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Prognostic Significance of Adenocarcinoma in situ, Minimally Invasive Adenocarcinoma, and Nonmucinous Lepidic Predominant Invasive Adenocarcinoma of the Lung in Patients with Stage I Disease

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Abstract

According to the IASLC/ATS/ERS classification, the lepidic predominant pattern consists of 3 subtypes: adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and nonmucinous lepidic predominant invasive adenocarcinoma. We reviewed tumor slides from 1038 patients with stage I lung adenocarcinoma, recording the percentage of each histologic pattern and measuring invasive tumor size. Tumors were classified according to the IASLC/ATS/ERS classification: 2 were AIS, 34 MIA, and 103 lepidic predominant invasive. Cumulative incidence of recurrence (CIR) was used to estimate the probability of recurrence. Patients with AIS and MIA experienced no recurrences. Patients with lepidic predominant invasive tumors had a lower risk of recurrence (5-year CIR, 8%) than non-lepidic predominant tumors (n=899; 19%; *P*=0.003). Patients with >50% lepidic pattern tumors experienced no recurrences (n=84), those with >10%–

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50% lepidic pattern tumors had an intermediate risk of recurrence (n=344; 5-year CIR, 12%), and those with ≤10% lepidic pattern tumors had the highest risk (n=610; 22%; *P*<0.001). CIR was lower for patients with ≤2 cm tumors than for those with >2–3 cm tumors (for both total and invasive tumor size), with the difference more pronounced for invasive tumor size (5-year CIR, 13% vs. 21% [total size; *P*=0.022] and 12% vs. 27% [invasive size; *P*<0.001]). Most patients with lepidic predominant adenocarcinoma who experienced a recurrence had potential risk factors, including sublobar resection with close margins (≤0.5 cm; n=2), 20%–30% micropapillary component (n=2), and lymphatic or vascular invasion (n=2). It therefore may be possible to identify lepidic predominant adenocarcinomas that carry a low or high risk of recurrence.

Keywords

Lung adenocarcinoma; Lepidic; Adenocarcinoma in situ; Minimally invasive adenocarcinoma; Recurrence

INTRODUCTION

The 2004 World Health Organization classification of lung cancer defines bronchioloalveolar carcinoma (BAC) as a noninvasive tumor that spreads along alveolar structures.[1] The newly proposed International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) international multidisciplinary lung adenocarcinoma classification recommends discontinuing the use of the term *BAC*, as tumors formerly referred to as BAC can now be classified as five different entities. The noninvasive growth pattern previously called BAC is now called lepidic pattern.[2] The origin of the term lepidic was recently reviewed and its origins traced to Dr. John George Adami in 1902.[3] Multiple studies have shown that patients with pure lepidic (noninvasive) tumors have 100% 5-year disease-free survival.[4–7] A smaller group of studies has shown that patients with lepidic predominant minimally invasive (≤5 mm) tumors have nearly 100% survival.[8–10] In addition, lepidic predominant invasive tumors have been correlated with favorable prognosis in patients with resected lung adenocarcinoma.[11–13] On the basis of these results, the IASLC/ATS/ERS classification includes 3 proposed adenocarcinoma subtypes with lepidic predominant components: (1) adenocarcinoma in situ (AIS), (2) minimally invasive adenocarcinoma (MIA), and (3) nonmucinous lepidic predominant invasive adenocarcinoma.[14]

Several reports on computed tomography (CT) screening for lung adenocarcinoma have suggested that there is a correlation between ground-glass opacity (an air density–containing area on CT) and lepidic growth pattern.[15–17] With the recent randomized trials assessing low-dose CT screening for lung cancer,[18–20] it is anticipated that an increasing number of patients will be diagnosed with lung adenocarcinoma with lepidic growth at an early stage, which may contribute to reduced disease-specific mortality from lung cancer in the future. These tumors are likely to be cured if completely resected, so they are of particular interest to thoracic surgeons who may be considering limited resection over standard lobectomy to treat them. Although most cases of AIS and MIA will be cured if completely resected, a small percentage of lepidic predominant adenocarcinomas will recur, and it would be of

great value to surgeons to be able to identify risk factors for recurrence in these tumors. Therefore, it is important to improve the clinical characterization of early-stage lung adenocarcinoma with lepidic predominant pattern. However, no large studies have investigated the clinical significance of the 3 lepidic predominant subtypes as defined by the IASLC/ATS/ERS classification.

We herein report clinicopathologic and prognostic findings from tumors with lepidic growth pattern. The aim of this study was to clarify the clinical significance of lung adenocarcinoma with lepidic growth and to identify factors of poor prognosis related to lepidic predominant invasive tumors.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Memorial Sloan-Kettering Cancer Center institutional review board (WA0269-08). We reviewed all patients with pathologic stage I solitary lung adenocarcinoma who underwent surgical resection at Memorial Sloan-Kettering Cancer Center between 1995 and 2009. Tumor slides from 1038 patients were available for histologic evaluation. Clinical data were collected from the prospectively maintained Thoracic Service lung adenocarcinoma database. Disease stage was based on the seventh edition of the *American Joint Committee on Cancer TNM Staging Manual*.[21] Subsets of the cases in this study have been previously published in manuscripts focused on architectural grading,[22] histologic classification,[23] nuclear grading,[24] and the immune microenvironment in lung adenocarcinoma.[25]

Histologic Evaluation

All available hematoxylin and eosin–stained slides were reviewed by 2 pathologists (K.K. and W.D.T.) who were blinded to the patients' clinical outcomes, using an Olympus BX51 microscope (Olympus, Tokyo, Japan) with a standard 22-mm diameter eyepiece. Each tumor was reviewed using comprehensive histologic subtyping, and the percentage of each histologic pattern was recorded in 5% increments. The predominant pattern was defined as the morphologic subtype present in the greatest proportion.[2]

Total tumor size and invasive tumor size were measured. Total tumor size was recorded on gross finding by use of a ruler. Invasive tumor size was measured 2 ways: (1) in cases where the tumor was small and the invasive area could be measured on a single slide, the invasive size was measured at ×20 or ×40 magnification on the microscope using a ruler; and (2) in cases where the tumor was large and the invasive area could not be measured on a single slide, the invasive size was calculated by multiplying the total tumor size by the percentage of invasive component.[23]

The following histologic factors were also investigated: (1) visceral pleural invasion, which was classified as absent (PL0) or present (PL1 and PL2)[21]; (2) lymphatic and vascular invasion; and (3) tumor necrosis.

Tumors were classified according to the IASLC/ATS/ERS classification as (1) AIS, (2) MIA, or invasive adenocarcinoma, which was further subclassified as (3) nonmucinous lepidic predominant, (4) acinar predominant, (5) papillary predominant, (6) micropapillary predominant, or (7) solid predominant. Variants included (8) invasive mucinous and (9) colloid predominant adenocarcinoma.[2]

The IASLC/ATS/ERS classification includes 3 subtypes with lepidic predominant features: (1) AIS, (2) MIA, and (3) nonmucinous lepidic predominant invasive adenocarcinoma. The definitions of these histologic subtypes are summarized in Table 1. Tumor invasion was defined as the following: (1) histologic pattern other than lepidic (acinar, papillary, micropapillary, or solid), (2) active myofibroblastic stroma correlated with invasive tumor cells, and (3) presence of lymphatic, vascular, or pleural invasion. AIS is defined as a ≤3 cm tumor with a pure lepidic pattern (Figure 1) but without lymphatic, vascular, or pleural invasion or tumor necrosis. MIA is defined as a ≤3 cm tumor with a lepidic predominant pattern and ≤5 mm stromal invasion (Figure 2) but without lymphatic, vascular, or pleural invasion or tumor necrosis. Lepidic growth was classified into 2 patterns according to the absence or presence of an intracellular mucinous feature: nonmucinous and mucinous. AIS and MIA were further subgrouped as nonmucinous, mucinous (Figure 3), or mixed mucinous/nonmucinous.[2] Invasive mucinous adenocarcinoma was excluded from lepidic predominant invasive adenocarcinoma even if the mucinous tumor cells showed predominantly lepidic pattern. Mucinous AIS and MIA were included since there is very little data published on these tumors and it is important to document that so far they also show no recurrence. Lepidic predominant invasive adenocarcinoma is defined as a tumor that is >3 cm in total size and/or >5 mm in invasive size with a nonmucinous lepidic predominant pattern (Figure 4). Any lepidic predominant tumors with lymphatic, vascular, or pleural invasion or tumor necrosis were classified as lepidic predominant invasive tumors, rather than AIS or MIA. Tumors were classified into 3 groups according to percentage of lepidic pattern: ≤10% lepidic pattern, >10%–50% lepidic pattern, and >50% lepidic pattern.

Nuclear features were examined with a high-power field (HPF) of ×400 magnification (0.237 mm^2). Nuclear atypia was identified in the area with the highest degree of atypia and was graded as follows: (1) mild: nuclei were uniform in size and shape; (2) moderate: nuclei were of intermediate size and had slight irregularities; and (3) severe: nuclei were enlarged to varying degrees, with some nuclei at least twice as large as others.[26–28] Mitoses were evaluated at 50 HPFs in areas with the highest mitotic activity and were counted as the average number of mitotic figures per 10 HPFs.[26, 29, 30] Tumors were classified according to mitotic count as follows: (1) low: 0–1 mitoses per 10 HPFs; (2) intermediate: 2–4 mitoses per 10 HPFs; and (3) high: ≥5 mitoses per 10 HPFs.[24, 31]

Statistical Analysis

Associations between histologic subtypes and clinicopathologic variables were analyzed using Fisher’s exact test (for categorical variables) and the Wilcoxon test (for continuous variables). Because traditional Kaplan-Meier estimates of survival probabilities can be biased when a large number of patients die without recurrence and are subsequently censored, especially if the rate of death is differential across groups, in this analysis, we

considered death from causes other than recurrence as a competing event. Cumulative incidence of recurrence (CIR) was used to estimate the probability of recurrence.[32, 33] Follow-up was calculated from the date of surgery to the date of the first recurrence, death from any cause, or last follow-up, whichever came first. Differences in CIR between groups were examined using Gray's methods.[34] Competing risks regression analysis was used to examine associations between each variable and recurrence, after adjustment for important potential confounders. All *P* values were based on 2-tailed statistical analysis and $P<0.05$ was considered to indicate statistical significance. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and R (R Development Core Team, 2010), including the "survival" and "cmprsk" packages.

RESULTS

Association between Clinicopathologic Factors and Recurrence

The clinicopathologic factors for all 1038 patients are shown in Table 2. The median age was 69 years (range, 23–96 years). The majority of patients were women (62%), and most had stage IA disease (70%). In total, 77% underwent lobectomy, and 23% underwent sublobar resection (segmentectomy [n=76] and wedge resection [n=166]). Visceral pleural invasion was observed in 17% of patients, lymphatic invasion in 32%, vascular invasion in 25%, and tumor necrosis in 16%.

Of all the patients, 144 (14%) experienced a recurrence, and 151 (15%) died from any cause without a recurrence. The median follow-up for patients who did not experience a recurrence was 37.4 months (range, 0.3–160.0 months). On univariate analysis, male sex ($P=0.002$), sublobar resection ($P<0.001$), pleural invasion ($P<0.001$), lymphatic invasion ($P<0.001$), vascular invasion ($P<0.001$), tumor necrosis ($P<0.001$), greater nuclear atypia ($P<0.001$), and higher mitotic count ($P<0.001$) were associated with a higher risk of recurrence.

Histologic Findings

On histologic analysis of the tumor specimens, 2 were identified as nonmucinous AIS (0.2%), 34 as MIA (3%) (nonmucinous [n=32], mucinous [n=1], and mixed mucinous/nonmucinous [n=1]), and 103 as nonmucinous lepidic predominant invasive adenocarcinoma (10%). The remaining tumors were identified as follows: 411 acinar predominant (40%), 239 papillary predominant (23%), 60 micropapillary predominant (6%), 136 solid predominant (13%), 44 invasive mucinous (4%), and 9 colloid predominant (1%).

Of the tumors with lepidic predominant pattern with either no invasion or ≤5 mm invasion, none had pleural, lymphatic, or vascular invasion or tumor necrosis. Therefore, AIS and MIA were differentiated from lepidic predominant invasive adenocarcinoma only on the basis of total tumor size and invasive size. All 34 MIA tumors had ≤5 mm invasion when measured using a ruler as well as by multiplying the total tumor size by the percentage of invasive component. Acinar was the most common predominant invasive pattern in MIA tumors (n=31; 91%), followed by papillary (n=3; 9%).

Among the 103 lepidic predominant invasive tumors, the average percentage of lepidic pattern was 50% (range, 40%-85%), and the most common predominant invasive pattern was acinar (n=83; 81%), followed by papillary (n=18; 17%) and micropapillary (n=2; 2%).

All of the ≤3 cm lepidic predominant invasive tumors (n=90) had >5 mm invasion when measured by a ruler; however, 21 of these had ≤5 mm invasion when measured using the multiplication method (none of these had pleural, lymphatic, or vascular invasion or necrosis). Of the >3 cm lepidic predominant invasive tumors (n=13), 1 had ≤5 mm invasion when measured by a ruler as well as by the multiplication method.

Correlation between Lepidic Predominant Subtypes and Clinicopathologic Factors

Table 2 presents the association between lepidic predominant subtypes and clinicopathologic factors. Lepidic predominant tumors (AIS, MIA, and lepidic predominant invasive adenocarcinoma) were observed more frequently among Asian patients (P<0.001) and never smokers (P=0.011), compared with non-lepidic predominant tumors. Lepidic predominant invasive tumors correlated with smaller tumor size (P=0.027) and lower T stage (P<0.001), compared with non-lepidic predominant tumors.. Tumors ≤2 cm had the highest percentage of lepidic pattern (mean ± SD, 21% ± 24%), followed by >2–3 cm tumors (16% ± 20%) and >3 cm tumors (12% ± 18%) (P<0.001). Lepidic predominant invasive tumors had pleural invasion (P<0.001), lymphatic invasion (P<0.001), vascular invasion (P<0.001), and necrosis (P<0.001) less frequently, compared with non-lepidic predominant invasive tumors. In addition, lepidic predominant tumors correlated with mild nuclear atypia (P<0.001) and lower mitotic count (P<0.001), compared with non-lepidic predominant invasive tumors.

Correlation between Lepidic Predominant Subtypes and Recurrence

Figure 5 presents CIR by lepidic predominant subtype. None of the patients with AIS or MIA (n=36) experienced a recurrence (5-year CIR, 0%). Of all the patients with lepidic predominant invasive tumors (n=103), 4 experienced a recurrence. Patients with lepidic predominant invasive tumors had a lower risk of recurrence (5-year CIR, 8%) than patients with non-lepidic predominant tumors (n=899; 5-year CIR, 19%; P=0.003). Interestingly, none of the patients with ≤3 cm lepidic predominant invasive tumors with >5 mm invasion when measured by a ruler but ≤5 mm when measured using the multiplication technique (n=21) experienced a recurrence.

In the cases of non-lepidic predominant invasive adenocarcinoma with recurrence (n=140), 91 had distant metastasis, 42 had local recurrence, and 7 had both distant and local recurrence. When the 4 cases of lepidic predominant invasive adenocarcinoma with recurrence were examined closely (Table 3), 2 had distant metastasis (bone and chest wall), and the other 2 had local recurrence (lung). Two of these cases underwent sublobar (wedge) resection with close staple margins from the tumor (0.2 cm and 0.5 cm). For comparison, in patients who underwent limited resection without a recurrence (n=20), the median distance between the staple margin and the tumor was 1.3 cm (range, 0.3–7.5 cm). In 2 of the 4 cases with recurrence, the tumors had a substantial micropapillary component (30% and 20%), with lymphatic invasion (Figure 6),—1 of these also had vascular invasion. In contrast,

among the 99 cases of lepidic predominant invasive adenocarcinoma without recurrence, 6 tumors (6%) had lymphatic invasion, and 4 tumors (4%) had vascular invasion; the median percentage of micropapillary pattern was 0% (range, 0%–35%).

Correlation between Percentage of Lepidic Pattern and Recurrence

Figure 7 presents CIR by percentage of lepidic pattern. Patients with >50% lepidic pattern tumors (n=84) experienced no recurrences (5-year CIR, 0%). Patients with >10%–50% lepidic pattern tumors (n=344) had a lower risk of recurrence (5-year CIR, 12%) than patients with ≤10% lepidic pattern tumors (n=610; 5-year CIR, 22%; $P<0.001$). Overall, higher percentage of lepidic pattern had a statistically significant correlation with lower risk of recurrence ($P<0.001$).

Correlation between Invasive Tumor Size and Recurrence

Figure 8 presents CIR in terms of total tumor size and invasive tumor size (according to T stage criteria: ≤2 cm, >2–3 cm, and >3–5 cm). Total tumor size ≤2 cm (n=564) had the lowest risk of recurrence (5-year CIR, 13%), followed by >2–3 cm (n=291; 21%) and >3–5 cm (n=183; 24%; $P<0.001$) (Figure 8A). Similarly, invasive tumor size ≤2 cm (n=680) had the lowest risk of recurrence (5-year CIR, 12%), followed by >2–3 cm (n=220; 5-year CIR, 27%) and >3–5 cm (n=138; 5-year CIR, 26%; $P<0.001$) (Figure 8B). CIR was lower for patients with ≤2 cm tumors than for those with >2–3 cm tumors (for both total and invasive tumor size), with the difference more pronounced for invasive tumor size (5-year CIR, 13% vs. 21% [total size; $P=0.022$] and 12% vs. 27% [invasive size; $P<0.001$]). When tumors were categorized according to invasive size, instead of total size, there were fewer tumors in the >2–3 cm group (n=291 [total size] vs 220 [invasive size]). By adjusting total tumor size to invasive size 116 (40%) of T1b (>2–3 cm) tumors were reclassified as T1a (≤2 cm) and 45 (25%) of T2a (>3–5 cm) tumors were reclassified as T1b (>2–3 cm) tumors.

DISCUSSION

In this study, we have demonstrated that (1) patients with AIS or MIA experienced no recurrences and that patients with lepidic predominant invasive adenocarcinoma had a low risk of recurrence, (2) higher percentage of lepidic pattern correlated with lower risk of recurrence, (3) the prognostic difference between ≤2 cm tumors and >2–3 cm tumors was more pronounced for invasive tumor size than for total tumor size, and (4) the lepidic predominant pattern correlated with several clinicopathologic characteristics, including predominantly Asian race/ethnicity, history of never smoking, smaller tumor size, lower incidence of invasion (lymphatic, vascular, and plural), less nuclear atypia, and lower mitotic count.

Previous studies have suggested that patients with pure lepidic (noninvasive) tumors have 100% 5-year disease-free survival (DFS)[4–7] and that patients with MIA have nearly 100% DFS if completely resected.[8–10, 35–39] Perhaps in the future, AIS and MIA may be combined into a single category on the basis of the very similar patient outcome between them. The addition of the entity MIA has been one of the most welcome additions in this new classification because the lack of recurrence of these tumors has removed the clinical

importance for pathologists to distinguish AIS from MIA based on whether a small focus represents invasion or not. However, at the present time, more data are needed on MIA to be certain there will be no recurrences, particularly if the invasive component of such tumors consists of solid, micropapillary or small amounts of sarcomatoid components. Furthermore, our current data suggest that less than 5 percent of lepidic predominant adenocarcinoma recur, so in the vast majority of cases, there may be few clinical implications for pathologists in the distinction between MIA and lepidic predominant adenocarcinoma. In addition, invasive tumors with nonmucinous lepidic predominant growth correlated with favorable prognosis in patients with lung adenocarcinoma.[11–13, 35–41] These results are compatible with our findings: patients with AIS or MIA experienced no recurrences, and patients with nonmucinous lepidic predominant invasive adenocarcinoma had a low risk of recurrence (5-year CIR, 8%). The data regarding MIA as a very favorable prognostic category has largely been based on nonmucinous tumors, as mucinous and mixed mucinous/nonmucinous MIA are extremely rare. We identified 2 patients with MIA with a mucinous lepidic pattern (1 pure mucinous and 1 mixed mucinous/nonmucinous), both of whom did not experience a recurrence. Noguchi et al. previously reported two cases that would probably qualify as mucinous AIS that had 100% 5-year DFS.[4] However, further investigations are needed to confirm the prognostic significance of mucinous and mixed mucinous/nonmucinous MIA.

One of the most interesting findings in our study was that most patients with lepidic predominant adenocarcinoma who experienced a recurrence (n=4) had 1 or more potential risk factors, including (1) limited resection with a close margin (≤0.5 cm), (2) lymphatic or vascular invasion, and (3) a substantial component of a high-grade pattern, such as micropapillary. The 2011 IASLC/ATS/ERS classification proposed a research question to determine whether patients with MIA with a high-grade invasive component—such as solid, micropapillary or sarcomatoid—would have 100% disease-free survival.[2] This question could be adapted to lepidic predominant adenocarcinomas, as tumors with these poorly differentiated invasive components may carry a greater risk of recurrence. We have recently shown that the presence of a micropapillary component and a close surgical margin (≤0.5 cm) are independent predictors of recurrence in patients with lung adenocarcinoma treated with limited resection.[42] In the future, the presence of these risk factors may help surgeons to choose lobectomy over limited resection for appropriate patients, and our data suggest that this principle may apply to lepidic predominant adenocarcinomas as well.

In this study, invasion (pleural, lymphatic, or vascular) and tumor necrosis were very rare in lepidic predominant tumors. In addition, none of the lepidic predominant tumors with ≤5 mm invasion (AIS or MIA) had these histologic factors. We have demonstrated that all of the tumors classified as MIA had ≤5 mm invasion when measured by a ruler as well as by multiplying the total tumor size by the percentage of invasive component, and none led to recurrence. Interestingly, 21 patients had ≤3 cm lepidic predominant invasive tumors with >5 mm invasion when measured by a ruler but they were reclassified as ≤5 mm, and would have met criteria for MIA when measured using the multiplication method, and none of these patients experienced a recurrence. With our results, it is possible the size criteria for minimal invasion and the method used to measure invasion size could be modified. It appears that measuring invasive size by multiplying the total tumor size by the percentage of

the invasive component may be a practical and reliable approach. Further investigation and validation would be helpful to address this question.

We have demonstrated that patients with >50% lepidic pattern tumors had no recurrences, patients with >10%–50% lepidic pattern tumors had an intermediate risk of recurrence, and patients with ≤10% lepidic pattern tumors had the highest risk of recurrence. However, in a small percentage of cases, the lepidic component may be the predominant pattern and be less than 50%. Lee et al. reported similar results, showing that patients with lung adenocarcinoma with >50% lepidic pattern had better disease-free survival than patients with <50% lepidic pattern.[11] Yokose et al. reported that patients with lung adenocarcinoma with >75% lepidic pattern had 100% survival.[12] In addition, Lin et al. demonstrated a clear stratification of survival on the basis of percentage of lepidic pattern (<50%, 50%–79%, 80%–99%, and 100%).[13] The percentage of lepidic pattern is inversely proportional to the extent of the invasive component; therefore, higher percentage of lepidic pattern correlates with better prognosis, as the extent of invasion is driving recurrence.

We have previously demonstrated that the prognostic difference between ≤2 cm tumors and >2–3 cm tumors is more pronounced when tumors are categorized by invasive size.[23] The current study validated this finding using a larger cohort of patients with stage I lung adenocarcinoma. With regard to total tumor size, CIR was stratified into 3 groups on the basis of T stage classification (5-year CIR, 13% for ≤2 cm, 21% for >2–3 cm, and 24% for >3–5 cm). However, the CIR for invasive tumors >2–3 cm (5-year CIR, 27%) was closer to that for invasive tumors >3–5 cm (26%) than for those ≤2 cm (12%). It is interesting that the greatest change in recurrence, when tumors were categorized according to invasive size, was observed in the >2–3 cm group, rather than in the ≤2 cm or >3–5 cm group. This may reflect the greater heterogeneity of lepidic component in >2–3 cm tumors, with less change in invasive size among the smaller or larger tumors. Therefore, if T stage is categorized by invasive tumor size, up to 40% of T1b (>2–3 cm) tumors may be reclassified as T1a (≤2 cm) tumors and 25% of T2a (>3–5 cm) tumors may be reclassified as T1b (>2–3 cm) tumors. At any rate, our data should be validated in anticipation of a possible revision of the TNM classification. A growing number of papers in the radiology literature where ground glass vs solid opacity corresponds to lepidic vs invasive histology as well as the pathology literature support this concept.[43–45]

The 2011 IASLC/ATS/ERS classification defines the lepidic pattern, formerly BAC pattern, as a tumor that spreads along alveolar walls without invasion.[2] To better identify the lepidic growth pattern, criteria for invasion should also be clearly established. Noguchi et al. suggested that active fibroblastic proliferation in tumors correlated with invasive tumor cell growth, indicating a prognostic correlation with the presence of active fibroblastic stroma in BAC.[4] It has also been suggested that the structural deformity of the stromal elastic fiber framework, as observed on elastin stain, should be considered a finding of invasion.[5] In the 2011 IASLC/ATS/ERS classification, the following 3 factors are considered to indicate invasion: (1) histologic pattern other than lepidic, (2) active myofibroblastic stroma, and (3) lymphovascular or pleural invasion. In the present study, we have used the IASLC/ATS/ERS classification criteria to identify tumor invasion.

We found that tumors with a lepidic predominant pattern correlated with Asian race/ethnicity and a history of never smoking. These associations have also correlated with epidermal growth factor receptor (*EGFR*) mutations, which are more frequently observed in Asian patients and never smokers.[46–48] These tumors generally correspond to tumors historically classified as adenocarcinoma with BAC features[49–51]; however, it is now recommended that the use of this term be discontinued, as tumors formerly referred to as BAC can now be classified as five different types of lung adenocarcinoma.[2]

Several important factors need to be considered in the diagnosis of AIS, MIA, and lepidic predominant adenocarcinoma. AIS and MIA should not be diagnosed unless the tumor has been completely resected. Furthermore, to correctly identify the extent of lepidic versus invasive patterns in lung adenocarcinoma, pathologists may need to correlate pathologic findings with CT findings as the lepidic component is often under-appreciated on gross evaluation of the tumor. This can lead to undersampling of the tumor and during microscopic assessment, misleading impressions about tumor size including total size and the size of the invasive components.[15–17] However, the final decision on lepidic pattern versus invasive pattern should be made by microscopic examinations even if the pathologists may refer to the CT findings. In addition, overall survival should not be used for evaluating outcomes of patients with stage I lung adenocarcinoma, in particular those with lepidic predominant tumors, as most of these patients die of causes other than recurrence. CIR analysis is a more reliable representation of prognosis according to recurrence since death without recurrence should be considered as a competing event.[52] Although our method of prognostic analysis (using CIR) is different from the traditional approach (using overall or disease-free survival), we have previously shown that CIR more accurately represents tumor behavior.[53, 54] Recent studies that have failed to demonstrate significance of adenocarcinoma histologic subtyping used overall survival rather than survival linked to recurrence such as DFS or CIR.[55, 56] Furthermore, a recurrence must be distinguished from a metachronous primary, as may have occurred in the single case of development of an additional lung nodule in a different lobe of the same lung in one of the MIA cases reported by Xu et al.[57] As raised in our study, it may also be important to take into consideration if lepidic predominant adenocarcinoma underwent limited resection with a close margin as it can be very difficult to assess lepidic growth at a staple line margin.

In conclusion, we have demonstrated the clinical and prognostic importance of the lepidic pattern using a large cohort of patients with stage I lung adenocarcinoma. According to the IASLC/ATS/ERS classification, performing comprehensive histopathologic subtyping for lung adenocarcinoma helps to characterize the extent of lepidic versus invasive components. As we have shown, this can also be used to estimate the size of tumor invasion, particularly in tumors in which the invasive component cannot be measured as a single focus on 1 slide. In addition, we have shown that it may be possible to stratify lepidic predominant adenocarcinomas according to risk factors for recurrence. In the future, this may guide surgeons to choose lobectomy over limited resection for the treatment of these patients if we can provide the evidence in the future study that the histologic subtyping on frozen section predicts the final diagnosis on the basis of the examinations for entire tumors.

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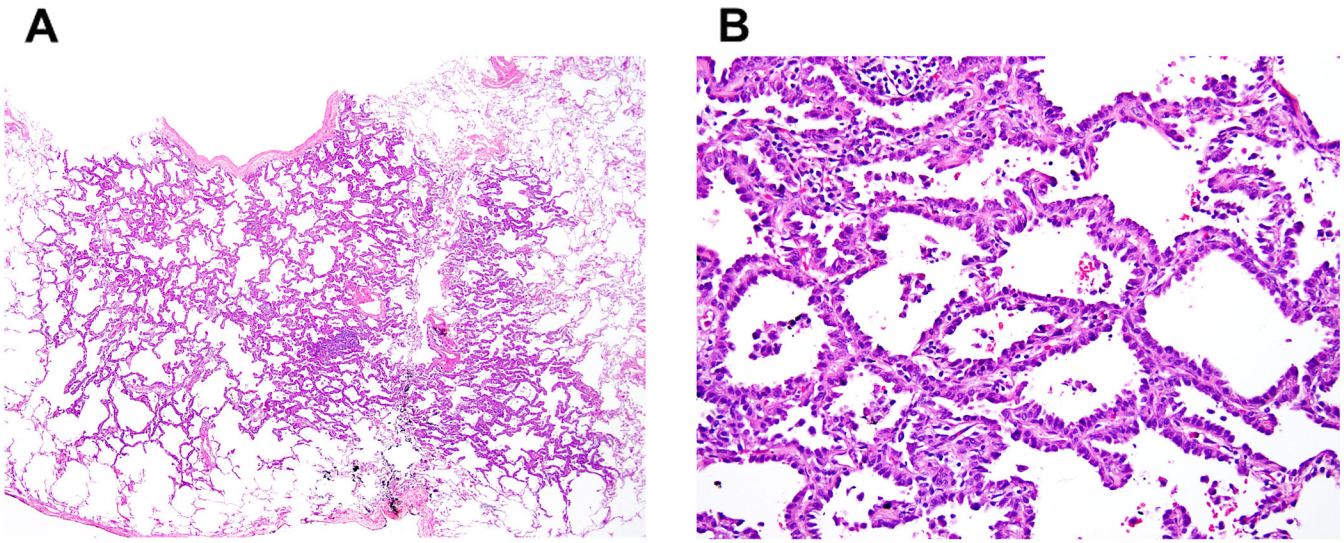

Figure 1. Adenocarcinoma in situ, nonmucinous type

(A) A small tumor shows a pure lepidic pattern. (B) Nonmucinous tumor cells spread along alveolar walls (lepidic pattern) without invasion.

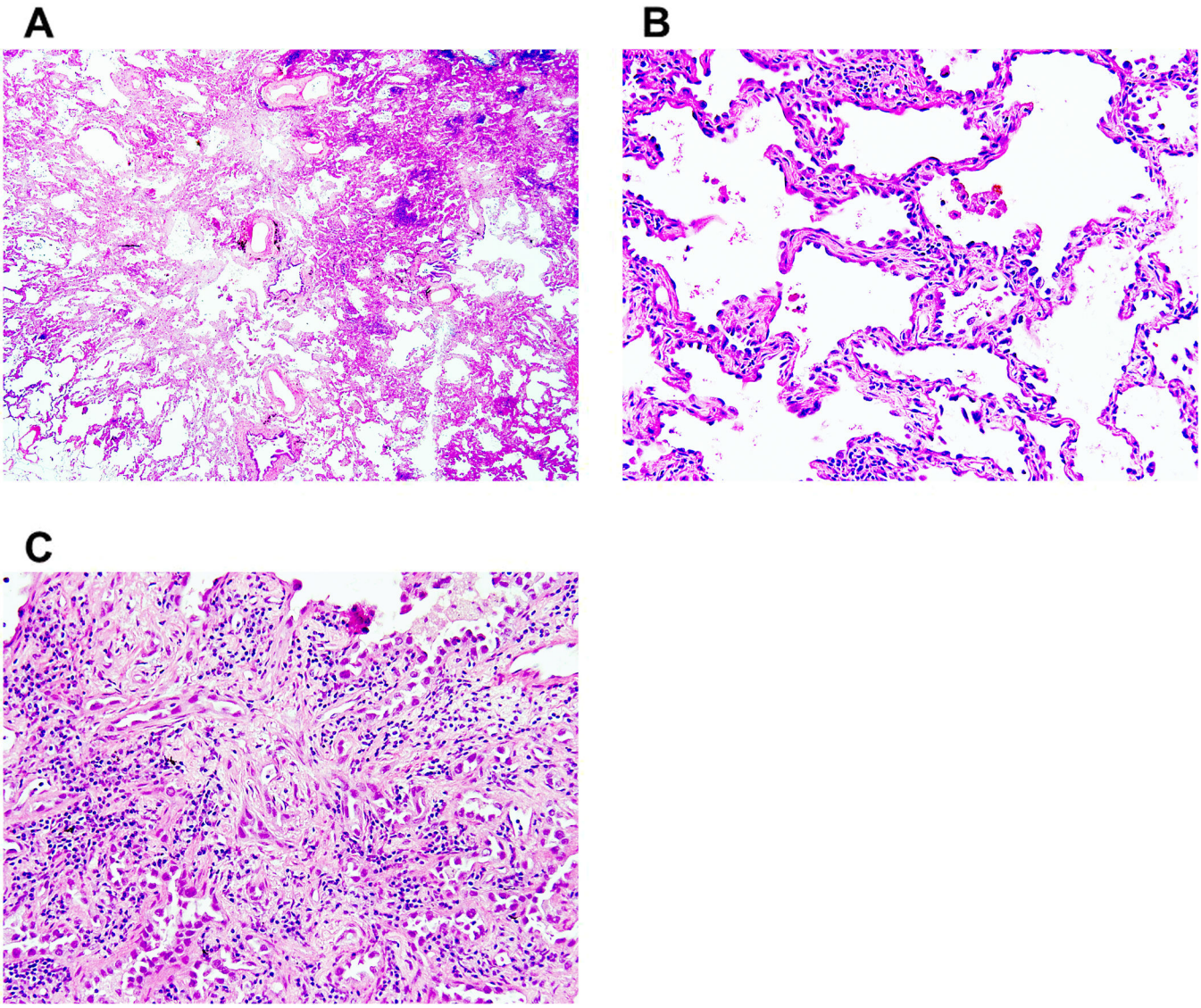

Figure 2. Minimally invasive adenocarcinoma, nonmucinous type

(A) A small tumor shows a predominant (>90%) lepidic pattern with <5 mm stromal invasion. (B) Nonmucinous tumor cells spread along alveolar walls (lepidic pattern) without invasion. (C) Small glandular tumor cells (acinar pattern) show stromal invasion with active myofibroblastic proliferation.

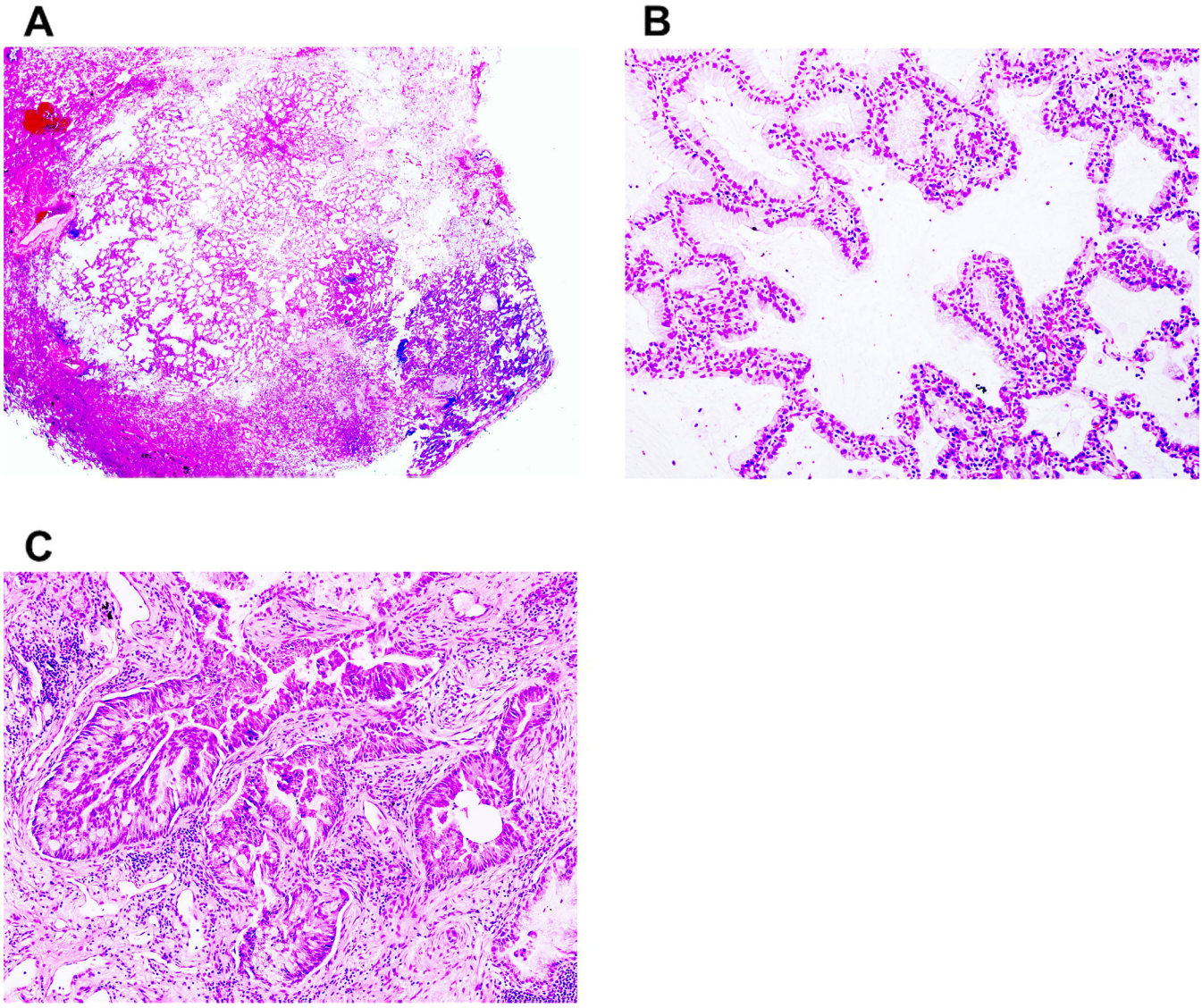

Figure 3. Minimally invasive adenocarcinoma, mucinous type

(A) A small tumor shows a predominant (>90%) lepidic pattern with <5 mm stromal invasion. (B) Mucinous tumor cells spread along alveolar walls (lepidic pattern) without invasion. (C) Fused glandular tumor cells (acinar pattern) show stromal invasion with active myofibroblastic proliferation.

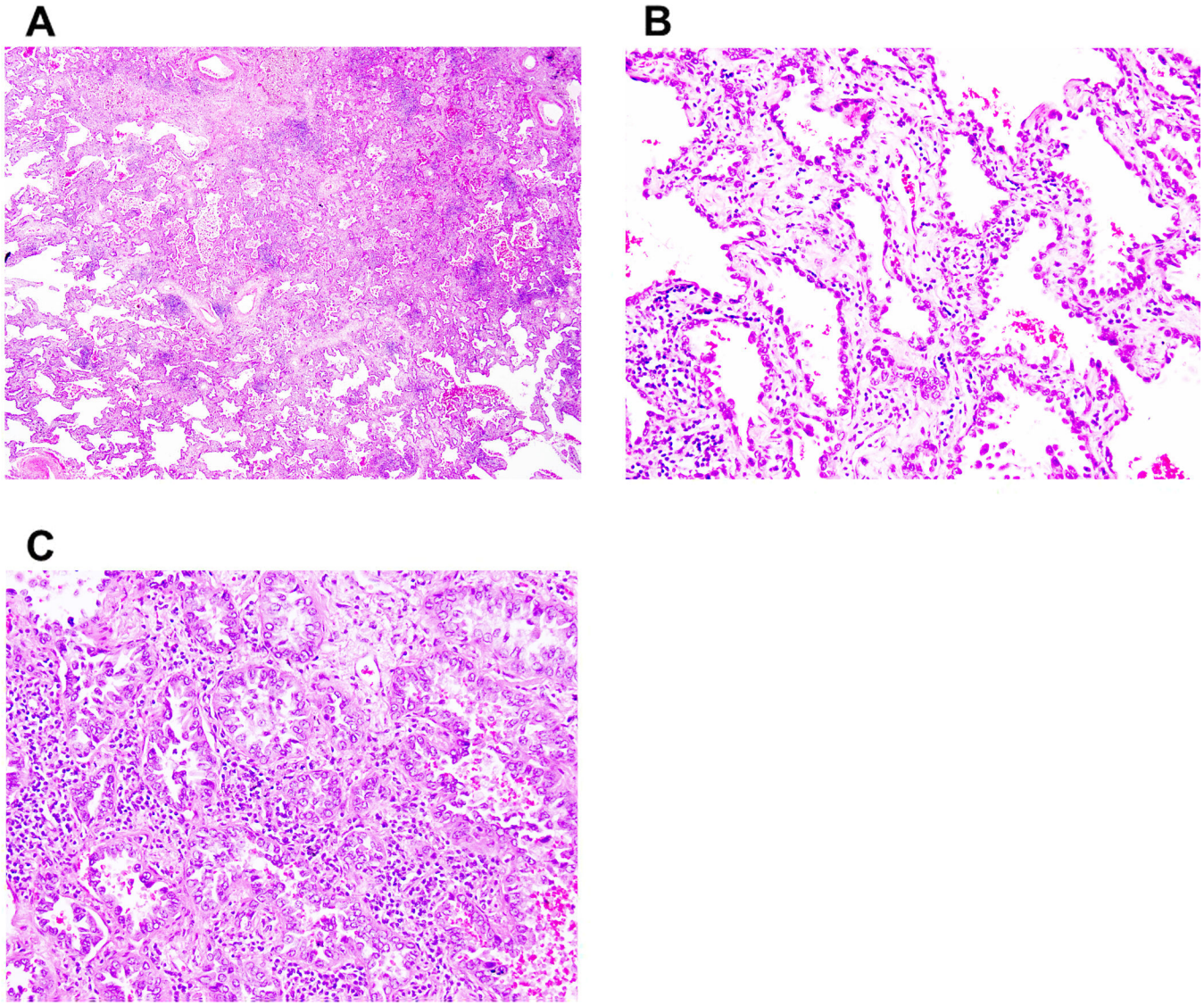

Figure 4. Nonmucinous lepidic predominant invasive adenocarcinoma

(A) A tumor shows a predominant (about 70%) lepidic pattern with >5 mm stromal invasion. (B) Nonmucinous tumor cells spread along alveolar walls (lepidic pattern) without invasion. (C) Tumor cells show small glandular morphology (acinar pattern).

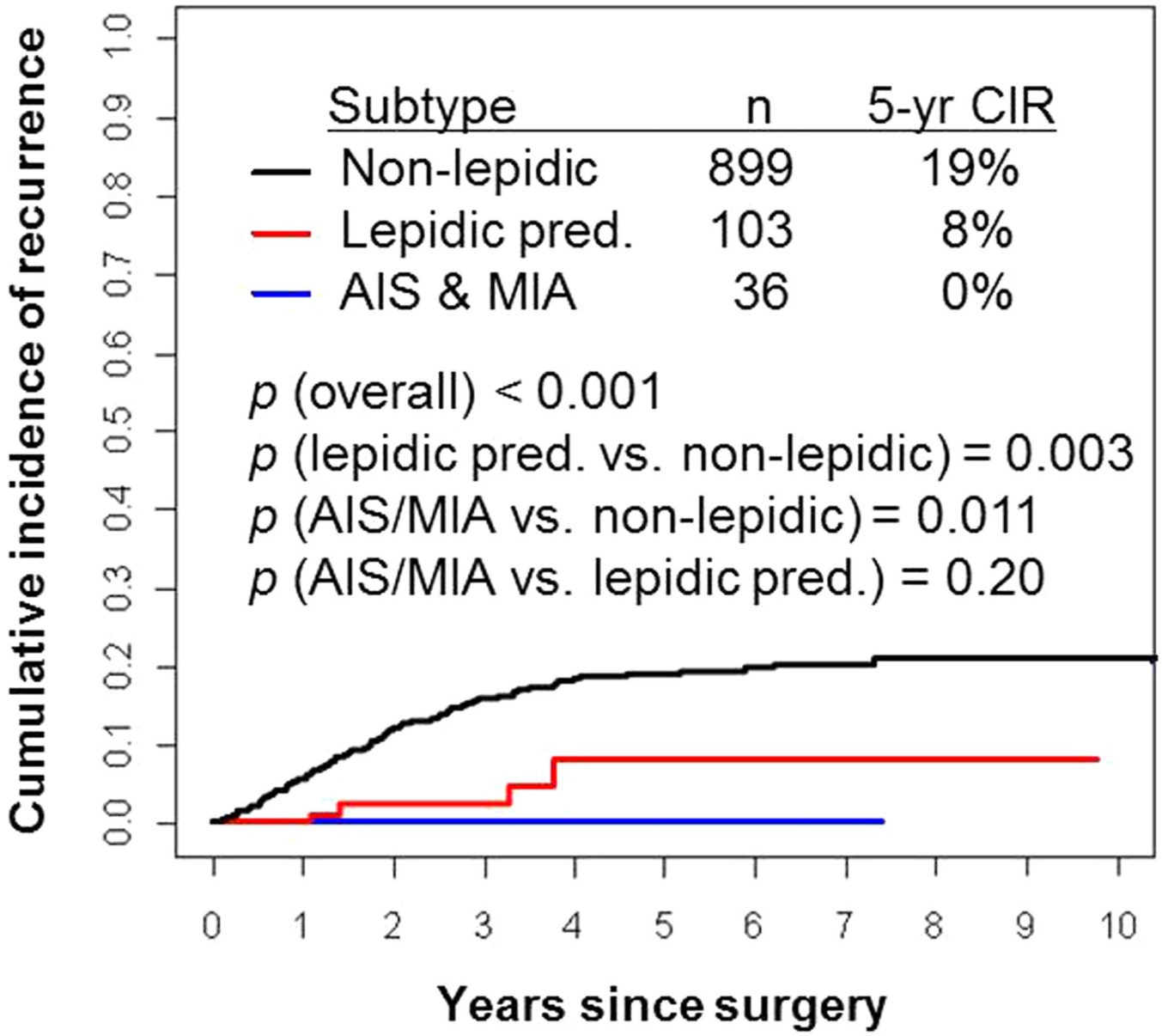

Figure 5. Cumulative incidence of recurrence (CIR) by lepidic predominant subtypes

Patients with AIS and MIA (n=36) experienced no recurrences (5-year CIR, 0%). Patients with lepidic predominant invasive adenocarcinoma had a lower risk of recurrence (n=103, 5-year CIR, 8%) than patients with non-lepidic predominant adenocarcinoma (n=899; 5-year CIR, 19%).

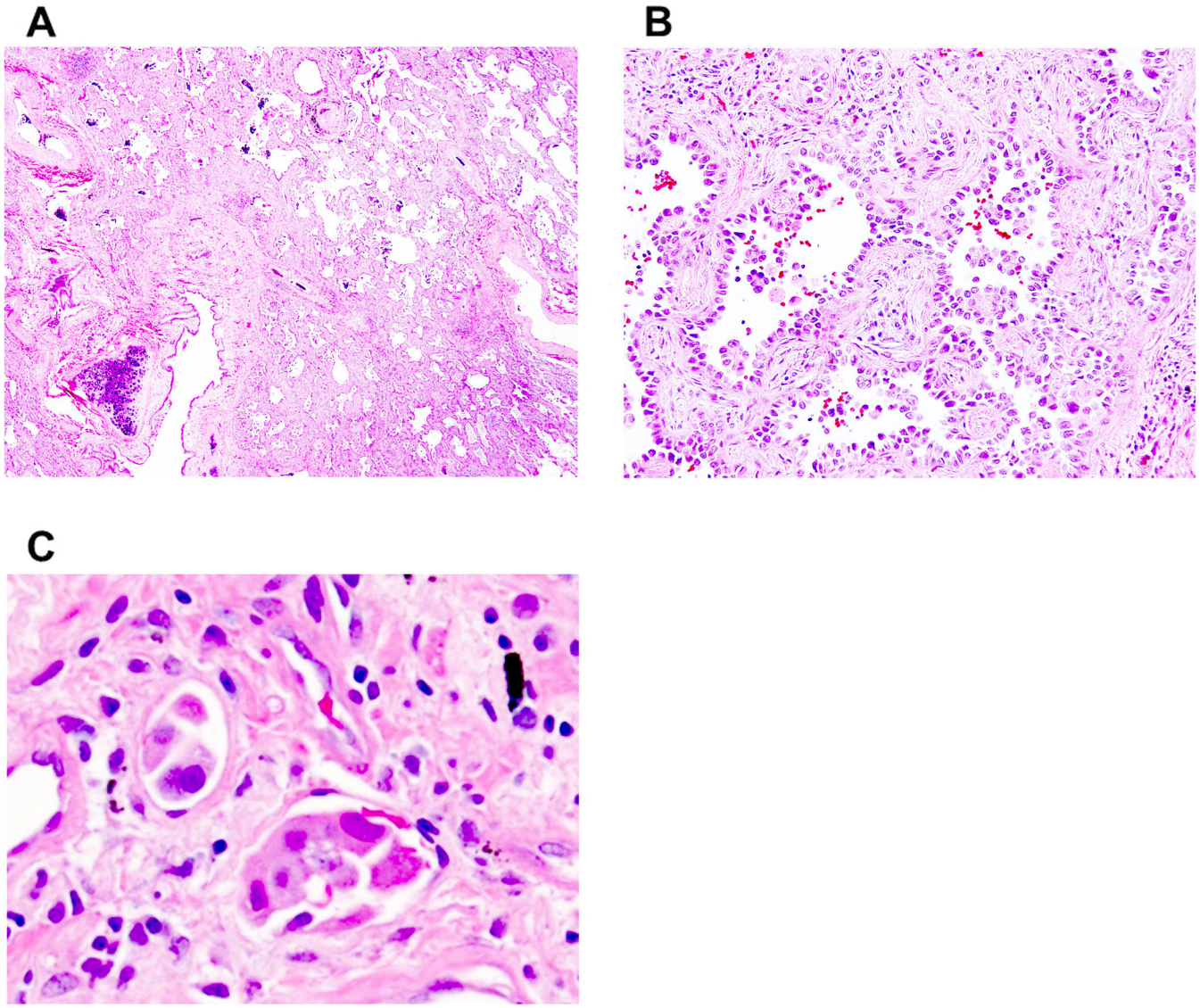

Figure 6. Nonmucinous lepidic predominant invasive adenocarcinoma with micropapillary pattern and lymphatic invasion

(A) A tumor shows a predominant (about 70%) lepidic pattern with >5 mm stromal invasion. (B) Micropapillary component is identified in part of the tumor. (C) Tumor cell shows lymphatic invasion.

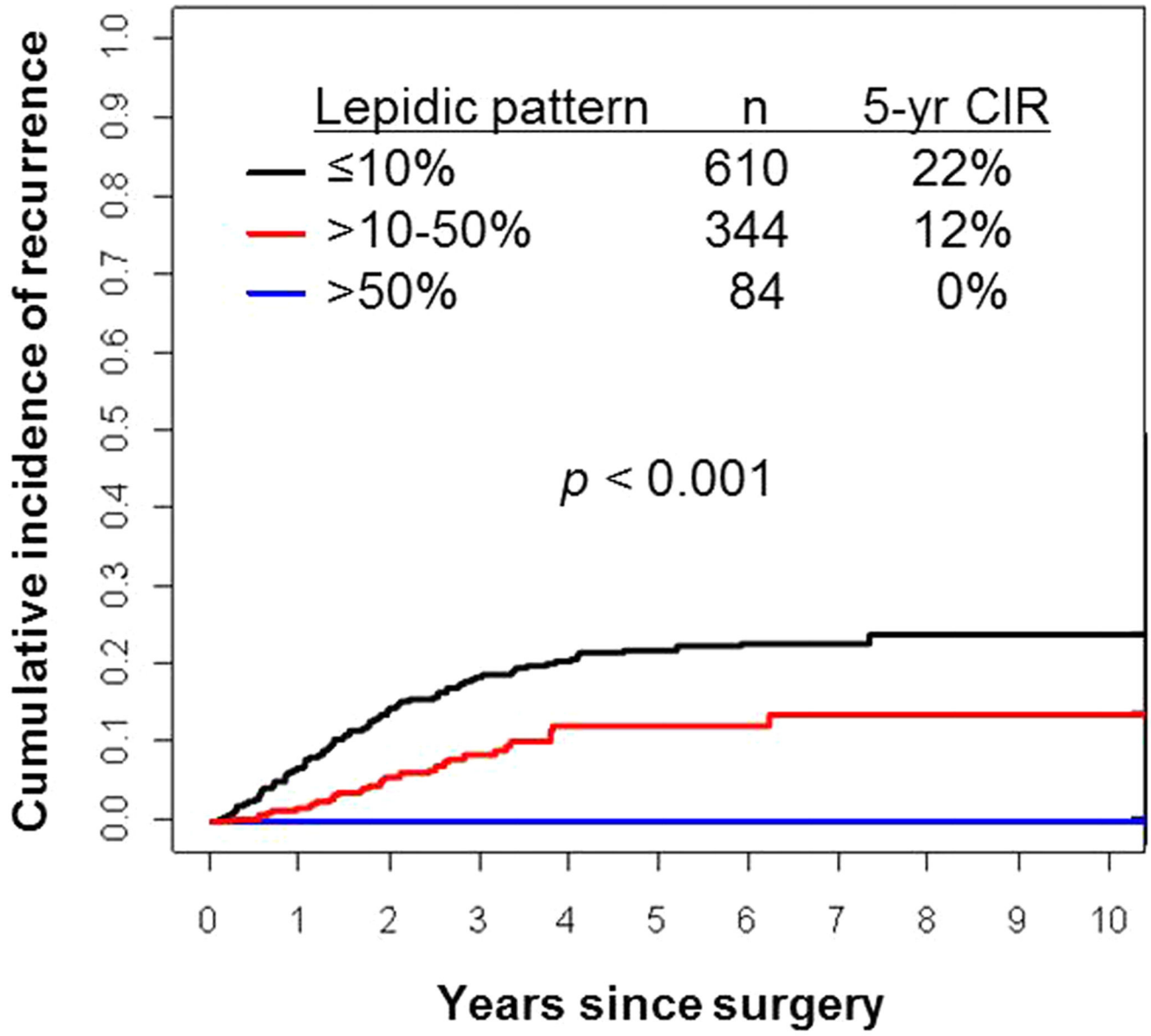

Figure 7. Cumulative incidence of recurrence (CIR) by percentage of lepidic pattern

Patients with >50% lepidic pattern tumors (n=84) experienced no recurrences (5-year CIR, 0%). Patients with >10%–50% lepidic pattern tumors (n=344) had a lower risk of recurrence (5-year CIR, 12%) than patients with ≤10% lepidic pattern tumors (n=610; 5-year CIR, 22%).

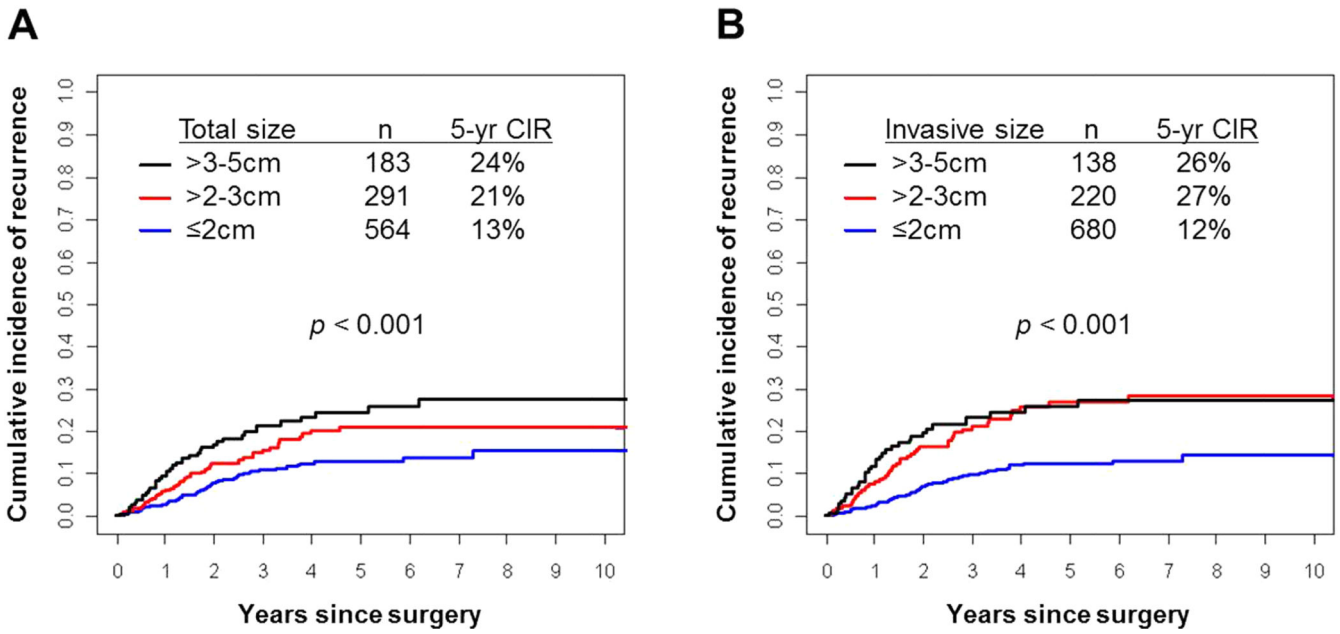

Figure 8. Cumulative incidence of recurrence (CIR) by total and invasive tumor size

(A) Patients with ≤2 cm total tumor size (n=564) had the lowest risk of recurrence (5-year CIR, 13%), followed by >2–3 cm (n=291; 21%) and >3–5 cm (n=183; 24%). (B) Patients with ≤2 cm invasive tumor size (n=680) had a lower risk of recurrence (5-year CIR, 12%) than those with >2–3 cm (n=220; 5-year CIR, 27%) or >3–5 cm (n=138; 5-year CIR, 26%). There were fewer tumors measuring >2–3 cm according to invasive size than to total size (220 vs 291); the CIR was worse for tumors measured according to invasive size than total size (27% vs 21%).

Table 1

Definition of Adenocarcinoma in situ, Minimally Invasive Adenocarcinoma, and Nonmucinous Lepidic Predominant Invasive Adenocarcinoma

Subtype	Size and Invasion	Lepidic Pattern Distribution	Lymphatic Invasion	Vascular Invasion	Pleural Invasion	Tumor Necrosis
Adenocarcinoma in situ	≤3 cm and no invasion	100%	Absent	Absent	Absent	Absent
Minimally invasive adenocarcinoma	≤3 cm and ≤5 mm invasion	Predominant	Absent	Absent	Absent	Absent
Lepidic predominant invasive adenocarcinoma	>3 cm and/or >5 mm invasion	Predominant	Absent or present	Absent or present	Absent or present	Absent or present

Table 2

Association between Clinicopathologic Factors and Lepidic Predominant Subtype

Variables	All	AIS/MIA, no. (%)	Lepidic predominant adenocarcinoma, no. (%)	Non-lepidic predominant, no. (%)	*P*
All patients	1038	36 (3)	103 (10)	899 (87)	
Age, years					0.63*
Median (range)	69 (23–96)	69 (23–86)	70 (41–89)	69 (33–96)	
Sex					0.92*
Female	646	26 (4)	60 (9)	560 (87)	
Male	392	10 (3)	43 (11)	339 (86)	
Race					**<0.001***
Asian	40	5 (13)	10 (25)	25 (63)	
Non-Asian	998	31 (3)	93 (9)	874 (88)	
Smoking					**0.011***
Never	176	7 (4)	27 (15)	142 (81)	
Ever	862	29 (3)	76 (9)	757 (88)	
Laterality					0.56*
Right	611	24 (4)	61 (10)	526 (86)	
Left	427	12 (3)	42 (10)	373 (87)	
Surgical resection					0.10*
Lobar	796	18 (2)	81 (10)	697 (88)	
Sublobar	242	18 (7)	22 (9)	202 (83)	
Tumor size, cm					**0.027****
Median (range)	2.0 (0.3–5)	1.2 (0.4–2.9)	1.8 (0.7–5.0)	2.0 (0.3–5.0)	
T stage					**<0.001****
T1a	494	31 (6)	66 (13)	397 (80)	
T1b	237	5 (2)	23 (10)	209 (88)	
T2	307	0 (0)	14 (5)	293 (95)	
Pleural invasion					**<0.001****
Absent	866	36 (4)	100 (12)	730 (84)	

Variables	All	AIS/MIA, no. (%)	Lepidic predominant adenocarcinoma, no. (%)	Non-lepidic predominant, no. (%)	*P*
Present	172	0 (0)	3 (2)	169 (98)	
Lymphatic invasion					**<0.001****
Absent	707	36 (5)	95 (13)	576 (81)	
Present	331	0 (0)	8 (2)	323 (98)	
Vascular invasion					**<0.001****
Absent	778	36 (5)	98 (13)	644 (83)	
Present	260	0 (0)	5 (2)	255 (98)	
Necrosis					**<0.001****
Absent	869	36 (4)	101 (12)	732 (84)	
Present	169	0 (0)	2 (1)	167 (99)	
Nuclear atypia					**<0.001***
Mild	451	32 (7)	72 (16)	347 (77)	
Moderate	360	4 (1)	28 (8)	328 (91)	
Severe	227	0 (0)	3 (1)	224 (99)	
Mitotic count, mitoses, median (range)	1 (0–76)	0 (0–2)	1 (0–6)	2 (0–76)	**<0.001***

Significant *P* values are shown in bold.

* AIS/MIA and lepidic predominant invasive vs. nonlepidic predominant.

** Lepidic predominant invasive vs. nonlepidic predominant.

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

Table 3

Clinicopathologic Characteristics of Recurrent or Nonrecurrent Lepidic Predominant Invasive Adenocarcinoma

Variable	Nonrecurrent (n=99)	Recurrent (n=4)			
		Case 1	Case 2	Case 3	Case 4
Surgical resection		Lobar	Sublobar	Sublobar	Lobar
Lobar	79				
Sublobar	20				
Distance to staple margin, cm					
Median (range)	1.3 (0.3–7.5)	NA	0.2	0.5	NA
Location of recurrence	NA	Bone	Lung	Chest wall	Lung
Time till recurrence, years	NA	1.4	1.1	3.3	3.8
Total tumor size, cm					
Median (range)	1.7 (0.7–5.0)	2.1	2.0	1.6	2.5
Invasive tumor size, cm					
Median (range)	0.8 (0.6–2.8)	1.3	1.2	0.8	1.3
T stage		T1b	T1a	T1a	T1b
T1a	64				
T1b	21				
T2	14				
Pleural invasion		Absent	Absent	Absent	Absent
Present	3				
Absent	96				
Lymphatic invasion		Present	Present	Absent	Absent
Present	6				
Absent	93				
Vascular invasion		Present	Absent	Absent	Absent
Present	4				
Absent	95				
Necrosis		Absent	Absent	Absent	Absent
Present	2				
Absent	97				

Variable	Nonrecurrent (n=99)	Recurrent (n=4)			
		Case 1	Case 2	Case 3	Case 4
Histologic pattern, %					
Median (range)					
Lepidic	50 (40–85)	40	40	50	50
Acinar	30 (0–45)	20	10	20	20
Papillary	10 (0–40)	10	30	30	30
Micropapillary	0 (0–35)	30	20	0	0
Solid	0 (0–20)	0	0	0	0
Nuclear atypia		Mild	Moderate	Mild	Mild
Mild	69				
Moderate	27				
Severe	3				
Mitotic count, mitoses, median (range)	1 (0–6)	0	1	1	0

NA, not applicable.