Prognostic Factors of Survival after Recurrence in Patients with Resected Lung Adenocarcinoma

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Objective: Recurrence after surgical resection is the most common cause of treatment failure in patients with non–small-cell lung cancer. The aim of the study is to investigate the prognostic factors of postrecurrence survival (PRS) in patients of resected lung adenocarcinoma.

Methods: The clinicopathological characteristics of 179 patients with recurrence after complete resection of lung adenocarcinoma at Taipei Veterans General Hospital between 2004 and 2010 were retrospectively reviewed. The prognostic and predictive effects of these clinicopathological variables in PRS were analyzed.

Results: The pattern of recurrence included local only in 25 (15.4%), distant only in 56 (34.6%), and both local and distant in 81 (50.0%) of patients. The 2-year and 5-year PRS were 65.2% and 29.8%, respectively. The most common organ sites of metastasis were the contralateral lung (39.1%), followed by the brain (33.5%) and the bone (31.3%). Multivariate analysis revealed that micropapillary/solid predominant pattern group (versus acinar/papillary; hazard ratio = 2.615; 95% confidence interval: 1.395–4.901; $p = 0.003$) and no treatment for recurrence ($p < 0.001$) were significant prognostic factors of worse PRS. For patients receiving treatment for recurrence, micropapillary/solid predominant pattern group (versus acinar/papillary; hazard ratio = 2.570; 95% confidence interval: 1.357–4.865; $p = 0.004$) was a significant predictive factor of worse PRS. Treatment for recurrence with surgery ($p = 0.067$) tended to be a significant predictive factor of better PRS.

Conclusions: In lung adenocarcinoma, micropapillary/solid predominant pattern group (versus acinar/papillary) was a significant poor prognostic factor for PRS.

Key Words: Lung adenocarcinoma, Postrecurrence survival, Prognostic factor, Predictive factor, Histology.

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Lung cancer is the main cause of cancer-related death worldwide. Surgical resection is the treatment of choice for early-stage non—small-cell lung cancer (NSCLC).[1–5] Tumor recurrence after surgical resection is the most common cause of treatment failure.[3–9] The recurrence rates in resected stage I NSCLC range between 22% and 38%.[3–7] Even with multimodality treatments, including chemotherapy, radiotherapy, or a combination of other therapeutic modalities, most patients with recurrence after resection have little possibility of cure.[6,9–11] Postrecurrence survival (PRS) in resected NSCLC is poor.[3–9,12,13] Several studies have demonstrated the prognostic factors of PRS in patients with resected NSCLC after recurrence.[3–9,12–15] Treatment for recurrence and disease-free interval are significant prognostic predictors for PRS in resected NSCLC with recurrence.[12–15] However, most published reports investigated the predictors of PRS in resected NSCLC, without separating lung adenocarcinoma from squamous cell carcinoma. Adenocarcinoma and squamous cell carcinoma are the most common histological types of NSCLC.[16,17] Several major differences exist between the two histological subtypes.[18–20] Therefore, demonstration of the prognostic and predictive factors separately in squamous cell carcinoma and adenocarcinoma is necessary. The predictors of PRS in resected lung adenocarcinoma have not been well demonstrated in the literature.

In 2011, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society proposed a new classification system of lung adenocarcinoma.[21] They recommended the use of comprehensive histological subtyping to assess histologic patterns

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semiquantitatively in 5% increments to choose a single predominant pattern (lepidic, acinar, papillary, micropapillary, or solid) for invasive adenocarcinomas.[21] Several studies have reported the significant prognostic value of the new classification on death and recurrence in lung adenocarcinoma.[22–25] However, the prognostic value of the new classification in PRS of resected lung adenocarcinoma has not been investigated.

In our previous studies,[12,13] we have demonstrated the patterns of recurrence and prognostic factors of PRS in resected stage I NSCLC after local recurrence or distant metastasis. We have also shown that patients with micropapillary/solid predominant patterns of lung adenocarcinoma had significantly worse prognosis.[26,27] In this article, we focus on the prognostic factors of PRS in patients of resected lung adenocarcinoma with recurrence.

PATIENTS AND METHODS

From January 2004 to December 2010, all patients underwent complete resection for lung adenocarcinomas at Taipei Veterans General Hospital were retrospectively reviewed. Patients undergoing neoadjuvant chemotherapy or with stage IV disease were excluded. A total of 590 patients were eligible for the study. The preoperative staging workup was routinely performed as previously described.[12,13,26–28] Mediastinoscopy was performed only when enlarged mediastinal lymph nodes (diameter > 1.0 cm) were shown by computed tomography scan. Positron emission tomography scan was available as a staging modality in 177 (30.0%) of the 590 patients. Complete resection of lung cancer and mediastinal lymph nodes dissection/sampling were performed as previously described.[12,13,26–28] One hundred and eighty-six (31.5%) of the 590 patients developed recurrence after surgical resection. Seven (3.8%) of the 186 patients were diagnosed as lepidic predominant adenocarcinoma. The number of patients with lepidic predominant adenocarcinoma was small when compared with the other four subtypes of adenocarcinoma. Because of small number and lack of complete follow-up in five of the seven patients with lepidic predominant adenocarcinoma, the seven patients with lepidic predominant adenocarcinoma were excluded for analysis. Of the two patients with known pattern of recurrence, one (lepidic, 60%; acinar, 10%; papillary, 20%; solid, 10%) developed ipsilateral lung metastasis during follow-up. The other patient (lepidic, 40%; acinar, 30%; colloid, 30%) developed bilateral lung-to-lung metastasis during follow-up. The remained 179 patients were included for analysis in this study. Determination of disease stages were based on the tumor, node, metastasis (TNM) classification (7th edition) of the American Joint Committee on Cancer and the International Union Against Cancer.[29,30] All resected specimens were formalin fixed and stained with hematoxylin and eosin.[27] Each tumor was reviewed using comprehensive histological subtyping, recording the percentage of each histologic component (lepidic, acinar, papillary, micropapillary, and solid) in 5% increments as previous described.[27] For tumors with diameter of 3 cm or smaller, the entire tumors were submitted for microscopic assessment. For tumors with diameter greater than 3 cm, at least 1 section was taken in every additional 1-cm breadth of the greatest tumor dimension for microscopic assessment. The predominant pattern is defined according to the most dominant pattern.

All patients were followed-up at our outpatient department quarterly in the first 2 years after resection and semiannually thereafter. The modalities and protocols during follow-up were used as previously described.[26,27] Computed tomography scans of chest and upper abdomen were routinely done in every scheduled outpatient department visit for follow-up. Nuclear medicine survey of the bone was arranged every 6 months in the first 2 years after resection and annually thereafter during follow-up. Suspicious bony lesions were confirmed by radiography or bone biopsy. Computed tomographic scan of brain was done when neurological symptoms occurred or when clinical suspicions were raised. Once a metastasis was discovered, a routine investigation was arranged to look for other metastatic sites. After initial diagnosis of recurrence, further examinations were arranged to discover other metastatic sites if symptoms occurred or clinical suspicions were raised. The hospital charts of all patients were reviewed to collect data of patterns of recurrence, organ sites of recurrence, and treatment for recurrence. Data collected from telephone call and correspondence letters during follow-up were also included.

To investigate their impact on PRS, clinicopathologic factors were examined in univariate and multivariate analyses. Local recurrence was defined as tumor recurrence in contiguous anatomical sites, including the ipsilateral hemithorax and mediastinum after surgical resection. Distant metastasis was defined as tumor recurrence in the contralateral lung or outside the hemithorax and mediastinum after surgical resection. Local-only recurrence was defined as only local recurrence identified from initial operation to death or last follow-up. Distant-only metastasis was defined as only distant metastasis discovered from initial operation to death or last follow-up. Secondary primary lung cancer was differentiated from recurrent NSCLC in patients undergoing surgical resection or biopsy according to the criteria proposed by Girard et al.[31] For those not undergoing resection or biopsy, judgment was made according to clinical course, eg, progression or aggressive clinical behavior (multiple lesions). The length of PRS was defined as the interval in months from the date of initial recurrence identified to death or the date of the last follow-up.

The PRS was calculated by the Kaplan–Meier method.[32] The log-rank test was used to make group comparisons. Univariate and multivariate analyses were performed by means of the Cox proportional hazards model using SPSS software (version 20; IBM, Armonk, NY). All variables with p value less than 0.1 in univariate analysis were entered into multivariate analysis. Age at recurrence, sex, adjuvant therapy, and pattern of recurrence were also entered for mutual adjustment despite p value greater than 0.1. Statistical significance was defined as p value less than 0.05.

RESULTS

The median follow-up time for these 179 patients was 47.3 months (range, 3.2–110.0 months). The median time to recurrence was 18.0 months (range, 0.7–93.4 months). The 2-year and 5-year PRS were 65.2% and 29.8%, respectively

(Fig. 1). On the last follow-up session, 90 (50.3%) patients were alive, 88 (49.3%) patients died, and 1 (0.6%) patient was with unknown survival status. The characteristics of the 179 patients are listed in Table 1. Treatments for recurrence included surgery alone in two patients, surgery with any of chemotherapy (C/T), radiotherapy (R/T), and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy in 24, C/T alone in 28, R/T alone in 11, EGFR TKI therapy alone in 8, and a combination of C/T or R/T or EGFR TKI in 86 patients. Five (2.8%) patients had no treatment after recurrence (four patients were because of poor performance status and one refused treatment).

Organ Sites of Recurrence

The pattern of recurrence and frequency of organ sites of distant metastases are listed in Table 2. The pattern of recurrence included local only in 25 (15.4%), distant only in 56 (34.6%), and both local and distant in 81 (50.0%) of patients. Among these patients, 30 (16.8%) presented with pleural seeding/effusion, 70 (39.1%) presented with contralateral lung, 60 (33.5%) presented with brain, 56 (31.3%) presented with bone, 14 (7.8%) presented with liver, and 7 patient (3.9%) presented with adrenal gland metastases. Of the whole cohort of 590 patients, several patients with ipsilateral or contralateral lung tumors underwent resection and were diagnosed as secondary primary lung cancer according to the criteria proposed by Girard et al.[31] These patients were not included in this study because they were not considered to have recurrent or metastasis disease. For patients with ipsilateral or contralateral lung nodules not undergoing resection, the decision of secondary primary lung cancer or metastasis was sometimes difficult. In our study, the majority of the patients presented with ipsilateral or contralateral lung metastasis were judged by clinical course. Most of them presented with multiple ipsilateral, contralateral or bilateral pulmonary nodules, or demonstrated with aggressive clinical behavior.

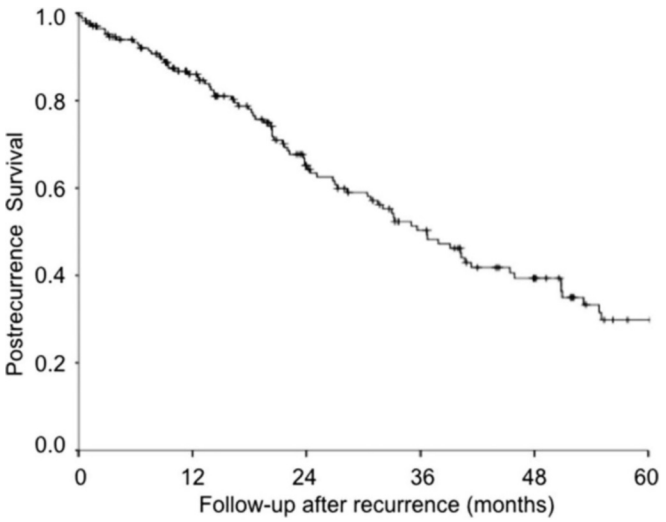

FIGURE 1. Cumulative probability of postrecurrence survival in 179 patients of resected lung adenocarcinoma with recurrence.

TABLE 1. Characteristics of 179 Patients of Resected Lung Adenocarcinoma with Recurrence

Variables	Data
Age at recurrence, years (mean ± SD)	66.0 ± 11.3
Sex, n (%)	
Male	102 (57.0)
Female	77 (43.0)
Tumor size, cm (mean ± SD)	3.4 ± 1.4
Extent of pulmonary resection, n (%)	
Sublobar resection	19 (10.6)
Lobectomy	157 (87.7)
Bilobectomy	3 (1.7)
T status, n (%)	
T1a	14 (7.8)
T1b	12 (6.7)
T2a	118 (65.9)
T2b	5 (2.8)
T3	22 (12.3)
T4	8 (4.5)
N status, n (%)	
N0	76 (42.5)
N1	38 (21.2)
N2	65 (36.3)
TNM stage, n (%)	
IA	12 (6.7)
IB	50 (27.9)
IIA	32 (17.9)
IIB	11 (6.1)
IIIA	71 (39.7)
IIIB	3 (1.7)
Visceral pleural invasion, n (%)	
Absent	40 (22.3)
Present	133 (74.4)
Unknown	6 (3.4)
Angiolymphatic invasion, n (%)	
Absent	86 (48.1)
Present	82 (45.8)
Unknown	11 (6.1)
Histological grade, n (%)	
Well differentiated	2 (1.1)
Moderately differentiated	90 (50.3)
Poorly differentiated	77 (43.0)
Unknown	10 (5.6)
Adjuvant therapy, n (%)	
No	75 (41.9)
With C/T	95 (53.1)
With R/T	4 (2.2)
With C/T and R/T	5 (2.8)
Predominant pattern, n (%)	
Acinar	47 (26.3)
Papillary	43 (24.0)
Micropapillary	54 (30.2)
Solid	35 (19.5)

(*Continued*)

TABLE 1. (Continued)

Variables	Data
Disease-free interval, mo (median [IQR])	18.0 (9.4–28.1)
Treatment for recurrence, n (%)	
None	5 (2.8)
With surgery	26 (14.5)
Surgery alone	2
Surgery and (any of C/T or R/T or EGFR TKI therapy)	24
C/T and/or R/T and/or EGFR TKI therapy	133 (74.3)
C/T alone	28
R/T alone	11
EGFR TKI therapy alone	8
C/T and EGFR TKI therapy	34
C/T and R/T	19
R/T and EGFR TKI therapy	7
C/T and R/T and EGFR TKI therapy	26
Unknown	15 (8.4)

SD, Standard deviation; IQR, interquartile range; C/T, chemotherapy; R/T, radiotherapy; EGFR, epidermal growth factor receptor; TKI; tyrosine kinase inhibitor; TNM, tumor, node, metastasis.

PRS Analysis

Univariate analysis indicated that N2 (versus N0 or N1; $p = 0.006$), TNM stage III (versus stage I or II; $p = 0.020$), micropapillary/solid predominant pattern group (versus acinar/papillary; $p = 0.009$), bone metastasis ($p = 0.036$), liver metastasis ($p = 0.033$), and no treatment for recurrence (versus with surgery, $p < 0.001$; versus C/T and/or R/T and/or EGFR TKI therapy, $p < 0.001$) were significant prognostic factors of worse PRS (Table 3) (see Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/JTO/A852, for complete results of the univariate analysis). Larger tumor size ($p = 0.066$) and disease-free interval less than or equal to 18 months (versus >18 months; $p = 0.056$) tended to be significant prognostic factors of worse PRS.

Predominant pattern group and treatment for recurrence were still significant prognostic indicators in multivariate analysis (Table 3). Patients with micropapillary/solid predominant pattern (hazard ratio [HR] = 2.615; 95% confidence interval [CI]: 1.395–4.901; $p = 0.003$) had significantly worse PRS than those with acinar/papillary predominant pattern. Patients received treatment for recurrence with surgery (HR = 0.053; 95% CI: 0.014–0.199; $p < 0.001$) or with C/T and/or R/T and/or EGFR TKI therapy (HR = 0.122; 95% CI: 0.040–0.368; $p < 0.001$) had significantly better PRS than those received no treatment for recurrence. Patients received adjuvant C/T (HR = 0.441; 95% CI: 0.210–0.926; $p = 0.030$) after initial resection had significantly better PRS than those without adjuvant therapy.

PRS Analysis in Patients Undergoing Treatment for Recurrence

Although no treatment for recurrence was a significant prognostic factor of worse PRS, only five patients had no treatment in our study. Furthermore, whether undergoing treatment for recurrence or not was unknown in 15 of the 179 patients. To identify prognostic and predictive factors in a more realistic clinical scenario, we excluded the 20 patients. The remained 159 patients undergoing treatment for recurrence in the second cohort were included for further analysis of predictive factors for PRS. There was no significant association between pattern of recurrence and treatment for recurrence with surgery ($p = 0.538$; see Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/JTO/A852). Univariate analysis indicated that N2 (versus N0 or N1) ($p = 0.004$), TNM stage III (versus stage I or II; $p = 0.012$), micropapillary/solid predominant pattern group (versus acinar/papillary; $p = 0.008$; Fig. 2), bone metastasis ($p = 0.048$), and liver metastasis ($p = 0.034$) were significant prognostic factors of worse PRS (Table 4; see Supplementary Table 3, Supplemental Digital Content, http://links.lww.com/JTO/A852, for complete results of the univariate analysis). EGFR mutation status was only available in 43 (27.0%) of the 159 patients undergoing treatment for recurrence. EGFR activated mutation and wild type were identified in 35 and 8 patients, respectively. In univariate analysis, EGFR activated mutation was not a prognostic factor for PRS ($p = 0.732$). Treatment for recurrence with EGFR TKI therapy ($p = 0.044$) was a significant prognostic factor of better PRS (Table 4). Greater tumor size ($p = 0.062$), disease-free interval less than

TABLE 2. The Pattern of Recurrence and the Frequency of Organ Sites of Distant Metastases in 179 Patients of Resected Lung Adenocarcinoma with Recurrence

Variables	Data
Pattern of recurrence, n (%)	
Local only	25 (14.0)
Distant only	56 (31.2)
Both local and distant	81 (45.3)
Not specified	17 (9.5)
Pleural seeding/effusion, n (%)	
Absent	133 (74.3)
Present	30 (16.8)
Unknown	16 (8.9)
Contralateral lung metastasis, n (%)	
Absent	92 (51.4)
Present	70 (39.1)
Unknown	17 (9.5)
Brain metastasis, n (%)	
Absent	102 (57.0)
Present	60 (33.5)
Unknown	17 (9.5)
Bone metastasis, n (%)	
Absent	106 (59.2)
Present	56 (31.3)
Unknown	17 (9.5)
Liver metastasis, n (%)	
Absent	148 (82.7)
Present	14 (7.8)
Unknown	17 (9.5)

TABLE 3. Univariate and Multivariate Analyses for Postrecurrence Survival in 179 Patients with Resected Lung Adenocarcinoma

	Univariate Analysis			Multivariate Analysis		
Variables	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age at recurrence (yr)[a]	1.003	0.983–1.024	0.767	1.027	0.999–1.056	0.057
Gender						
Female	1					
Male	1.316	0.842–2.058	0.228	1.075	0.608–1.901	0.802
Tumor size (cm)[b]	1.148	0.991–1.329	0.066	1.018	0.826–1.256	0.864
N status						
N0 or N1	1			1		
N2	1.850	1.196–2.863	0.006[c]	2.673	0.848–8.428	0.093
TNM stage						
I or II	1			1		
III	1.683	1.087–2.607	0.020[c]	0.967	0.264–3.545	0.960
Adjuvant therapy			0.664			0.083
No	1			1		
With C/T	0.828	0.528–1.299	0.411	0.441	0.210–0.926	0.030[c]
With R/T	1.262	0.303–5.257	0.747	1.853	0.167–4.349	0.848
With C/T and R/T	1.493	0.457–4.884	0.507	1.272	0.318–5.092	0.734
Predominant pattern group						
Acinar/papillary	1			1		
Micropapillary/solid	1.797	1.158–2.791	0.009[c]	2.615	1.395–4.901	0.003[c]
Disease-free interval (mo)						
≤18	1			1		
>18	0.630	0.392–1.011	0.056	0.806	0.437–1.486	0.490
Pattern of recurrence			0.377			0.100
Local only	1			1		
Distant only	1.824	0.755–4.409	0.182	1.236	0.422–3.625	0.699
Both local and distant	1.804	0.766–4.252	0.177	2.183	0.757–6.293	0.148
Bone metastasis						
Absent	1			1		
Present	1.625	1.032–2.558	0.036[c]	1.054	0.598–1.856	0.856
Liver metastasis						
Absent	1			1		
Present	2.077	1.062–4.063	0.033[c]	1.846	0.835–4.080	0.130
Treatment for recurrence			<0.001[c]			<0.001[c]
None	1			1		
With surgery	0.039	0.012–0.125	<0.001	0.053	0.014–0.199	<0.001[c]
C/T and/or R/T and/or EGFR TKI therapy	0.077	0.029–0.205	<0.001	0.122	0.040–0.368	<0.001[c]

[a]The HR associated with age is that the increase in hazard is associated with a 1-year increase in age.
[b]The HR associated with tumor size is that the increase in hazard is associated with a 1-cm increase in tumor size.
[c]Significant difference.
HR, Hazard ratio; CI, confidence interval; C/T, chemotherapy; R/T, radiotherapy; EGFR, epidermal growth factor receptor; TKI; tyrosine kinase inhibitor; TNM, tumor, node, metastasis.

or equal to 18 months (versus >18 months; $p = 0.060$), and treatment for recurrence with surgery ($p = 0.066$) tended to be significant prognostic factors of PRS. Pattern of recurrence ($p = 0.420$), treatment for recurrence with C/T ($p = 0.185$) or R/T ($p = 0.208$) was not significant prognostic factor of PRS.

In multivariate analysis, we also added adjuvant therapy and pattern of recurrence for mutual adjustment. Only micropapillary/solid predominant pattern group (versus acinar/papillary; HR = 2.570; 95% CI: 1.357–4.865; $p = 0.004$) was a significant predictive indicator in multivariate analysis (Table 4). Patients received treatment for recurrence with surgery (HR = 0.449; 95% CI: 0.191–1.057; $p = 0.067$) still tended to have significant better PRS than those treated without surgery after adjustment with adjuvant therapy and pattern of recurrence. Patients received adjuvant C/T (HR = 0.486; 95% CI: 0.228–1.039; $p = 0.063$) after initial resection tended to have significantly better PRS than those without adjuvant therapy. Pattern of recurrence was not a significant factor for PRS ($p = 0.263$).

We further demonstrated the association between histological subtypes and number of local-only recurrence/organ

TABLE 4. Univariate and Multivariate Analyses for Postrecurrence Survival in 159 Patients who Underwent Treatment for Recurrence

	Univariate Analysis			Multivariate Analysis		
Variables	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age at recurrence (yr)[a]	1.010	0.987–1.033	0.412	1.027	0.999–1.057	0.059
Gender						
Female	1			1		
Male	1.277	0.782–2.088	0.327	1.161	0.636–2.123	0.627
Tumor size (cm)[b]	1.169	0.992–1.378	0.062	0.998	0.805–1.237	0.983
N status						
N0 or N1	1			1		
N2	2.014	1.250–3.246	0.004[c]	2.664	0.801–8.858	0.110
TNM stage						
I or II	1			1		
III	1.860	1.147–3.016	0.012[c]	1.063	0.285–3.968	0.928
Adjuvant therapy			0.606			0.156
No	1			1		
With C/T	0.820	0.501–1.343	0.430	0.486	0.228–1.039	0.063
With R/T	0.703	0.095–5.177	0.729	0.623	0.072–5.377	0.667
With C/T and R/T	1.563	0.472–5.182	0.465	1.379	0.345–5.504	0.649
Predominant pattern group						
Acinar/papillary	1			1		
Micropapillary/solid	1.933	1.192–3.134	0.008[c]	2.570	1.357–4.865	0.004[c]
Disease-free interval (mo)						
≤18	1			1		
>18	0.612	0.367–1.020	0.060	0.827	0.435–1.574	0.563
Pattern of recurrence			0.420			0.263
Local only	1			1		
Distant only	1.896	0.725–4.957	0.192	1.284	0.407–4.050	0.699
Both local and distant	1.781	0.699–4.541	0.227	1.949	0.647–5.872	0.236
Contralateral lung recurrence						
Absent	1					
Present	0.835	0.512–1.362	0.471			
Pleural seeding/effusion						
Absent	1					
Present	0.912	0.563–1.477	0.707			
Brain metastasis						
Absent	1					
Present	1.272	0.781–2.074	0.334			
Bone metastasis						
Absent	1			1		
Present	1.629	1.004–2.643	0.048[c]	1.147	0.624–2.108	0.658
Liver metastasis						
Absent	1			1		
Present	2.149	1.058–4.365	0.034[c]	1.782	0.798–3.978	0.158
EGFR mutation						
Absent	1					
Present	0.681	0.076–6.132	0.732			
Treatment for recurrence with surgery						
No	1			1		
Yes	0.500	0.239–1.046	0.066	0.449	0.191–1.057	0.067

(*Continued*)

TABLE 4. (*Continued*)

	Univariate Analysis			Multivariate Analysis		
Variables	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Treatment for recurrence with C/T						
No	1					
Yes	0.662	0.360–1.218	0.185			
Treatment for recurrence with R/T						
No	1					
Yes	1.358	0.843–2.185	0.208			
Treatment for recurrence with EGFR TKI therapy						
No	1			1		
Yes	0.611	0.378–0.987	0.044[c]	0.891	0.463–1.713	0.728

[a]The HR associated with age is that the increase in hazard is associated with a 1-year increase in age.
[b]The HR associated with tumor size is that the increase in hazard is associated with a 1-cm increase in tumor size.
[c]Significant difference.
HR, hazard ratio; CI, confidence interval; C/T, chemotherapy; R/T, radiotherapy; EGFR, epidermal growth factor receptor; TKI; tyrosine kinase inhibitor; TNM, tumor, node, metastasis.

site of recurrence. Nine (11.1%) of 81 patients with acinar/papillary predominant pattern developed local-only recurrence, whereas 14 (17.9%) of 78 patients with micropapillary/solid predominant pattern developed local-only recurrence. There was no significant difference in percentages of local-only recurrences between acinar/papillary and micropapillary/solid subtypes ($p = 0.907$). For patients with acinar/papillary predominant pattern, 42 (51.9%) of 81 patients had recurrence at only one organ site. For patients with micropapillary/solid predominant pattern, 40 (51.3%) of 78 patients had recurrence at only one organ site. There was no significant difference in number of organ sites between acinar/papillary and micropapillary/solid subtypes ($p = 0.732$).

DISCUSSION

This study has investigated the organ sites of recurrence and the prognostic and predictive factors of PRS in patients with resected lung adenocarcinoma after recurrence. Micropapillary/solid predominant pattern group and treatment for recurrence were significant prognostic factors of PRS in multivariate analysis. For patients undergoing treatment for recurrence, micropapillary/solid predominant pattern group was a significant predictive factor of worse PRS in multivariate analysis.

Yoshino et al.[11] reported that the 2-year survival rate of NSCLC patients after recurrence at distant organs was 15.7%. Shimada et al.[14] reported that 2-year PRS for resected stage I NSCLC patients was 51.4%. In our previous study, the 2-year PRS in patients with resected stage I NSCLC was 10.6%, 25.4%, and 43.2%, during 1980 to 1990, 1991 to 2000, and 2001 to 2006, respectively.[33] In this study, the 2-year and 5-year PRS for patients of resected stages I to III lung adenocarcinoma during 2006 to 2010 were 65.2% and 29.8%, respectively. The PRS in resected lung cancer further significantly improved in recent years.

The lung, brain, and bone are the most common organ sites of metastasis in resected NSCLC.[3,11–15] In our previous study,[13] bone was the most common site of single organ metastasis in patients with resected stage I NSCLC, followed by the brain. In this study of resected stages I to III lung adenocarcinoma, contralateral lung was the most common site of metastasis, followed by the brain and the bone. Although bone and liver metastasis were significant factors for worse PRS in univariate analysis, they showed no prognostic and predictive significance in multivariate analysis.

Disease-free interval has been reported to be a prognostic factor of PRS in resected NSCLC.[9,10,14,15,34] Walsh et al.[34] reported that disease-free interval greater than 12 months was a favorable predictor of PRS in NSCLC after complete resection. Song et al.[15] reported that disease-free interval less than or equal to 12 months was a significant predictor of worse PRS in resected stage I NSCLC. Our previous study showed that disease-free interval less than or equal to 16 months was a statistically significant predictor for PRS in patients with stage I NSCLC after distant metastasis.[13] However, disease-free interval was a significant predictor of PRS in univariate analysis but not in multivariate analysis in this study.

Treatment for recurrent NSCLC significantly prolongs overall survival and PRS.[6,9,11,14,34] In our previous studies,[12,13] treatment for local recurrence or distant metastasis significantly improved PRS in resected stage I NSCLC after recurrence. Complete surgical resection may improve PRS in selected candidates with resectable local recurrent disease.[12] Yoshino et al.[11] reported that patients who underwent metastasectomy for recurrence in distant organs had significantly longer survival. In this study, treatment for recurrence was a significant prognostic factor for better PRS in patients of resected lung adenocarcinoma after recurrence. We further showed that patients treated for recurrence with surgery tended to have significantly better PRS. Because of small number of patients undergoing surgery after recurrence in our study, prospective multi-institutional studies and randomized clinical trials are mandatory to validate the therapeutic benefits of surgery for PRS.

The new classification of lung adenocarcinoma proposed by International Association for the Study of Lung

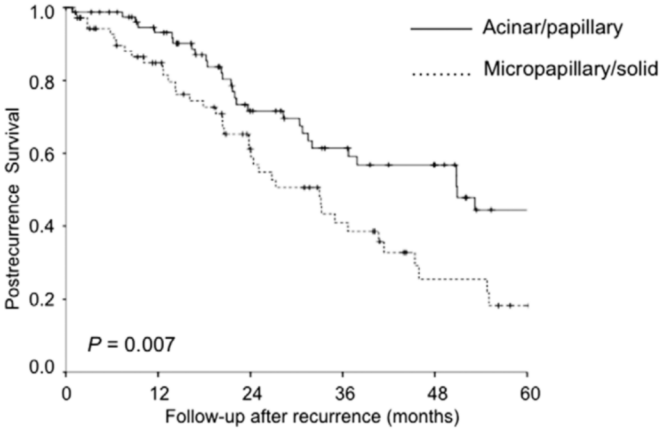

FIGURE 2. Cumulative probability of postrecurrence survival in patients of resected lung adenocarcinoma undergoing treatment for recurrence stratified by acinar/papillary and micropapillary/solid predominant pattern group (log-rank test).

Cancer/the American Thoracic Society/the European Respiratory Society in 2011 was a significant prognostic factor for survival and recurrence in lung adenocarcinoma.[22–25] In our previous study,[26] micropapillary/solid predominant pattern was a significant predictor of recurrence in resected stage I lung adenocarcinoma. In the study by Warth et al.,[25] solid-predominant tumors had an improved prognosis with adjuvant R/T. We have shown that solid predominant pattern was a significant poor prognostic factor for overall survival in patients undergoing adjuvant C/T after resection.[27] For most patients with advanced lung cancer, only biopsy specimens were available for diagnosis. The predominant type of the whole tumor was difficult to be determined only according to biopsy specimens. That is why the predictive value of the new classification in patients undergoing treatment (C/T, R/T or EGFR TKI therapy) for advanced lung cancer was difficult to be determined. In this article, we investigated the prognostic factors of survival after recurrence of patients with resected adenocarcinoma. In this case, the predominant type of the original tumor could be well determined after examination of the surgical specimens by pathologists. For patients undergoing treatment for recurrence, micropapillary/solid predominant pattern was a significant predictor of worse PRS. Our report was the first to demonstrate the predictive value of the new classification of lung adenocarcinoma in PRS of resected lung adenocarcinoma after recurrence (or advanced lung adenocarcinoma).

In our previous studies analyzing prognostic factors of PRS in resected stage I NSCLC,[12,13] only disease-free interval and treatment for recurrence influenced PRS. Most variables related to tumor biology were not significant predictors for PRS in our previous studies. We supposed that PRS in patients with resected lung cancer might be affected by the individual patient's tumor biology, which has not been well understood. In this article, we found that micropapillary/solid predominant pattern was a significant worse prognostic factor for PRS. The relationship between biological effects of the new classification and patient survival needs further examination.

There are some limitations and biases of this study that should be mentioned. As a retrospective single institute study, patient selection bias and time trend bias regarding the treatment for recurrence were inevitable. Because the majority of patients diagnosed with contralateral lung metastasis were judged by clinical course in this study, there were also biases in defining a new primary lung cancer from a recurrent NSCLC. Furthermore, the therapeutic effects for PRS by C/T or R/T or EGFR TKI therapy after recurrence might have been influenced by the presence of EGFR mutations. The lack of complete data of EGFR mutation status is another limitation of this study.

In conclusion, micropapillary/solid predominant pattern group (versus acinar/papillary) is a significant prognostic factor for worse PRS. Treatment for recurrence with surgery tends to improve PRS. Although further validation is needed, this information is important for further design of clinical randomized trials for aggressive therapy after recurrence.

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REFERENCES

1. Ichinose Y, Yano T, Asoh H, Yokoyama H, Yoshino I, Katsuda Y. Prognostic factors obtained by a pathologic examination in completely resected non-small-cell lung cancer. An analysis in each pathologic stage. *J Thorac Cardiovasc Surg* 1995;110:601–605.
2. Nesbitt JC, Putnam JB Jr, Walsh GL, Roth JA, Mountain CF. Survival in early-stage non-small cell lung cancer. *Ann Thorac Surg* 1995;60:466–472.
3. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg* 1995;109:120–129.
4. Harpole DH Jr, Herndon JE 2nd, Young WG Jr, Wolfe WG, Sabiston DC Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. *Cancer* 1995;76:787–796.
5. Jones DR, Daniel TM, Denlinger CE, Rundall BK, Smolkin ME, Wick MR. Stage IB nonsmall cell lung cancers: are they all the same? *Ann Thorac Surg* 2006;81:1958–1962; discussion 1962.
6. Nakagawa T, Okumura N, Ohata K, Igai H, Matsuoka T, Kameyama K. Postrecurrence survival in patients with stage I non-small cell lung cancer. *Eur J Cardiothorac Surg* 2008;34:499–504.
7. al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. *Eur J Cardiothorac Surg* 1997;12:380–384.
8. Martin J, Ginsberg RJ, Venkatraman ES, et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. *J Clin Oncol* 2002;20:1989–1995.
9. Sugimura H, Nichols FC, Yang P, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. *Ann Thorac Surg* 2007;83:409–417; discussion 417.
10. Williams BA, Sugimura H, Endo C, et al. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. *Ann Thorac Surg* 2006;81:1021–1027.
11. Yoshino I, Yohena T, Kitajima M, et al. Survival of non-small cell lung cancer patients with postoperative recurrence at distant organs. *Ann Thorac Cardiovasc Surg* 2001;7:204–209.
12. Hung JJ, Hsu WH, Hsieh CC, et al. Post-recurrence survival in completely resected stage I non-small cell lung cancer with local recurrence. *Thorax* 2009;64:192–196.
13. Hung JJ, Jeng WJ, Hsu WH, et al. Prognostic factors of postrecurrence survival in completely resected stage I non-small cell lung cancer with distant metastasis. *Thorax* 2010;65:241–245.

14. Shimada Y, Saji H, Yoshida K, et al. Prognostic factors and the significance of treatment after recurrence in completely resected stage I non-small cell lung cancer. *Chest* 2013;143:1626–1634.
15. Song IH, Yeom SW, Heo S, et al. Prognostic factors for post-recurrence survival in patients with completely resected stage I non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2014;45:262–267.
16. Youlden DR, Cramb SM, Baade PD. The international epidemiology of lung cancer: geographical distribution and secular trends. *J Thorac Oncol* 2008;3:819–831.
17. Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer* 2005;117:294–299.
18. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J Thorac Oncol* 2011;6:64–70.
19. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) plus Carboplatin and Paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. *Oncologist* 2007;12:713–718.
20. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
21. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–285.
22. Sica G, Yoshizawa A, Sima CS, et al. A grading system of lung adenocarcinomas based on histologic pattern is predictive of disease recurrence in stage I tumors. *Am J Surg Pathol* 2010;34:1155–1162.
23. Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA. Does lung adenocarcinoma subtype predict patient survival?: A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. *J Thorac Oncol* 2011;6:1496–1504.
24. Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. *Mod Pathol* 2011;24:653–664.
25. Warth A, Muley T, Meister M, et al. The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. *J Clin Oncol* 2012;30:1438–1446.
26. Hung JJ, Jeng WJ, Chou TY, et al. Prognostic value of the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification on death and recurrence in completely resected stage I lung adenocarcinoma. *Ann Surg* 2013;258:1079–1086.
27. Hung JJ, Yeh YC, Jeng WJ, et al. Predictive value of the international association for the study of lung cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma in tumor recurrence and patient survival. *J Clin Oncol* 2014;32:2357–2364.
28. Hung JJ, Jeng WJ, Hsu WH, Chou TY, Lin SF, Wu YC. Prognostic significance of the extent of visceral pleural invasion in completely resected node-negative non-small cell lung cancer. *Chest* 2012;142:141–150.
29. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
30. International Union Against Cancer. *TNM Classification of Malignant Tumours*. 7th ed. Oxford, UK: Wiley-Blackwell; 2009.
31. Girard N, Deshpande C, Lau C, et al. Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases. *Am J Surg Pathol* 2009;33:1752–1764.
32. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
33. Hung JJ, Jeng WJ, Hsu WH, Huang BS, Wu YC. Time trends of overall survival and survival after recurrence in completely resected stage I non-small cell lung cancer. *J Thorac Oncol* 2012;7:397–405.
34. Walsh GL, O'Connor M, Willis KM, et al. Is follow-up of lung cancer patients after resection medically indicated and cost-effective? *Ann Thorac Surg* 1995;60:1563–1570; discussion 1570.