1.** Study cohort flow chart. Between 1995 and 2009, 1421 patients with lung adenocarcinoma of 2 cm or less were identified. After exclusion, 734 were included in the analysis, of whom 258 underwent limited resection (LR) and 476 underwent lobectomy (LO). H&E = hematoxylin and eosin; MSKCC = Memorial Sloan-Kettering Cancer Center.

group, and 311 and 165 patients in the training and validation sets, respectively, in the LO group. Clinicopathologic variables are listed in Table 1. The validation set had a higher percentage of stage IB disease, wedge resection, no lymph node dissection, and tumor with lymphatic invasion.

The 5-year CIR was 21.1% (95% confidence interval [CI] = 15.5% to 25.8%) in the LR group and 15.1% (95% CI = 11.0% to 19.5%) in the LO group (Table 2), in concordance with published results. The median clinical follow-up was 37 months (range = 0.2 to 171 months; IQR = 21 months; IQR = 61 months) in the LR group and 32 months (range = 0.2 to 202 months; IQR = 13 months; IQR = 53 months) in the LO group. Of the available clinicopathologic variables, lymphatic invasion (LR: $P = .004$; LO: $P < .001$) and vascular invasion (LR: $P = .008$; LO: $P < .001$) in both groups and tumor morphologic pattern ($P < .001$) in the LO group were statistically significantly associated with a higher CIR (Table 2), in concordance with published results.

### Relationship Between MIP Component, CIR, and Type of Surgical Resection

A classification and regression tree analysis performed in the training set that used MIP morphologic pattern as a continuous variable identified high-risk tumors as those with an MIP component of 5% or greater and low-risk tumors as those with an MIP component of less than 5%. Among patients who underwent LR, high-risk tumors were statistically significantly associated with a higher CIR (5-year CIR = 34.2%, 95% CI = 23.5% to 49.7%), compared with low-risk tumors (5-year CIR = 12.4%, 95% CI = 6.9% to 22.1%; $P < .001$ (Figure 2A). After adjustment for both vascular and lymphatic invasion, which were associated with recurrence in univariable

**Table 1.** Patient characteristics for the two cohorts*

| Characteristic | Limited resection | | P | Lobectomy | | P |
|---|---|---|---|---|---|---|
| | Training | Validation | | Training | Validation | |
| Overall | 176 | 82 | | 311 | 165 | |
| Age | | | .94 | | | .19 |
| years, median (range) | 69 (28–88) | 70 (42–87) | | 67 (36–86) | 66 (23–87) | |
| <65 | 55 (31) | 26 (32) | | 124 (40) | 76 (46) | |
| ≥65 | 121 (69) | 56 (68) | | 187 (60) | 89 (54) | |
| Sex | | | .90 | | | .87 |
| Female | 113 (64) | 52 (63) | | 189 (61) | 99 (60) | |
| Male | 63 (36) | 30 (37) | | 122 (39) | 66 (40) | |
| Smoking history | | | .16 | | | .23 |
| Never | 31 (18) | 7 (8) | | 45 (15) | 34 (21) | |
| Former | 120 (68) | 63 (77) | | 218 (70) | 108 (65) | |
| Current | 25 (14) | 12 (15) | | 48 (15) | 23 (14) | |
| Tumor size, cm | | | .65 | | | .81 |
| Mean (range) | 1.2 (0.1–2.0) | 1.3 (0.4–2.0) | | 1.5 (0.1–2.0) | 1.5 (0.4–2.0) | |
| 0.1–1.0 | 53 (30) | 27 (33) | | 52 (17) | 29 (18) | |
| 1.1–2.0 | 123 (70) | 55 (67) | | 259 (83) | 136 (82) | |
| Predominant histologic subtype | | | .82 | | | .13 |
| LEP | 37 (21) | 14 (17) | | 52 (17) | 22 (13) | |
| ACI | 70 (39) | 31 (38) | | 139 (44) | 68 (41) | |
| PAP | 26 (15) | 16 (20) | | 60 (19) | 33 (20) | |
| MIP | 8 (5) | 6 (7) | | 22 (7) | 7 (4) | |
| SOL | 27 (15) | 11 (13) | | 30 (10) | 26 (16) | |
| Others | 8 (5) | 4 (5) | | 8 (3) | 9 (6) | |
| Lymphatic invasion | | | .005† | | | .17 |
| Absent | 124 (70) | 43 (52) | | 219 (70) | 106 (64) | |
| Present | 52 (30) | 39 (48) | | 92 (30) | 59 (36) | |
| Vascular invasion | | | .63 | | | .26 |
| Absent | 148 (84) | 67 (82) | | 253 (81) | 127 (77) | |
| Present | 28 (16) | 15 (18) | | 58 (19) | 38 (23) | |
| Pathologic stage (pleural invasion) | | | .05† | | | .36 |
| Stage IA (PL0) | 149 (85) | 61 (74) | | 280 (90) | 144 (87) | |
| Stage IB (PL1, PL2) | 27 (15) | 21 (26) | | 31 (10) | 21 (13) | |
| Nodal evaluation | | | .008† | | | .40 |
| None | 71 (40) | 50 (61) | | 1 (1) | 1 (1) | |
| Lymph node dissection | 39 (22) | 13 (16) | | 293 (94) | 150 (91) | |
| Lymph node sampling | 66 (38) | 19 (23) | | 17 (5) | 14 (8) | |
| Surgical procedure | | | .05† | | | — |
| Wedge resection | 121 (69) | 66 (80) | | — | — | |
| Segmentectomy | 55 (31) | 16 (20) | | — | — | |
| Surgical margin, cm | | | .14‡ | | | — |
| Mean (range) | 1.1 (0.1–7.5) | 1.0 (0.1–3.0) | | — | — | |
| 0.1–0.9 | 51 (29) | 28 (34) | | — | — | |
| ≥1.0 | 85 (48) | 29 (35) | | — | — | |
| Unknown | 40 (23) | 25 (31) | | — | — | |

* Data are No. (%) of patients, unless otherwise noted. ACI = acinar; LEP = lepidic; MIP = micropapillary; PAP = papillary; PL0 = absent for visceral pleura invasion; PL1 = visceral pleura invasion beyond the elastic layer; PL2 = visceral pleura invasion to the pleural surface; SOL = solid.

† Statistically significant ($P < .05$).

‡ Patients with unknown surgical margin were excluded from the calculation.

analysis ($P = .008$ and $P = .004$, respectively), the presence of an MIP component of 5% or greater remained independently associated with CIR (hazard ratio [HR] = 3.11, 95% CI = 1.48 to 6.54; $P = .003$). These results were replicated in the validation set (Figure 2B).

Among patients who underwent LO, tumors with an MIP component of 5% or greater were not statistically significantly associated with a higher CIR (5-year CIR = 19.1%, 95% CI = 12.0% to 30.5%), compared with tumors with an MIP component of less than 5% (5-year CIR = 12.9%, 95% CI = 7.6% to 21.9%; $P = .13$) (Figure 2C). This lack of association was maintained in a multivariable analysis that adjusted for both lymphatic and vascular invasion (HR = 1.09, 95% CI = 0.51 to 2.36; $P = .82$) and was confirmed in the validation set (Figure 2D).

Figure 3A presents the CIR at 5 years as a percentage function of MIP components. As shown, as the percentage of MIP increases from 0, the CIR at 5 years increases. Statistically significant differences were noticed between the analyses for the LR and LO groups. Among patients with tumors with an MIP component of less than 5%, there was no statistically significant difference in the

**Table 2.** Univariate analysis of 5-year cumulative incidence of recurrence and clinicopathologic characteristics among the training set*

| Characteristic | Limited resection | | | Lobectomy | | |
|---|---|---|---|---|---|---|
| | No. of patients | 5-year CIR (95% CI) | Univariate *P* | No. of patients | 5-year CIR (95% CI) | Univariate *P* |
| Overall | 176 | 0.21 (0.15 to 0.29) | | 311 | 0.15 (0.11 to 0.22) | |
| Age | | | .67 | | | .24 |
| <65 | 55 | 0.28 (0.17 to 0.47) | | 124 | 0.23 (0.13 to 0.38) | |
| ≥65 | 121 | 0.17 (0.11 to 0.26) | | 187 | 0.11 (0.07 to 0.19) | |
| Sex | | | .38 | | | .45 |
| Female | 113 | 0.20 (0.13 to 0.32) | | 189 | 0.12 (0.07 to 0.21) | |
| Male | 63 | 0.22 (0.13 to 0.35) | | 122 | 0.19 (0.12 to 0.31) | |
| Smoking history | | | .09 | | | .22 |
| Never | 31 | 0.09 (0.02 to 0.37) | | 45 | 0.07 (0.02 to 0.28) | |
| Former | 120 | 0.25 (0.17 to 0.35) | | 218 | 0.14 (0.09 to 0.22) | |
| Current | 25 | 0.13 (0.04 to 0.39) | | 48 | 0.26 (0.13 to 0.51) | |
| Tumor size, cm | | | .83 | | | .34 |
| 0.1–1.0 | 53 | 0.20 (0.11 to 0.37) | | 52 | 0.14 (0.05 to 0.39) | |
| 1.1–2.0 | 123 | 0.21 (0.14 to 0.31) | | 259 | 0.15 (0.11 to 0.22) | |
| Predominant histologic subtype | | | .13 | | | < .001† |
| LEP | 37 | 0.03 (0.00 to 0.23) | | 52 | 0.10 (0.01 to 0.73) | |
| ACI | 70 | 0.26 (0.17 to 0.41) | | 139 | 0.08 (0.04 to 0.16) | |
| PAP | 26 | 0.20 (0.09 to 0.45) | | 60 | 0.13 (0.06 to 0.31) | |
| MIP | 8 | 0.25 (0.07 to 0.91) | | 22 | 0.58 (0.34 to 0.99) | |
| SOL | 27 | 0.17 (0.07 to 0.44) | | 30 | 0.38 (0.21 to 0.68) | |
| Others | 8 | 0.38 (0.14 to 0.99) | | 8 | 0 | |
| Lymphatic invasion | | | .004† | | | < .001† |
| Absent | 124 | 0.15 (0.09 to 0.25) | | 219 | 0.09 (0.05 to 0.17) | |
| Present | 52 | 0.33 (0.22 to 0.50) | | 92 | 0.29 (0.19 to 0.44) | |
| Vascular invasion | | | .008† | | | < .001† |
| Absent | 148 | 0.17 (0.11 to 0.25) | | 253 | 0.11 (0.07 to 0.18) | |
| Present | 28 | 0.39 (0.23 to 0.66) | | 58 | 0.32 (0.20 to 0.52) | |
| Pathologic stage (pleural invasion) | | | .89 | | | .33 |
| Stage IA (PL0) | 149 | 0.21 (0.15 to 0.31) | | 280 | 0.14 (0.10 to 0.21) | |
| Stage IB (PL1, PL2) | 27 | 0.19 (0.08 to 0.42) | | 31 | 0.24 (0.10 to 0.53) | |
| Nodal evaluation | | | .15 | | | .19 |
| None | 71 | 0.22 (0.13 to 0.36) | | 1 | NA | — |
| Lymph node dissection | 39 | 0.11 (0.04 to 0.28) | | 293 | 0.15 (0.10 to 0.21) | |
| Lymph node sampling | 66 | 0.25 (0.15 to 0.40) | | 17 | 0.21 (0.07 to 0.63) | |
| Surgical procedure | | | .06 | | | — |
| Wedge resection | 121 | 0.24 (0.17 to 0.35) | | — | — | |
| Segmentectomy | 55 | 0.12 (0.06 to 0.26) | | — | — | |
| Surgical margin, cm | | | .80‡ | | | — |
| 0.1–0.9 | 51 | 0.22 (0.13 to 0.38) | | — | — | |
| ≥1.0 | 85 | 0.22 (0.13 to 0.36) | | — | — | |
| Unknown | 40 | 0.17 (0.08 to 0.35) | | — | — | |

* ACI = acinar; CI = confidence interval; CIR = cumulative incidence of recurrence; LEP = lepidic; MIP = micropapillary; NA = not applicable; PAP = papillary; PL0 = absent for visceral pleura invasion; PL1 = visceral pleura invasion beyond the elastic layer; PL2 = visceral pleura invasion to the pleural surface; SOL = solid.

† Statistically significant ($P < .05$).

‡ Patients with unknown surgical margin were excluded from the calculation.

risk of recurrence by type of surgical resection performed (5-year CIR = 11.6%, 95% CI = 7.9% to 16.0% for the LO group vs 5-year CIR = 11.1%, 95% CI = 6.6% to 16.3% for the LR group; $P = .25$) (Figure 3B). However, among patients with tumors with a higher MIP component, those treated with LO had a reduced risk of recurrence compared with those treated with LR: for tumors with an MIP component of 5% to 10%, the 5-year CIR was 15.3% (95% CI = 8.3% to 23.1%) for LO vs 34.0% (95% CI = 23.6% to 44.6%) for LR ($P = .002$); for tumors with an MIP component of greater than 10%, the 5-year CIR was 21.4% (95% CI = 12.5% to 32.6%) for LO vs 41.0% (95% CI = 28.1% to 53.7%) for LR ($P = .04$). In the LO group, CIR was similar between patients with tumors with an MIP component of 5% to 10% and patients with tumors with an MIP component of less than 5% ($P = .51$); however, in the LR group, patients with tumors with an MIP component of 5% to 10% had a statistically significantly higher CIR than patients with tumors with an MIP component of less than 5% ($P < .001$) (Figure 3B).

### Recurrence Pattern in Relation to MIP Morphologic Pattern and Surgical Margin

Among patients treated with LR who had tumors with an MIP component of 5% or greater, most recurrences (n = 26 patients; 63.4%) were locoregional, which implies that MIP morphologic

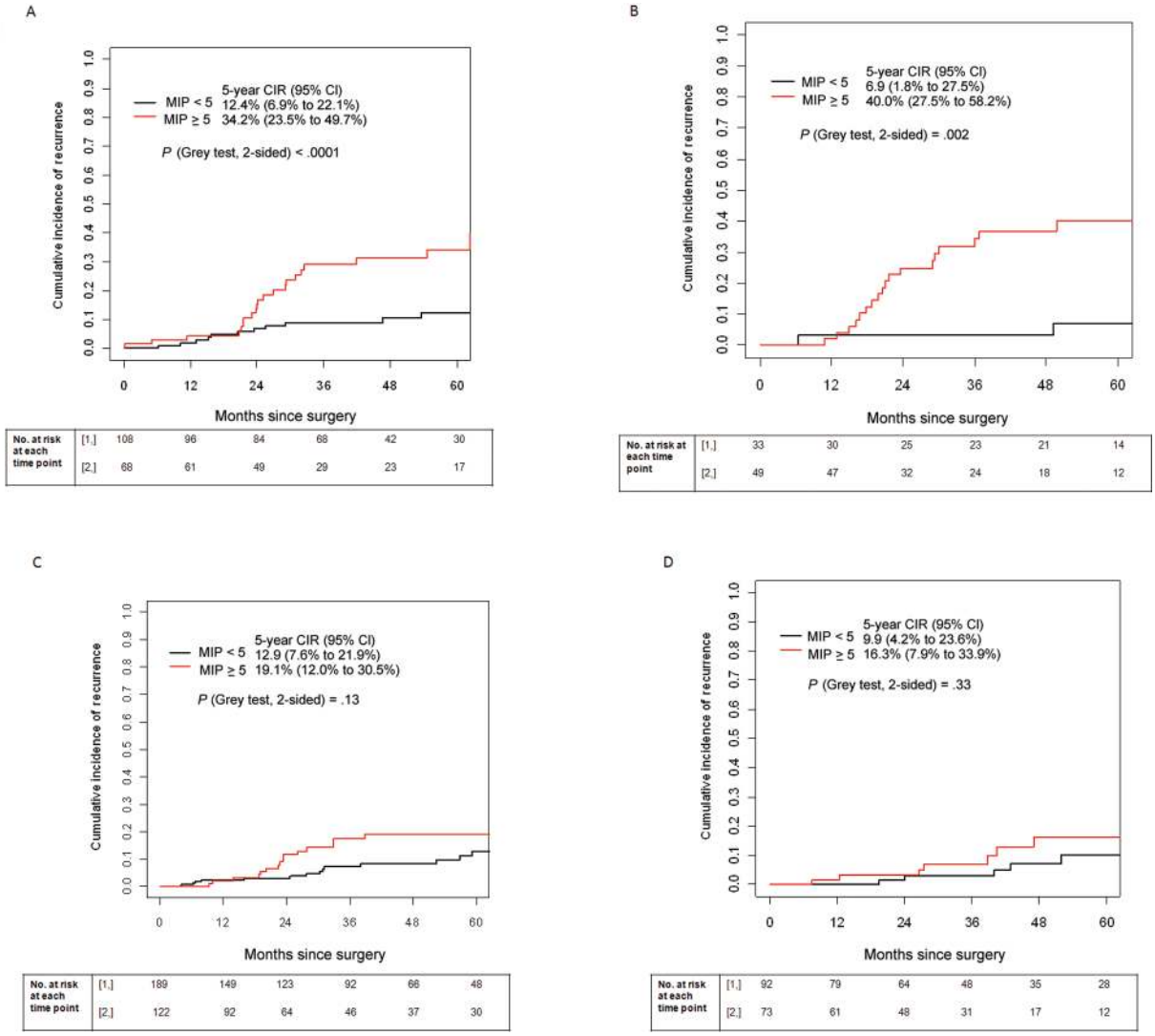


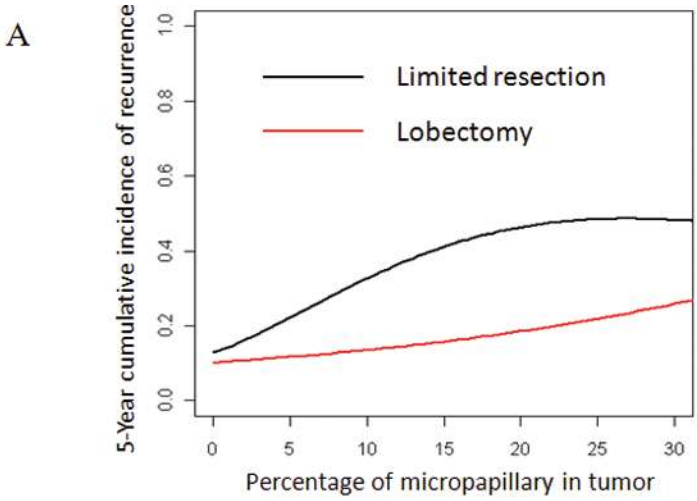

**Figure 2.** Five-year cumulative incidence of recurrence (CIR) by extent of resection and percentage of micropapillary (MIP) component. **A** and **B**) Five-year CIR for the training (**A**) and validation (**B**) sets, stratified by MIP percentage, in the limited resection group. **C** and **D**) Five-year CIR for the training (**C**) and validation (**D**) sets, stratified by MIP percentage, in the lobectomy group. CI = confidence interval

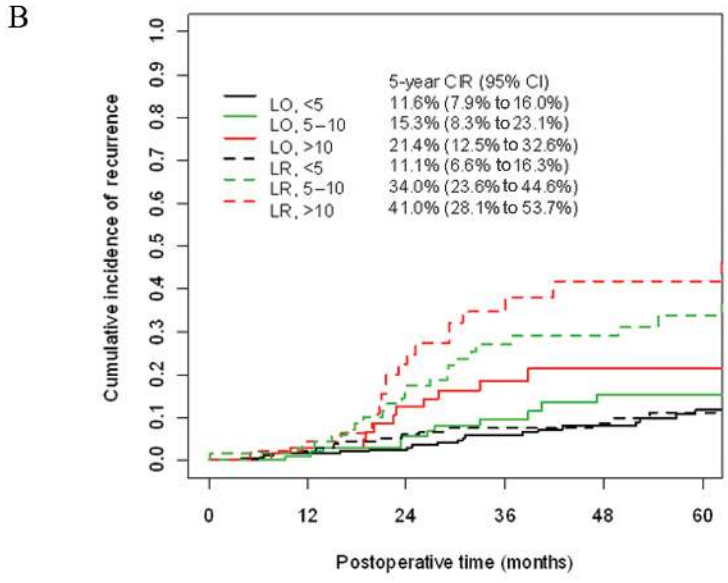
pattern may exhibit a locally invasive pattern, an observation also noted by our pathologists when examining hematoxylin and eosin–stained slides. In view of this observation, we next examined the effect of surgical margin on recurrence among patients with tumors with MIP morphologic pattern. Data on surgical margins were available for 193 patients (74.8%) who underwent LR: 79 had a surgical margin of less than 1 cm, and 114 had a surgical margin of 1 cm or greater (Table 1). There were 54 recurrences (n = 24 local; n = 10 regional; n = 20 distant) detected during the follow-up period among patients treated with LR.

Among patients with a surgical margin of less than 1 cm, the presence of an MIP component of 5% or greater resulted in a higher rate of local recurrence (5-year CIR = 32.0%, 95% CI = 18.6% to 46.0%), compared with the presence of an MIP component of less than 5% (5-year CIR = 7.6%, 95% CI = 2.3% to 15.6%; $P$ = .007). However, in patients with a surgical margin of 1 cm or greater, the presence of an MIP component of 5% or greater was not statistically significantly associated with a higher rate of local recurrence (5-year CIR = 13.0%, 95% CI = 4.1% to 22.1%), compared with the presence of an MIP component of less than 5% (5-year CIR = 3.4%, 95% CI = 0% to 7.7%; $P$ = .10 (Supplementary Figure 1, available online).

## Discussion

Histologic subtyping according to the recently proposed IASLC/ATS/ERS classification is an efficient discriminator for prognosis of patients with stage I to IV lung ADC (17). However, to date, no study has investigated the prognostic utility of the newly proposed IASLC/ATS/ERS classification for patients with small early-stage lung ADC treated with LR or LO. Here, we have validated the prognostic significance of the histologic subtypes in a large cohort of patients with small early-stage lung ADC treated at a single institution during a 15-year period. In fact, the predominant morphologic pattern predicted




| No. at risk at each time point | | | | | | | |
|---|---|---|---|---|---|---|---|
| | [1,] | 281 | 228 | 187 | 140 | 101 | 76 |
| | [2,] | 116 | 97 | 73 | 50 | 38 | 30 |
| | [3,] | 79 | 56 | 39 | 27 | 16 | 12 |
| | [4,] | 141 | 126 | 109 | 91 | 63 | 44 |
| | [5,] | 70 | 65 | 51 | 36 | 28 | 19 |
| | [6,] | 47 | 43 | 30 | 17 | 13 | 10 |

***P* values for lobectomy vs limited resection**
MIP < 5%: *P* = .25
MIP 5%–10%: *P* = .002
MIP > 10%: *P* = .04

**Figure 3.** Five-year cumulative incidence of recurrence as a function of micropapillary percentage. **A**) Five-year cumulative incidence of recurrence (CIR) among the training set, as a function of the micropapillary (MIP) percentage for each surgical treatment group. **B**) CIR among the training set for patients with tumors with an MIP component of less than 5%, 5% to 10%, or greater than 10% who underwent lobectomy, compared with those who underwent limited resection. CI = confidence interval; LO = lobectomy; LR = limited resection.

recurrence in patients treated with LO ($P < .001$). Of importance, we have identified MIP morphologic pattern as an independent risk factor for recurrence in patients with small lung ADC. In particular, patients with tumors with an MIP component of 5% or greater treated with LR are at a higher risk of recurrence than similar patients treated with LO. Our findings may carry increasing importance as the number of cases of early-stage lung ADC is expected to increase during the next decade as a result of the National Lung Screening Trial (5).

Although the most recent WHO classification only briefly references the MIP histologic subtype (19), this histologic subtype is now

established as a factor of poor prognosis, and it was recognized as a major category of lung ADC in the 2011 IASLC/ATS/ERS classification (15,28–34). Among patients treated with LR in the training set, tumors with an MIP component of 5% or greater were associated with a higher CIR (5-year CIR = 34.2%) compared with tumors with an MIP component of less than 5% (5-year CIR = 12.1%). These results were replicated in the validation set. Of importance, in the LR group, the presence of any MIP component remained an independent predictor of recurrence in multivariable analysis. This suggests that LR may not be the optimal surgical approach for lung ADC with an MIP component of 5% or greater. Furthermore, among patients treated with LR who had tumors with an MIP component of 5% or greater, recurrences were mainly locoregional; there was a reduced probability of recurrence in cases with a surgical margin of 1 cm or greater. These findings suggest that ADC with an MIP component spreads through the lung tissue, in contrast with other histologic subtypes, which have a greater capacity for local infiltration.

Our study has practical implications for the management of patients diagnosed with small early-stage lung ADC who are undergoing surgical resection. In our dataset, at least four of 10 patients with small lung ADC had tumors with an MIP component of 5% or greater; for these patients, LR may not be the ideal surgical resection. In addition, the results of this study are strengthened by several key characteristics. Our study comprises, to our knowledge, the largest uniform stage IA lung ADC cohort in the published literature. More important, we focused on the probability of recurrence, rather than on overall survival, an important feature when reviewing the prognostic criteria for stage IA lung ADC because many of these tumors do not recur and patients die of other causes. The risk of recurrence (defined as CIR) more accurately documents the behavior of the tumor.

Our study does, however, possess the limitations associated with a noncontrolled, retrospective study that is reflective of the practice and outcomes at one tertiary care institution. Other histologic subtypes were also investigated in preliminary analyses, but their relationships with risk of recurrence were inconclusive and are not reported here. Although we performed internal validation of all results, the associations that we found warrant validation using an independent dataset from a different institution.

In this study, among patients with tumors with any MIP component present, local recurrence was strongly associated with a surgical margin of less than 1 cm, suggesting that LR may not be appropriate for patients with lung ADC containing any MIP component. At present, reporting the presence of MIP morphologic pattern on frozen sections is not the standard of care, with histopathologic confirmation occurring only by use of permanent sections. Hopefully, our findings will encourage further investigations to determine whether pathologists can recognize and report this feature on frozen sections of lung ADC. Given our findings, patients treated with LR whose tumors are determined to have MIP morphologic pattern by use of permanent sections may require completion segmentectomy or LO. Among patients for whom a larger anatomical resection is not feasible, treatment options include adjuvant external-beam radiation therapy and postoperative iodine-125 brachytherapy (35–38), which have been shown to decrease local recurrence after wedge resection (39). Brachytherapy after LR is being investigated in an ongoing multicenter phase II trial (ACOSOG z4032) (40). Finally, our findings provide a rationale to select a study cohort that is at high risk of local recurrence for these investigations.

In conclusion, histologic subtyping according to the newly proposed IASLC/ATS/ERS classification identifies the presence of an MIP component of 5% or greater as an independent predictor of local recurrence in patients treated with LR.

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