

# Solid Predominant Histologic Subtype in Resected Stage I Lung Adenocarcinoma Is an Independent Predictor of Early, Extrathoracic, Multisite Recurrence and of Poor Postrecurrence Survival

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## A B S T R A C T

### Purpose

To examine the significance of the proposed International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) histologic subtypes of lung adenocarcinoma for patterns of recurrence and, among patients who recur following resection of stage I lung adenocarcinoma, for postrecurrence survival (PRS).

### Patients and Methods

We reviewed patients with stage I lung adenocarcinoma who had undergone complete surgical resection from 1999 to 2009 (N = 1,120). Tumors were subtyped by using the IASLC/ATS/ERS classification. The effects of the dominant subtype on recurrence and, among patients who recurred, on PRS were investigated.

### Results

Of 1,120 patients identified, 188 had recurrent disease, 103 of whom died as a result of lung cancer. Among patients who recurred, 2-year PRS was 45%, and median PRS was 26.1 months. Compared with patients with nonsolid tumors, patients with solid predominant tumors had earlier ( $P = .007$ ), more extrathoracic ( $P < .001$ ), and more multisite ( $P = .011$ ) recurrences. Multivariable analysis of primary tumor factors revealed that, among patients who recurred, solid predominant histologic pattern in the primary tumor (hazard ratio [HR], 1.76;  $P = .016$ ), age older than 65 years (HR, 1.63;  $P = .01$ ), and sublobar resection (HR, 1.6;  $P = .01$ ) were significantly associated with worse PRS. Presence of extrathoracic metastasis (HR, 1.76;  $P = .013$ ) and age older than 65 years at the time of recurrence (HR, 1.7;  $P = .014$ ) were also significantly associated with worse PRS.

### Conclusion

In patients with stage I primary lung adenocarcinoma, solid predominant subtype is an independent predictor of early recurrence and, among those patients who recur, of worse PRS. Our findings provide a rationale for investigating adjuvant therapy and identify novel therapeutic targets for patients with solid predominant lung adenocarcinoma.

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## INTRODUCTION

Despite curative-intent surgical resection, tumor recurrence and spread remain the primary causes of cancer-related death among patients with early-stage lung cancer.<sup>1</sup> Among patients with stage I lung adenocarcinoma—the most common histologic subtype of lung cancer—outcomes after surgical resection vary. The current staging system fails to distinguish patients at a higher risk of recurrence following surgical resection.<sup>2</sup> With the results of the National Lung Screening Trial and the recent approval of Centers for Medicare and Medicaid Service

coverage for screening computed tomography (CT) scans, an increase in the detection and treatment of early-stage lung cancer is expected.<sup>3-5</sup> This underscores the need for better prognostic factors to identify patients at risk of early recurrence after curative-intent surgical resection and those who have a high risk of death after recurrence.

The new International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) classification characterizes lung adenocarcinoma as a heterogeneous mixture of histologic subtypes, with the predominant histologic subtype

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able to stratify recurrence-free survival.<sup>6-8</sup> To date, few studies have investigated the prognostic utility of this classification with respect to recurrence patterns and postrecurrence survival (PRS).<sup>9</sup> Several researchers have investigated the effects of clinicopathologic factors on PRS among patients with lung cancer (Appendix Table A1, online only).<sup>9-14</sup> However, the cohorts in these studies were heterogeneous with respect to histologic profile (adenocarcinoma or nonadenocarcinoma) and/or TNM stage (early or advanced). In this study, we examined the prognostic significance of histologic subtypes and clinicopathologic factors in a large, homogeneous cohort of patients with stage I lung adenocarcinoma treated at a single institution during a 10-year period. In addition, by focusing on patients who recurred following initial surgical resection, we were able to investigate the effects of both primary tumor factors and postrecurrence factors on PRS.

## PATIENTS AND METHODS

### Patient Cohort

This retrospective study was approved by the institutional review board at Memorial Sloan Kettering Cancer Center (MSKCC). We reviewed the medical records of all patients diagnosed with pathologic stage I solitary lung adenocarcinoma who had undergone surgical resection at MSKCC between January 1999 and December 2009. Our inclusion criterion was a diagnosis of lung adenocarcinoma, with hematoxylin and eosin–stained slides available for pathologic review. Our exclusion criteria were that the patient must have had multicentric, metachronous, or metastatic disease, undergone lung cancer surgery within the last 2 years, undergone incomplete resection (R1 or R2), or received induction therapy. Correlative clinical data were retrieved from our prospectively maintained Thoracic Surgery Service Lung Cancer Database. Analysis for recurrence was performed on all eligible patients who underwent resection, and analysis for PRS was performed on all patients who experienced recurrence.

### Histologic Evaluation

All available hematoxylin and eosin–stained tumor slides (mean, five slides per patient; range, one to 12 slides per patient) were reviewed by two pathologists who were blinded to patient clinical outcomes (K.K. and W.D.T.); an Olympus BX51 microscope (Olympus, Tokyo, Japan) with a standard 22-mm diameter eyepiece was used. Any discrepancies between the pathologists during determination of predominant subtypes were resolved via consensus by using a multiple-headed microscope. The percentage of each histologic pattern was recorded in 5% increments. Tumors were classified according to the IASLC/ATS/ERS classification as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma, which was subdivided into lepidic predominant (LEP), acinar predominant (ACI), papillary predominant (PAP), micropapillary predominant (MIP), solid predominant (SOL), colloid predominant (COL), and invasive mucinous (MUC) adenocarcinoma.<sup>15</sup> Tumors were grouped by architectural grading as low (AIS, MIA, or LEP), intermediate (PAP or ACI), or high (MIP, SOL, COL, or MUC).<sup>6,7</sup> The following factors were also investigated: visceral pleural invasion, lymphatic and vascular invasion, and the presence of necrosis. Lymphatic invasion was defined as the presence of tumor cells within endothelium-lined lymphatic spaces. Vascular invasion was defined as the presence of tumor cells within blood vessels.<sup>6-8</sup>

### Surveillance Protocol

Postoperative lung cancer surveillance was performed in accordance with National Comprehensive Cancer Network guidelines.<sup>16</sup> During the first 2 years after surgery, each patient received a physical examination, interval history, and chest/upper-abdominal CT scan with or without contrast every 6 to 12 months. Bronchoscopy, serum markers, and positron emission tomog-

raphy (PET) scans were not used during routine follow-up. Follow-up visits and surveillance CT scans were performed yearly after the first 2 years. At each follow-up visit, all new studies were reviewed by the clinician. Patients were monitored either by their thoracic surgeon or by a nurse practitioner trained in thoracic survivorship care.

The study had two primary end points: recurrence after initial resection with curative intent (evaluated in all patients) and death after development of recurrence (evaluated in patients who experienced recurrence only). The data extracted included type of recurrence (distant, regional, or local), method of detection, and whether the event was detected at a scheduled clinic visit as part of routine surveillance or at an unscheduled visit outside the follow-up protocol.<sup>17,18</sup> Recurrences were defined as in our previous publication<sup>19</sup>: local recurrence was defined as any new lesion adjacent to a staple line or the bronchial stump or in the residual lobe (in cases of sublobar resection). Regional recurrence was defined as 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 as evidence of a tumor in the contralateral lung, in the contralateral mediastinal or ipsilateral supraclavicular lymph nodes (N3), or elsewhere outside the hemithorax.<sup>19</sup> Diagnosis of recurrence was confirmed via biopsy, and imaging (ie, PET scan or brain magnetic resonance imaging) was performed to support the clinical diagnosis and the decision to initiate treatment. In cases in which a new tumor developed in the lung or pleura and a biopsy specimen was available, the histologic profile was reviewed to determine whether the new tumor was a metachronous primary tumor or a recurrence or metastasis, in accordance with the method developed by our group.<sup>20</sup> A combined recurrence was defined as the detection of both locoregional and distant metastasis, either simultaneously or within 30 days of each other.<sup>21</sup>

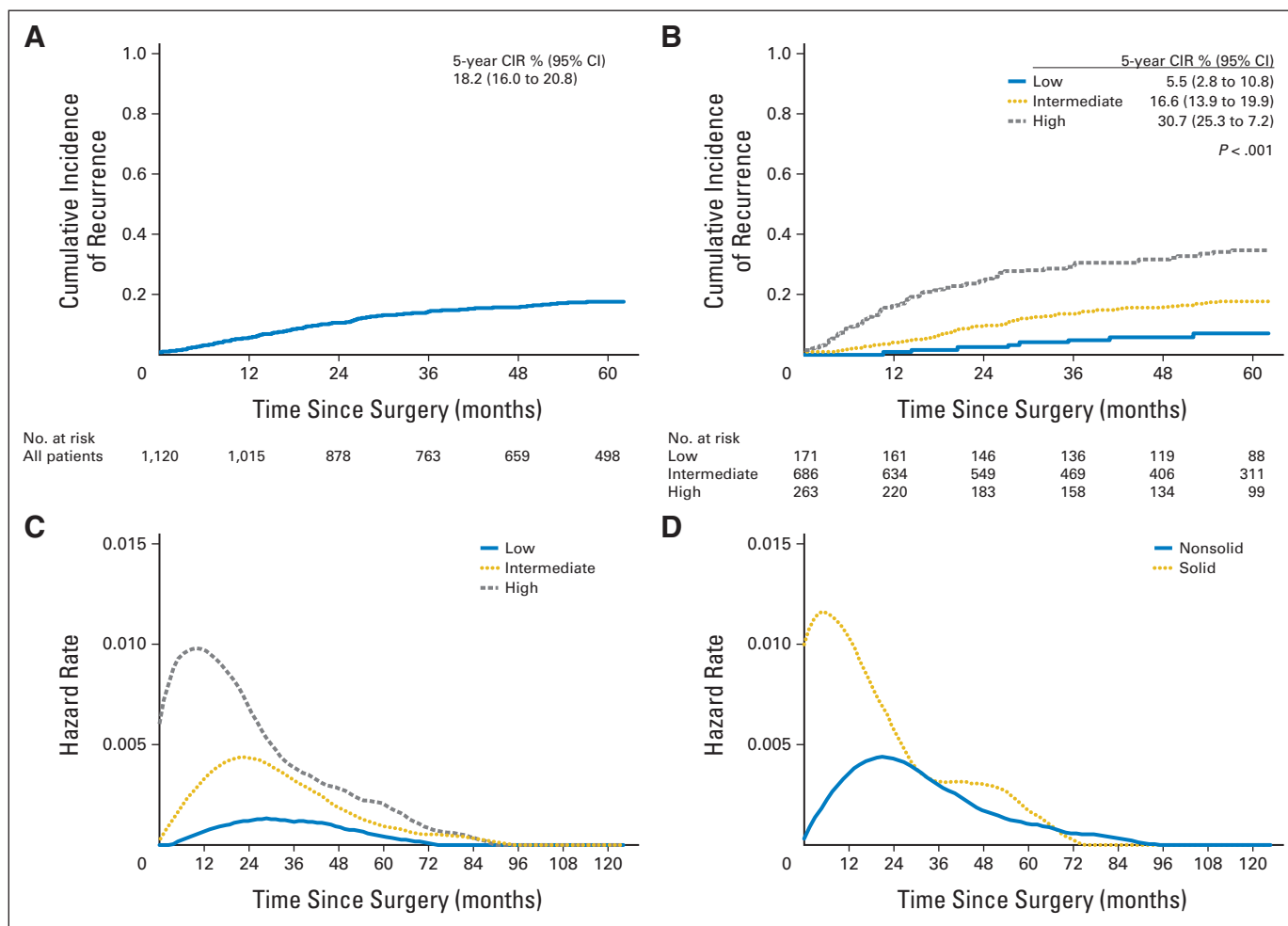
### Statistical Analysis

The risk of recurrence was evaluated among all patients included in the study by using competing risks methods, which account for deaths in the absence of a documented recurrence as competing events. The cumulative incidence function was used to estimate the cumulative incidence of recurrence (CIR) after surgical resection with curative intent.<sup>22</sup> Patients who did not experience recurrence or die during the study period were censored at the time of the last available follow-up. Differences in CIR between groups were assessed by using the Gray method<sup>23</sup> (for univariable nonparametric analyses) and the Gray and Fine<sup>24</sup> model (for multivariable analyses). Overall survival (OS) from time of surgery was estimated by using the Kaplan and Meier method and was compared across groups by using the log-rank test.

For patients who experienced recurrence, PRS was estimated by using the Kaplan-Meier method. Patients were monitored from the time of cancer recurrence until the time of death as a result of any cause. Patients who were alive at the end of the study were censored at the last available follow-up. Differences in PRS between groups were evaluated by using the log-rank test (for univariable analysis) and Cox proportional hazards model (for multivariable analysis). For architectural grade analysis, the low and intermediate grades were combined because there were few events being observed among patients with low-grade disease, and the effect of high-grade disease was evaluated separately for predominant micropapillary and predominant solid subtypes. Hazard rates were estimated by using the kernel-smoothing method.<sup>25,26</sup> Statistical analyses were performed by using SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.14.1. All significance tests were two-sided, and 5% was set as the level of statistical significance.

## RESULTS

The study cohort consisted of 1,120 patients with resected stage I lung adenocarcinoma. Median follow-up was 60 months (range, 0.3 to 178 months); median age was 69 years (range, 23 to 96 years). Of the 1,120 patients identified, 188 (17%) experienced recurrence. At the end of the study period, 308 patients had died. The 5-year CIR for all patients was 18.2% (95% CI, 16% to 20.8%; Fig 1A). On univariable analysis,



**Fig 1.** (A) Cumulative incidence of recurrence (CIR) of patients with stage I lung adenocarcinoma. (B) CIR for patients with stage I lung adenocarcinoma for each architectural grade. (C) Hazard function of recurrence for architectural grade tumors. (D) Hazard function of recurrence for solid predominant tumors.

male sex ( $P = .038$ ), sublobar resection ( $P < .001$ ), lymphatic invasion ( $P < .001$ ), vascular invasion ( $P < .001$ ), pleural invasion ( $P < .001$ ), stage IB disease ( $P < .001$ ), and high architectural grade ( $P < .001$ ; Fig 1B) were correlated with a higher risk of recurrence (Table 1). Of patients with stage IB disease ( $n = 273$ ), 24 (10%) received adjuvant chemotherapy. In this small cohort of patients, adjuvant chemotherapy did not have any significant effect on risk of recurrence in the adjuvant chemotherapy group (5-year CIR, 21.5% [95% CI, 8.7% to 53.4%]) compared with the nonadjuvant chemotherapy group (5-year CIR, 29.6% [95% CI, 24.1% to 36.4%];  $P = .15$ ).

The smoothed graph of the hazard function for each architectural grade shows that the risk of recurrence was highest for high-grade tumors, followed by intermediate- and low-grade tumors (Fig 1B). In addition, the risk of recurrence peaked earlier for high-grade tumors (between 12 and 24 months) than for intermediate- or low-grade tumors (Fig 1C). The risk of recurrence was highest for solid predominant tumors (Fig 1D). Compared with patients with nonsolid tumors, patients with solid predominant tumors had earlier (recurrence within 2 years, 75% v 51%;  $P = .007$ ), more extrathoracic (77% v 37%;  $P < .001$ ), and more multisite (47% v 26%;  $P = .011$ ) recurrences (Table 2). When analyzing OS by architectural grade, patients with high-architectural grade tumors had significantly worse OS com-

pared with patients with intermediate- and low-grade tumors (5-year OS, high [69%] v intermediate [80%] v low [87%];  $P < .001$ ; Appendix Fig A1, online only).

Of the 188 patients who experienced relapse, 59 (31%) had locoregional recurrence, 100 (53%) had distant recurrence, and 29 (15%) had both (Appendix Table A2, online only). The most commonly involved organs for distant recurrences were bone, contralateral lung, and brain. The majority of recurrences were detected by scheduled surveillance CT scan (123 [65%]: 56 locoregional and 67 distant). Symptomatic recurrences occurred in 60 patients (32%; two locoregional and 58 distant). Postrecurrence therapy was given to 157 patients (84%). Initial therapy was chemotherapy with or without radiation in 66 patients (35%); 69 patients (37%) received local therapy with either surgery or radiation (Appendix Table A2). Forty-nine patients received first-line chemotherapy, as detailed in Appendix Table A3 (online only). Of the patients who experienced recurrence, 134 died (103 as a result of cancer-related disease). Overall, 1- and 2-year PRS rates were 67% and 45%, respectively. Median PRS was 26.1 months (95% CI, 20.4 to 36.3 months; Fig 2A).

We next focused on the group of patients who experienced cancer recurrence during the study period. Because this set is a selected subgroup of the large cohort diagnosed with stage I tumors, the risk

**Table 1.** Patient Characteristics and Univariable Analyses of Recurrence

Characteristic	No. (%)	5-Year CIR (95% CI), %	P*
All patients	1,120	18.2 (16.0 to 20.8)	
Age, years			.45
≤ 65	404 (36)	20.2 (16.4 to 24.9)	
> 65	716 (64)	17.1 (14.4 to 20.3)	
Sex			<b>.038</b>
Female	696 (62)	16.5 (13.7 to 19.7)	
Male	434 (39)	21.1 (17.4 to 25.7)	
Smoking history			.243
Never	197 (18)	16.0 (11.3 to 22.6)	
Ever	923 (82)	18.7 (16.2 to 21.6)	
Surgical procedure†			<b>&lt; .001</b>
Lobectomy	807 (72)	15.5 (13.0 to 18.4)	
Sublobar resection	313 (28)	25.1 (20.5 to 30.7)	
T factor			<b>&lt; .001</b>
T1a	632 (56)	14.0 (11.4 to 17.2)	
T1b	215 (19)	17.2 (12.5 to 23.8)	
T2a	273 (24)	29.0 (23.7 to 35.5)	
Pathologic stage			<b>&lt; .001</b>
IA	847 (76)	14.8 (12.5 to 17.6)	
IB	273 (24)	29.0 (23.7 to 35.5)	
Predominant histologic subtype			<b>&lt; .001</b>
Adenocarcinoma in situ	2 (0.2)	NA	
Minimally invasive adenocarcinoma	32 (3)	0	
Lepidic	137 (12)	6.8 (3.5 to 13.4)	
Acinar	453 (40)	16.6 (13.3 to 20.7)	
Papillary	244 (22)	16.6 (12.2 to 22.7)	
Micropapillary	68 (6)	40.9 (29.9 to 56.0)	
Solid	146 (13)	29.1 (22.3 to 37.9)	
Invasive mucinous	40 (4)	19.8 (10.1 to 39.1)	
Colloid	9 (0.8)	NA	
Architectural grade			<b>&lt; .001</b>
Low	171 (15)	5.5 (2.8 to 10.8)	
Intermediate	686 (61)	16.6 (13.9 to 19.9)	
High	263 (23)	30.7 (25.3 to 37.2)	
Lymphatic invasion			<b>&lt; .001</b>
Absent	751 (67)	11.6 (9.4 to 14.4)	
Present	369 (33)	31.6 (27.0 to 37.0)	
Vascular invasion			<b>&lt; .001</b>
Absent	862 (77)	13.5 (11.2 to 16.2)	
Present	258 (23)	33.8 (28.2 to 40.5)	
Pleural invasion			<b>&lt; .001</b>
Absent	966 (86)	16.2 (13.9 to 18.9)	
Present	154 (14)	30.9 (24.0 to 39.8)	
Mutation			.11
Wild	326 (29)	20.6 (16.3 to 26.0)	
EGFR	96 (9)	12.8 (6.6 to 24.8)	
KRAS	133 (12)	16.2 (10.4 to 25.0)	
Adjuvant chemotherapy (stage IB)			.15
No	249 (90)	29.6 (24.1 to 36.4)	
Yes	24 (10)	21.5 (8.7 to 53.4)	

Abbreviations: CIR, cumulative incidence of recurrence; EGFR, epidermal growth factor receptor; NA, not applicable.

\*Significant *P* values (< .05) are shown in **bold** type.

†Lobectomy: pneumonectomy, bilobectomy, or lobectomy; sublobar resection: segmentectomy or wedge resection.

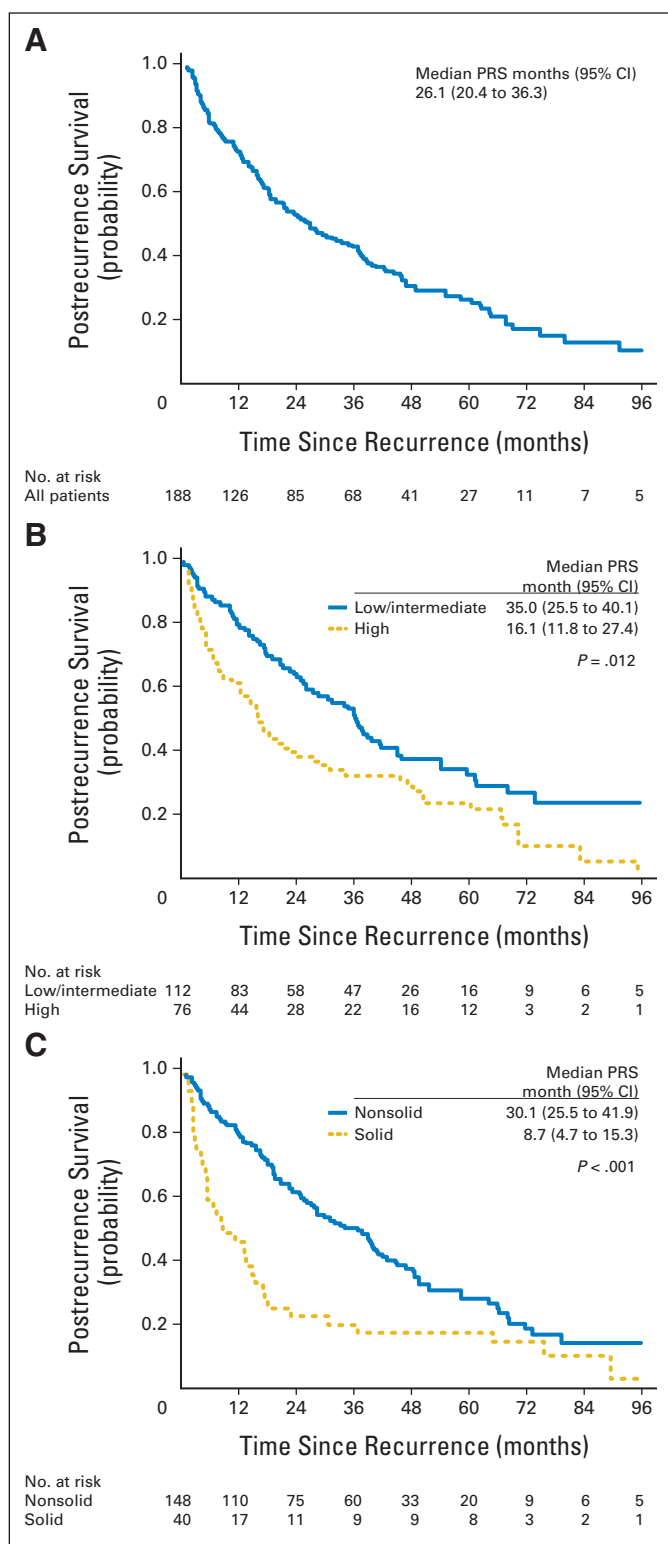
**Table 2.** Correlation Between Solid Predominant Histologic Pattern and Recurrence

Variable	Solid No. (%)	Nonsolid No. (%)	P*
Total No. of patients	40 (21)	148 (79)	
Recurrence pattern			<b>&lt; .001</b>
Locoregional	6 (15)	53 (36)	
Distant	24 (60)	76 (51)	
Both	10 (25)	19 (13)	
Recurrence pattern			<b>&lt; .001</b>
Intrathoracic	9 (23)	93 (63)	
Extrathoracic	31 (77)	55 (37)	
Recurrence pattern			<b>.011</b>
Single site	21 (53)	110 (74)	
Multiple site	19 (47)	38 (26)	
Bone metastasis			.51
Absent	30 (75)	119 (80)	
Present	10 (25)	29 (20)	
Brain metastasis			<b>.007</b>
Absent	28 (70)	131 (89)	
Present	12 (30)	17 (11)	
Contralateral lung			.82
Absent	32 (80)	122 (82)	
Present	8 (20)	26 (18)	
Pleural effusion			.84
Absent	35 (88)	126 (85)	
Present	5 (12)	22 (15)	
Adrenal metastasis			<b>.034</b>
Absent	34 (85)	141 (95)	
Present	6 (15)	7 (5)	
Distant lymph node metastasis			> .99
Absent	36 (90)	134 (91)	
Present	4 (10)	14 (9)	
Liver metastasis			<b>.038</b>
Absent	35 (88)	143 (97)	
Present	5 (12)	5 (3)	
Chest wall metastasis			> .99
Absent	39 (98)	142 (96)	
Present	1 (2)	6 (4)	
Recurrence-free interval, months			<b>.007</b>
≤ 24	30 (75)	75 (51)	
> 24	10 (25)	73 (49)	

\*Significant *P* values (< .05) are shown in **bold** type.

factors identified in the entire cohort (male, sublobar resection, stage IB, high architectural grade, and the presence of lymphatic, vascular, or pleural invasion) will be comparatively overrepresented among patients who recurred (Tables 1 and 3). We further evaluated risk

factors related to the primary tumor and postrecurrence risk factors. On univariable analysis, the risk factors related to the primary tumor that were associated with PRS were age older than 65 years ( $P = .003$ ), ever smoker ( $P = .037$ ), sublobar resection ( $P = .043$ ), vascular invasion ( $P = .019$ ), high architectural tumor grade ( $P = .012$ ; Fig 2B), and solid predominant histologic pattern ( $P < .001$ ; Fig 2C). On multivariable analysis, solid predominant histologic pattern (hazard ratio [HR], 1.76; 95% CI, 1.11 to 2.77;  $P = .016$ ), older age (HR, 1.63; 95% CI, 1.12 to 2.37;  $P = .01$ ), and sublobar resection (HR, 1.60; 95% CI, 1.12 to 2.29;  $P = .01$ ) remained independently associated with worse PRS. On univariable analysis of postrecurrence factors, age older than 65 years at recurrence ( $P = .003$ ), distant metastasis ( $P = .007$ ), multiple site recurrence ( $P = .001$ ), extrathoracic metastasis ( $P < .001$ ), and shorter ( $\leq 24$  months) recurrence-free interval ( $P = .034$ ) were significantly associated with worse PRS (Table 3). Of these factors, presence of distant (extrathoracic) metastasis (HR, 1.76; 95% CI, 1.13 to 2.76;  $P = .013$ ) and age older than 65 years at



**Fig 2.** (A) Postrecurrence survival (PRS) curve for patients with stage I lung adenocarcinoma. (B) PRS curves for patients with high-architectural grade tumors versus patients with low- and intermediate-architectural grade tumors. (C) PRS curves for patients with solid predominant tumors versus patients with nonsolid predominant tumors.

recurrence (HR, 1.70; 95% CI, 1.12 to 2.6;  $P = .014$ ) remained independent predictors of worse PRS on multivariable analysis (Table 4).

We compared 24 metastatic site (brain, 19; adrenal, five) morphology components with primary site morphology components. The predominant subtype of the metastatic sites in patients with primary tumors with solid predominant subtype was solid (100%). The solid predominant subtype occurred at a high frequency in metastatic sites, even in patients in whom the primary tumor showed other predominant subtypes (Appendix Table A4 and Appendix Fig A2A, online only). At metastatic sites, the solid morphology component had the greatest increase compared with any other component (Appendix Fig A2B).

## DISCUSSION

In this study, we have shown that high architectural grade tumors carry a high risk of recurrence after surgical resection and, among patients who recur, are associated with a uniquely unfavorable PRS. Of importance, we have identified that the risk of recurrence for tumors with solid predominant histologic subtype peaked within 12 months and that these tumors were associated with a higher incidence of extrathoracic, multiple-site recurrences in patients with stage I lung adenocarcinoma. Furthermore, our study showed that, in the selected group of patients who recurred after initial surgical resection for stage I lung adenocarcinoma, several factors determined at the time of initial surgery (solid predominant histologic pattern, sublobar resection, and age older than 65 years) were independently associated with worse PRS; among factors determined at time of recurrence, distant (extrathoracic) metastases and age older than 65 years at recurrence were independently associated with worse PRS.

The effect of disease pathology on recurrence has been reported before by our group and others; we were able to confirm it in a large, single-center cohort in this study. Furthermore, we focused on PRS to assess whether the effect of morphology on the primary tumor extends beyond affecting risk of recurrence and if, for patients who recur, it increases likelihood of early death.

The strengths of our study are that it includes the largest cohort of patients with stage I lung adenocarcinoma published to date with a median follow-up of 60 months, comprehensive clinicopathologic and histologic assessment were performed, detailed analysis of recurrence patterns was documented, and to the best of our knowledge, this is the first study to analyze recurrence patterns and PRS in relation to the IASLC/ATS/ERS classification. Investigation of the hazard function<sup>27-29</sup> indicated that the instantaneous risk of recurrence was highest and the risk of recurrence peaked earlier for solid predominant tumors than for the other tumor types. Most recurrences, including recurrences from solid predominant tumors, occurred within 2 years of surgery. Although our findings support the importance of routine CT surveillance, in accordance with National Comprehensive Cancer Network guidelines, we have shown that regular surveillance is even more important when tumors of aggressive predominant subtypes (eg, solid predominant histologic pattern) are present.

Our previous publications have documented that the solid predominant subtype and the presence of solid pattern are associated with poor prognostic factors: higher maximum standardized uptake value on preoperative PET scan,<sup>30</sup> higher mitotic count,<sup>8</sup> visceral pleural invasion,<sup>31</sup> high grade of tumor budding,<sup>32</sup> presence of tumor

**Table 3.** Patient Characteristics and Univariable Analyses of Postrecurrence Survival

Characteristic	No. (%)	Median PRS (95% CI), Months	P*
Total No. of patients	188	26.1 (20.4 to 36.3)	
Primary tumor factor			
Age at surgery, years			
≤ 65	73 (39)	37.1 (22.6 to 62.5)	<b>.003</b>
> 65	115 (61)	21.2 (16.1 to 28.7)	
Sex			
Female	104 (55)	23.4 (17.3 to 38.2)	.66
Male	84 (45)	26.3 (21.2 to 38.1)	
Smoking history			
Never	28 (15)	46.5 (27.4 to NA)	<b>.037</b>
Ever	160 (85)	23.4 (17.5 to 32.8)	
Surgical procedure†			
Lobectomy	113 (60)	29.5 (21.1 to 42.1)	<b>.043</b>
Sublobar resection	75 (40)	20.7 (14.8 to 34.3)	
T factor			
T1a	83 (44)	27.5 (19.0 to 45.5)	.61
T1b	33 (18)	30.8 (22.9 to 45.7)	
T2a	72 (38)	17.4 (13.2 to 38.1)	
Pathologic stage			
IA	116 (62)	27.5 (22.9 to 38.2)	.62
IB	72 (38)	17.4 (13.2 to 38.1)	
Predominant histologic subtype			
Lepidic	8 (4)	NA	<b>&lt; .001</b>
Acinar	69 (37)	27.6 (22.6 to 39.1)	
Papillary	35 (19)	38.1 (28.7 to NA)	
Micropapillary	26 (14)	43.8 (17.6 to NA)	
Solid	40 (21)	8.7 (4.7 to 15.3)	
Invasive mucinous	8 (4)	NA	
Colloid	2 (1)	NA	
Architectural grade			
Low and intermediate	112 (60)	35.0 (25.5 to 40.1)	<b>.012</b>
High	76 (40)	16.1 (11.8 to 27.4)	
Solid predominant			
No	148 (79)	30.1 (25.5 to 41.9)	<b>&lt; .001</b>
Yes	40 (21)	8.7 (4.7 to 15.3)	
Micropapillary predominant			
No	162 (86)	26.1 (18.9 to 36.2)	.68
Yes	26 (14)	43.8 (17.6 to N/A)	
Lymphatic invasion			
Absent	80 (43)	28.7 (16.3 to 45.5)	.96
Present	108 (57)	26.1 (20.4 to 36.3)	
Vascular invasion			
Absent	107 (57)	36.5 (25.5 to 45.7)	<b>.019</b>
Present	81 (43)	17.4 (14.8 to 31.6)	
Pleural invasion			
Absent	144 (77)	27.5 (20.7 to 37.4)	.53
Present	44 (23)	17.2 (10.1 to 41.9)	
Postrecurrence factor			
Age at recurrence, years			
≤ 65	53 (28)	45.7 (20.4 to NA)	<b>.007</b>
> 65	135 (72)	23.4 (17.4 to 32.8)	
Recurrence pattern			
Locoregional only	59 (31)	42.1 (31.6 to 60.3)	<b>.007</b>
Distant	129 (69)	17.6 (15.2 to 27.4)	
Recurrence site			
Single site	131 (70)	35.0 (26.2 to 43.8)	<b>.001</b>
Multiple site	57 (30)	11.4 (6.2 to 17.5)	

(continued on next column)

**Table 3.** Patient Characteristics and Univariable Analyses of Postrecurrence Survival (continued)

Characteristic	No. (%)	Median PRS (95% CI), Months	P*
Intrathoracic	102 (54)	41.9 (32.8 to 55.0)	<b>&lt; .001</b>
Extrathoracic	86 (46)	12.0 (9.8 to 17.5)	
Recurrence-free interval, months			
≤ 24	105 (56)	17.2 (14.0 to 26.2)	<b>.034</b>
> 24	83 (44)	37.4 (31.6 to 48.3)	

Abbreviations: NA, not applicable; PRS, postrecurrence survival.

\*Significant P values (< .05) are shown in **bold** type.

†Lobectomy: pneumonectomy, bilobectomy, or lobectomy; sublobar resection: segmentectomy or wedge resection.

spread throughout the alveolar space,<sup>33</sup> high risk of occult lymph node metastases,<sup>34</sup> thyroid transcription factor-1 negativity,<sup>35</sup> and less frequent epidermal growth factor receptor (EGFR) mutations.<sup>36</sup> Our finding of a correlation between the presence of solid pattern and unfavorable prognosis is consistent with the observations of others. Bryant et al<sup>37</sup> reported that tumors with solid pattern had more genes promoting cell proliferation, which correlated with decreased survival, compared with tumors without solid pattern.

We have shown that the presence of micropapillary pattern in stage I lung adenocarcinoma is associated with a higher incidence of locoregional recurrence.<sup>19</sup> By analyzing patterns of relapse in this study, we have shown that the solid predominant subtype is correlated with distant (extrathoracic) metastasis and multiple-site recurrence in patients with primary lung adenocarcinoma; there were especially high rates of metastasis to the brain, contralateral lung, and liver (Table 2). In this study, the solid subtype was predominant in two thirds of the metastatic tissues (brain and adrenal metastases) examined (n = 24; Appendix Table A4). Clay et al<sup>38</sup> showed that the presence of solid histologic subtype at the site of metastasis was associated with shorter OS. These observations highlight the importance

**Table 4.** Multivariable Analysis in Predicting Postrecurrence Survival

Factor	HR	95% CI	P*
Primary tumor factors			
Age at diagnosis (> 65 v ≤ 65 years)	1.63	1.12 to 2.37	<b>.01</b>
Smoking (ever v never)	1.64	0.94 to 2.88	.083
Surgical procedure (sublobar resection v lobectomy)	1.6	1.12 to 2.29	<b>.01</b>
Vascular invasion (present v absent)	1.41	0.97 to 2.06	.073
Histologic pattern			
High-grade v low- or intermediate-grade SOL	1.76	1.11 to 2.77	<b>.016</b>
High-grade v low- or intermediate-grade non-SOL†	1.2	0.75 to 1.91	.44
Postrecurrence factors			
Age at recurrence (> 65 v ≤ 65 years)	1.7	1.12 to 2.6	<b>.014</b>
Recurrence-free interval (≤ 24 v > 24 months)	1.22	0.84 to 1.77	.31
Recurrence pattern (multiple-site v single-site)	1.5	0.99 to 2.28	.058
Distant, intrathoracic v locoregional	0.88	0.51 to 1.49	.62
Distant, extrathoracic v locoregional	1.76	1.13 to 2.76	<b>.013</b>

Abbreviations: HR, hazard ratio; SOL, solid predominant.

\*Significant P values (< .05) are shown in **bold** type.

†High-grade: SOL v non-SOL, P = .19.

of performing a molecular characterization of solid lung adenocarcinomas to identify novel molecular targets. Our observations and those of others show that, despite curative-intent surgical resection, solid predominant histologic pattern is associated with an aggressive metastasis and recurrence profile, thereby providing a rationale for investigating the role of adjuvant therapies for this cohort of patients.

For early-stage lung adenocarcinoma, the predictive effect of the new classification system on adjuvant chemotherapy or radiotherapy remains unknown. Recently, in patients with advanced lung adenocarcinoma, Warth et al<sup>39</sup> demonstrated that histologic pattern of the tumor influenced the effect of adjuvant chemoradiotherapy; in particular, solid predominant tumors had improved prognoses with adjuvant radiotherapy. However, this predictive effect of histologic pattern was not significant on multivariable analysis.

Publications from our group<sup>36</sup> and others<sup>40</sup> have shown that solid predominant lung adenocarcinomas are less likely to harbor EGFR mutations and more likely to harbor KRAS mutations compared with other predominant subtypes. This finding implies that there is currently no actionable target for the treatment of most solid lung adenocarcinomas. Extended molecular and clinicopathologic analysis of lung adenocarcinomas revealed an association between KRAS mutation and both solid histologic subtype and tumor-infiltrating lymphocytes.<sup>41</sup> Zhang et al<sup>42</sup> have shown that lung adenocarcinomas with positive programmed death-ligand 1 staining were most likely to be the solid predominant subtype. From these observations, it is tempting to speculate that immunotherapies can play a role in the treatment of solid predominant lung adenocarcinomas. Ongoing clinical trials on checkpoint blockade should document the histologic subtype of the lung adenocarcinomas encountered.

In conclusion, prognostic stratification using the IASLC/ATS/ERS classification system can be readily implemented in the treatment

of patients with early-stage lung adenocarcinoma. Future clinical studies should collect data on the histologic subtype of the lung adenocarcinomas encountered, which may yield more accurate information on the relationship between subtype, risk of recurrence, and PRS and lead to improvements in the clinical assessment of and the therapeutic strategies for recurrent non-small-cell lung cancer. Our finding of early, multisite, extrathoracic metastases in patients with solid predominant stage I lung adenocarcinoma who have undergone curative-intent resection underlines the need to investigate adjuvant therapeutic strategies for these patients.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Solid Predominant Histologic Subtype in Resected Stage I Lung Adenocarcinoma Is an Independent Predictor of Early, Extrathoracic, Multisite Recurrence and of Poor Postrecurrence Survival**

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**Appendix****Table A1.** Postrecurrence Survival of Patients in Previous Stage I NSCLC Series

Reference	Year of Publication	No. of Patients	Histologic Profile	Recurrence	Recurrence No. (%)	PRS		Independent Factors of Poor PRS
						Duration	%	
Current study	2014	1,120	ADC: 1,120	ADC: 188	188 (17) LR: 59 (31) D: 100 (53) LR + D: 29 (15)	1-year	67	Solid predominant histologic pattern Sublobar resection Old age Distant (extrathoracic) metastasis
						2-year	45	
						3-year	36	
						5-year	14	
Shimada et al <sup>10</sup>	2013	919	ADC: 706 Non-ADC: 213	ADC: 124 Non-ADC: 46	170 (18) LR: 43 (25) D: 113 (66) LR + D: 14 (9)	1-year	73	Male sex Non-postrecurrence therapy Poorly differentiated
						2-year	51	
Song et al <sup>11</sup>	2013	475	NSCLC	ADC: 46 SCC: 15 Other: 11	72 (15) LR: 36 (50) D: 36 (50)	1-year	88	Recurrence-free interval ≤ 12 months Bad response for treatment
						3-year	53	
Nakagawa et al <sup>12</sup>	2008	397	ADC: 300 SCC: 89 Other: 8	NA	87 (22) LR: 30 (34.5) D: 57 (65.5)	1-year	67	Non-postrecurrence therapy (surgery); symptoms at recurrence: liver or cervico-mediastinum metastasis
						3-year	35	
Hung et al <sup>13</sup>	2009	933	NSCLC	ADC: 45 SCC: 60 Other: 18	LR: 123 (13) LR: 74 LR + D: 49	1-year	48	Non-postrecurrence therapy (surgery, chemotherapy, and/or radiotherapy)
						2-year	19	
Hung et al <sup>14</sup>	2010	933	NSCLC	ADC: 95 SCC: 46 Other: 25	D: 166 (18) Single: 106 Multiple: 60	1-year	38	Non-postrecurrence therapy Recurrence-free interval ≤ 16 months
						2-year	19	
Hung et al <sup>9</sup>	2013	283	ADC: 283	ADC: 283	57 (20)	2-year	72.3	Solid predominant ( $P = .074$ ; not significant); non-papillary predominant ( $P = .056$ ; not significant)
						5-year	31.6	

Abbreviations: ADC, adenocarcinoma; D, distant metastasis; LR, locoregional recurrence; NA, not applicable; NSCLC, non-small-cell lung cancer; PRS, postrecurrence survival; SCC, squamous cell carcinoma.

Postrecurrence Survival in Stage I Lung Adenocarcinoma

**Table A2.** Characteristics of the 188 Patients Who Experienced Recurrence

Characteristic	No.	%
<b>Location</b>		
Locoregional	59	31
Regional lymph nodes	13	
Same side	34	
Residual lobe (sublobar resection)	9	
Staple line	5	
Distant metastasis	100	53
Single site	73	
Multisite	27	
Both (locoregional and distant)	29	15
Intrathoracic only	102	54
Extrathoracic	86	46
<b>Distant metastasis location*</b>		
Bone	39	
Contralateral lung	34	
Brain	29	
Pleural disease	27	
Distant lymph node	18	
Adrenal	13	
Liver	10	
Chest wall	7	
Other	8	
<b>Detection method</b>		
Scheduled computed tomography scan	123	65
Locoregional	56	
Distant metastasis	67	
Symptoms	60	32
Locoregional	2	
Distant metastasis	58	
Other (carcinoembryonic antigen)	4	2
Unknown	1	1
<b>Initial therapy of recurrence</b>		
Single therapy	120	64
Chemotherapy	49	
Radiation therapy	37	
Surgery	32	
Radiofrequency ablation	2	
Multimodality therapy	37	20
Chemotherapy + radiation therapy	17	
Surgery + radiation therapy	11	
Surgery + chemotherapy	8	
Surgery + chemotherapy + radiation therapy	1	
Palliative therapy	2	1
Observation	5	3
Unknown	24	13

\*Sites of multiple metastases were counted individually.

**Table A3.** First-Line Chemotherapy Regimen (N = 49)

Regimen	No. of Patients
Platinum-based chemotherapy	
Cisplatin (1) or carboplatin (1) + paclitaxel	2
Cisplatin (1) or carboplatin (2) + docetaxel	3
Cisplatin (1) or carboplatin (4) + gemcitabine	5
Cisplatin (2) or carboplatin (3) + pemetrexed	5
Bevacizumab/platinum combination	
Bevacizumab + carboplatin (3) + paclitaxel	3
Bevacizumab + cisplatin (4) or carboplatin (5) + pemetrexed	9
EGFR tyrosine kinase inhibitor	
Erlotinib	8
Gefitinib	1
Single-agent chemotherapy	
Paclitaxel	1
Pemetrexed	5
Gemcitabine	1
Other	
Clinical trial	3
Mitomycin + vinorelbine	1
Unknown*	2

\*Platinum-based therapy was administered at an outside hospital; additional details are unknown.

**Table A4.** Predominant Morphology of Primary and Metastatic Sites

Patient	Primary Site		Metastatic Site		
	Major Type	Secondary Type	Site	Major Type	Secondary Type
1	Acinar	Papillary	Brain	Papillary	Acinar
2	Acinar	Micropapillary	Brain	Micropapillary	Papillary
3	Acinar	Papillary	Brain	Micropapillary	Acinar
4	Acinar	Papillary	Brain	Solid	Acinar
5	Acinar	Papillary	Brain	Solid	Papillary
6	Acinar	Solid	Brain	Solid	—
7	Acinar	Solid	Adrenal	Solid	—
8	Papillary	Lepidic	Brain	Papillary	Micropapillary
9	Papillary	Acinar	Brain	Micropapillary	Papillary
10	Papillary	Acinar	Brain	Micropapillary	Papillary
11	Papillary	Micropapillary	Brain	Micropapillary	Solid
12	Papillary	Solid	Adrenal	Solid	Acinar
13	Micropapillary	Papillary	Brain	Papillary	Micropapillary
14	Micropapillary	Papillary	Brain	Micropapillary	Papillary
15	Solid	Micropapillary	Brain	Solid	Micropapillary
16	Solid	Micropapillary	Brain	Solid	Micropapillary
17	Solid	Acinar	Brain	Solid	Acinar
18	Solid	Papillary	Adrenal	Solid	Micropapillary
19	Solid	Acinar	Brain	Solid	Papillary
20	Solid	Acinar	Brain	Solid	—
21	Solid	Papillary	Brain	Solid	—
22	Solid	Acinar	Adrenal	Solid	—
23	Solid	—	Adrenal	Solid	—
24	Colloid	Acinar, solid	Brain	Solid	Acinar

Postrecurrence Survival in Stage I Lung Adenocarcinoma

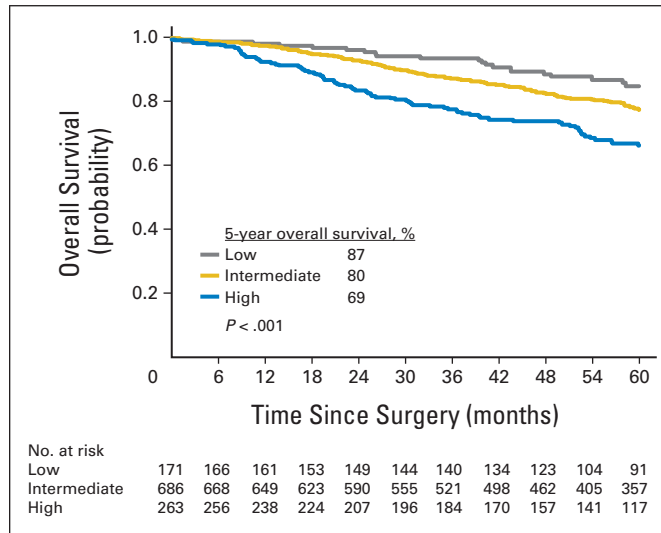


Fig A1. Overall survival of patients with stage I lung adenocarcinoma for each architectural grade.

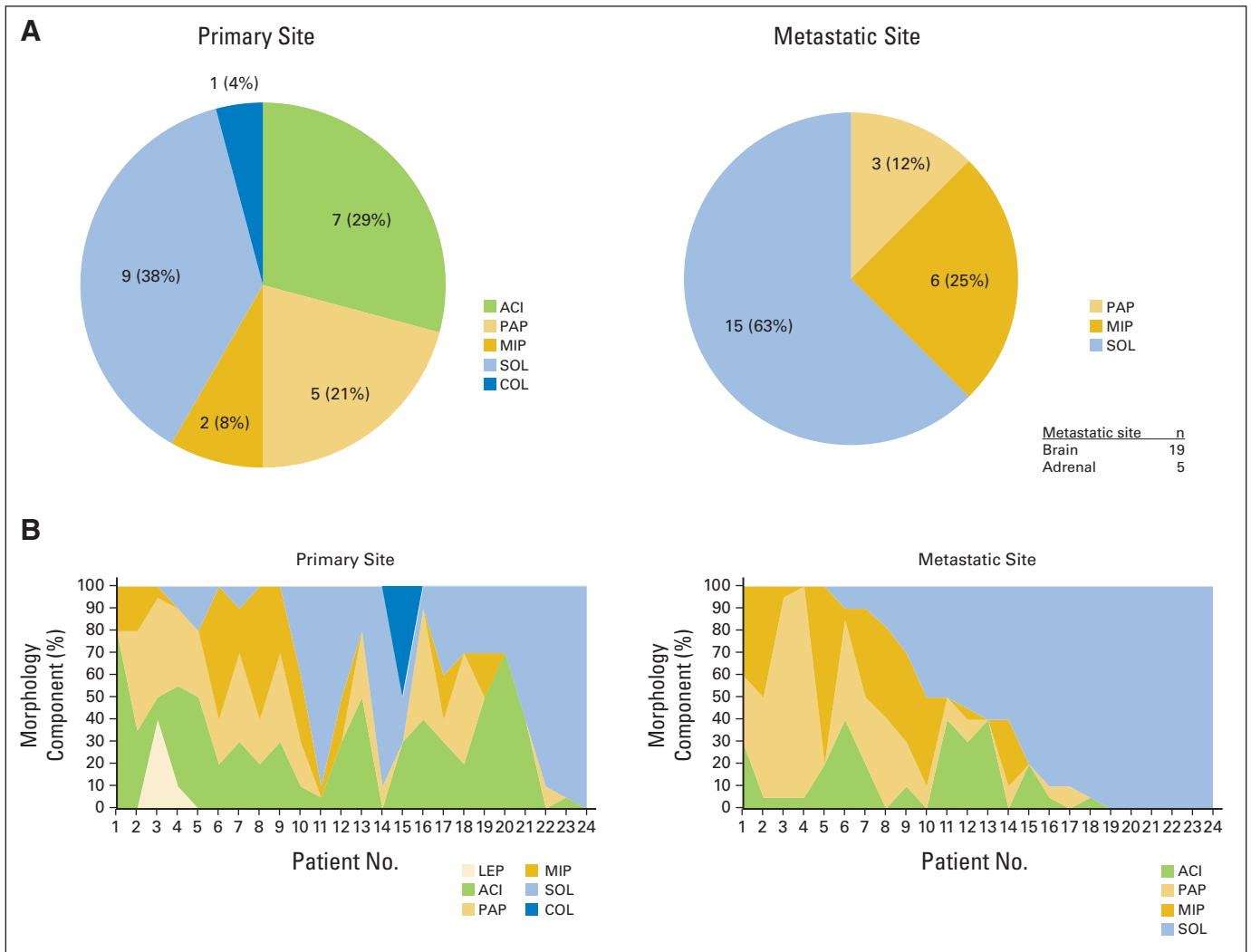


Fig A2. (A) Predominant morphology of primary site and metastatic site. (B) Morphology component of primary site and metastatic site. ACI, acinar predominant (invasive adenocarcinoma); COL, colloid predominant (invasive adenocarcinoma); LEP, lepidic predominant; MIP, micropapillary predominant (invasive adenocarcinoma); PAP, papillary predominant (invasive adenocarcinoma); SOL, solid predominant (invasive adenocarcinoma).