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Original contribution

Lepidic component at tumor margin: an independent prognostic factor in invasive lung adenocarcinoma☆,☆☆

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Summary Previous studies have proven that the lepidic component of lung adenocarcinoma is an independent prognostic factor and has a favorable effect on patient prognosis; however, no studies have reported the specific distribution of the lepidic component in lung cancer. In this study, we focused mainly on whether the lepidic component at the tumor margin was an independent prognostic factor for invasive lung adenocarcinoma. We reviewed 276 patients with invasive lung adenocarcinomas and divided them into 2 groups—181 with tumors of 3 cm or less and 95 with tumors of greater than 3 cm—to study their histopathologic and clinicopathological characteristics. The long lepidic structure at the tumor margin was designated as the marginal lepidic feature. In the group with tumors of 3 cm or less, the lepidic component and marginal lepidic feature were significantly associated with histologic subtype, TNM stage, and lymph node metastasis ($P < .05$), whereas in the group with tumors of greater than 3 cm, the lepidic component and marginal lepidic feature were not correlated with histopathologic or clinicopathological characteristics. Furthermore, the patients with tumors of 3 cm or less and marginal lepidic lesions demonstrated significantly longer overall survival than did those without the structure ($P < .001$). We concluded that the marginal lepidic feature of invasive lung adenocarcinoma is a significant histologic feature that suggests a better prognosis.

1. Introduction

Lung cancer remains the worldwide leading cause of malignancy-related death [1,2]. With the development of chemotherapy and targeted molecular therapy, information on the precise cancer subtype has become necessary for cancer treatment. Adenocarcinoma is becoming the most common histologic type of lung cancer [3]. Current studies are concerned mainly with the effects of the subtypes of adenocarcinoma

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on prognosis. New classifications were introduced in 2011 by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS). Invasive lung adenocarcinoma was included in the World Health Organization 2015 classification of lung tumors [4]. Common invasive lung adenocarcinoma is histologically heterogeneous and has the following 5 growth patterns: lepidic, acinar, papillary, micropapillary, and solid. The lepidic growth pattern consists of proliferation of bland pneumocytic cells that grow along the surface of the alveolar walls. The acinar growth pattern exhibits tumor cells that surround glands that are round or oval with a central luminal space. The papillary growth pattern is a major component of the growth of glandular cells along central fibrovascular cores. The micropapillary growth pattern shows tumor cells that grow in papillary tufts. The solid growth pattern with mucin production is a major component of polygonal tumor cells that form sheets [5].

More than 90% of invasive lung adenocarcinomas have 2 or more components, and the histologic subtype affects the invasiveness of the tumors and the prognosis of the patients [6-11]. Previous studies have reported that the prognosis for lepidic-predominant adenocarcinoma is better than that for the other subtypes [4,11]. Published studies show that the percentage of the lepidic component is negatively associated with the risk of recurrence [9], and Strand and colleagues [12] have proven that the percentage of the lepidic component is a significant prognostic indicator.

Previous studies have been concerned mainly with the biological markers that aid in the prognosis of lung adenocarcinoma; however, tumor size might also affect survival. In fact, tumor size is an indispensable prognostic factor and contributes to the determination of a therapeutic regimen [13-15].

In this study, we designated 2 groups according to tumor size (181 tumors ≤3 cm and 95 tumors >3 cm). We were concerned mainly with the effect of the marginal lepidic component on the prognosis of invasive lung adenocarcinoma and whether this component and its location were an independent prognostic indicator. To this end, we explored the association

Table 1 Correlation of lepidic components with clinicopathological characteristics

Variable	Lepidic									
	Size ≤3 cm					Size >3 cm				
	Total	% (n)	95% CI	χ^2	*P*	Total	% (n)	95% CI	χ^2	*P*
Age (y)				1.728	.189				0.065	.799
<60	94	63 (59)	52.99-72.54			37	59 (22)	43.64-75.28		
≥60	87	60 (52)	49.47-70.07			58	62 (36)	49.58-74.56		
Sex				0.171	.679				1.082	.298
Male	82	56 (46)	45.36-6.84			58	57 (33)	44.15-69.64		
Female	99	66 (65)	56.30-75.01			37	68 (25)	52.48-82.65		
Smoking				0.842	.359				1.717	.203
No	111	64 (71)	55.03-72.90			59	56 (33)	43.26-68.60		
Yes	70	57 (40)	45.55-68.74			36	69 (25)	54.40-84.49		
Histologic subtype				28.828	<.001 [a]				6.465	.189
Lepidic	33	100 (33)	100-100			3	100 (3)	100-100		
Acinar	63	60 (38)	48.24-72.40			15	80 (12)	59-76-100		
Papillary	33	52 (17)	34.46-68.57			18	67 (12)	44.89-8.44		
Micropapillary	13	38 (5)	12.01-64.91			36	50 (18)	33.67-6.33		
Solid	39	46 (18)	30.51-61.80			23	57 (13)	36.26-6.78		
TNM				33.125	<.001 [a]				5.225	.185
I	107	79 (84)	70.72-96.29			27	70 (19)	53.15-87.59		
II	41	34 (14)	19.63-48.66			23	65 (15)	45.75-84.68		
III	27	37 (10)	18.82-55.25			42	50 (21)	45.75-84.68		
IV	6	50 (3)	9.99-90.01			3	100 (3)	34.88-65.12		
Lymph node metastasis				33.593	<.001 [a]				3.622	.084
0	110	78 (86)	70.46-85.90			37	73 (27)	58.66-87.28		
>0	71	35 (25)	24.10-46.32			58	53 (31)	40.61-66.29		
VPI				0.037	1.000				0.67	.413
No	178	61 (109)	54.08-68.39			62	58 (36)	45.78-70.35		
Yes	3	67 (2)	13.32-100			33	67 (22)	50.58-82.75		
STAS				0.0003	.986				0.893	.394
No	132	61 (81)	53.06-69.67			38	55 (21)	39.45-71.07		
Yes	49	61 (30)	47.58-74.87			57	65 (37)	52.52-77.30		

[a] Statistically significant.

between the marginal lepidic feature and clinicopathological characteristics.

2. Materials and methods

2.1. Surgical specimens and patient characteristics

This investigation was approved by the local Human Research Ethics Committee of the Affiliated Hospital of Nantong University, China. The current research was a cohort study based on retrospective information. Patients with invasive lung adenocarcinoma who underwent resection at the Affiliated Hospital of Nantong University, China, between January 2005 and December 2009 were selected. The inclusion criteria were as follows: (1) lobectomy and pneumonectomy with mediastinal lymph node dissection or sampling and (2) tumor diagnosed as invasive lung adenocarcinoma by postoperative pathology examination. The exclusion criteria were as follows: (1) no mediastinal lymph node dissection or sampling or (2) a history of other malignancies. Written informed consent was obtained from all patients before the operation.

Clinicopathological characteristics of the patients were age, sex, smoking status, histologic subtype, TNM stage, lymph node metastasis, pulmonary visceral pleural invasion (VPI), and tumor invasion into air spaces. The median follow-up period was 42.5 months. The postoperative pathology stage was classified according to the *Union Internationale Contra Cancer TNM Classification for Lung Cancer Staging*, eighth edition [15].

2.2. Histologic evaluation

All pathological sections were stained with hematoxylin and eosin and embedded in paraffin. Elastic fiber staining was used in cases in which pleural invasion was difficult to determine. Two physicians evaluated the adenocarcinoma according to the IASLC/ATS/ERS classification. If there was controversy between the reviewers, a diagnosis was established using further microscopic exanimation and discussion.

Common invasive lung adenocarcinoma has 5 distinct histologic growth patterns—lepidic, acinar, papillary, micropapillary, and solid. The *lepidic* growth component is defined as a tumor cells growing along alveolar walls without stromal invasion [16]. All patients were found to have invasive lung adenocarcinoma (excluding minimal invasion and adenocarcinoma in situ). The lepidic component consists of a single layer of cancer cells that cover the alveolar structures. It is divided into marginal and nonmarginal lepidic features. With the marginal lepidic pattern, the growth is noninvasive at the tumor margin. With the nonmarginal lepidic pattern, the growth at the tumor margin is invasive.

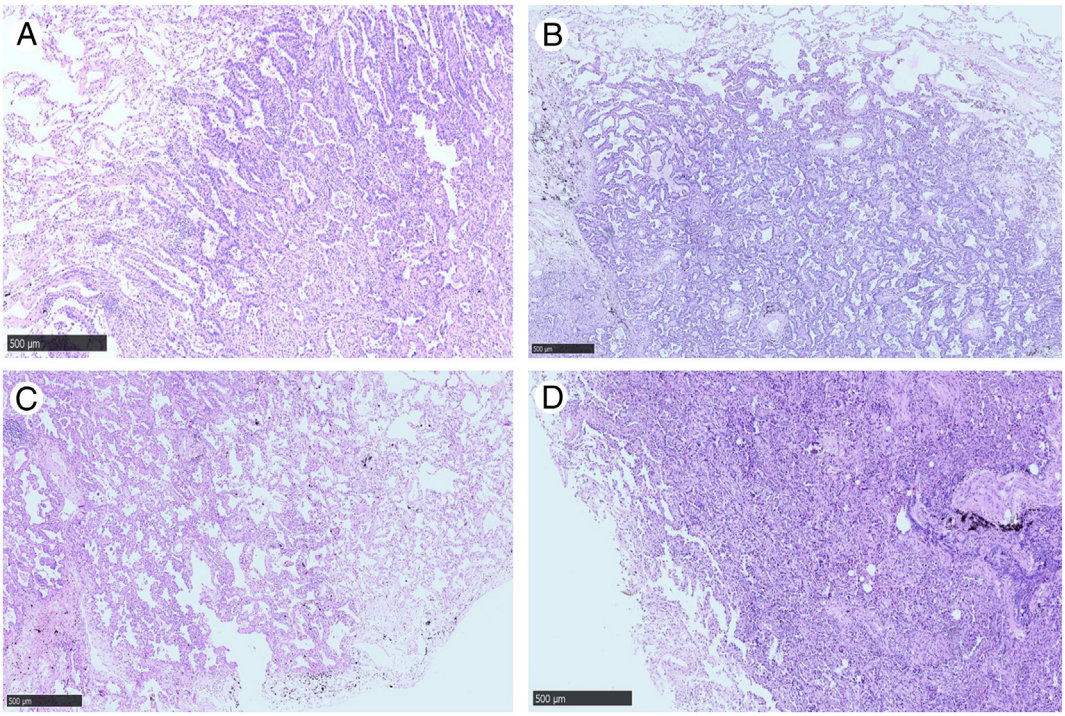

Fig. 1 Histologic features of marginal lepidic pattern in invasive lung adenocarcinoma (hematoxylin and eosin stain, original magnification ×40). Marginal lepidic tissues with acinar (A), papillary (B), micropapillary (C), and solid (D) features. Marginal lepidic pattern consists of proliferation of bland pneumocytic cells growing along the surface of alveolar walls at tumor margin.

2.3. Statistical analyses

The categorical variables of the characteristics among patients with the marginal and nonmarginal lepidic patterns were tested using the χ^2 or Fisher exact test as appropriate. The survival curve was calculated using the Kaplan-Meier method. The log-rank test was used for a statistical comparison between the groups. The proportional hazards assumption was evaluated with the Schoenfeld residual test. Cox regression was used for univariate and multivariate analyses. SPSS 21.0 (IBM, Armonk, NY) was used for statistical analyses. $P < .05$ was regarded as statistically significant.

3. Results

3.1. Patient characteristics and pathologic findings

Patient characteristics are listed in Table 1. In this study, 276 patients (140 men) were included. Among them, 52.5% (145/276) were older than 60 years; 38.4% (106/276) had a history of smoking; and 134 were in stage I, 64 in stage II, 69 in stage III, and 9 in stage IV lung cancer. Of the 276 patients, 181 had tumors of 3 cm or less, and 95 had tumors of greater than 3 cm; 61.2% presented with the lepidic component (169/276), and 37.3% presented with the marginal lepidic features (103/276). Approximately 13% of the patients (n = 36) had tumors that had invaded the pulmonary visceral pleura, and 38.4% (n = 106) had tumors that spread to the air spaces. Histologic examples of the marginal lepidic pattern in invasive lung adenocarcinoma are illustrated in Fig. 1.

3.2. Correlation with clinicopathological characteristics

The clinicopathological characteristics of the lung adenocarcinomas with and without the lepidic component are provided in Table 1. In the group with a tumor of 3 cm or less, the lepidic components were statistically different from those in the nonlepidic subtype and TNM stages of lung adenocarcinoma (χ^2 =

Table 2 Correlation of marginal lepidic components with clinicopathological characteristics [a]

Variable	Marginal lepidic									
	Size ≤3 cm					Size >3 cm				
	Total	% (n)	95% CI	χ^2	*P*	Total	% (n)	95% CI	χ^2	*P*
Age (y)				0.103	.842				0.770	.427
<60	59	64 (38)	52.19 to 76.62			22	59 (13)	38.55 to 79.64		
≥60	52	67 (35)	54.56 to 80.06			36	47 (17)	30.91 to 63.53		
Sex				1.734	.225				0.001	1.000
Male	46	59 (27)	44.47 to 72.92			33	52 (17)	34.46 to 68.57		
Female	65	71 (46)	59.71 to 81.83			25	52 (13)	32.42 to 71.58		
Smoking				0.296	.678				1.049	.427
No	71	68 (48)	56.72 to 78.49			33	58 (19)	40.71 to 74.44		
Yes	40	63 (25)	47.50 to 77.50			25	44 (11)	24.54 to 63.46		
Histologic subtype				11.256	.022				2.849	.624
Lepidic	33	73 (24)	57.53 to 87.92			3	33 (1)	−20.0 to 6.68		
Acinar	38	79 (30)	65.98 to 91.91			12	42 (5)	13.77 to 9.56		
Papillary	17	59 (10)	35.43 to 82.22			12	67 (8)	39.99 to 93.34		
Micropapillary	5	40 (2)	−2.94 to 82.94			18	44 (8)	21.49 to 67.40		
Solid	18	39 (7)	16.37 to 61.41			13	62 (8)	35.09 to 87.99		
TNM				13.147	.002				0.813	.913
I	84	75 (63)	65.74 to 84.26			19	47 (9)	24.92 to 69.82		
II	14	36 (5)	10.61 to 60.81			15	53 (8)	28.09 to 78.58		
III	10	40 (4)	9.64 to 70.36			21	57 (12)	35.98 to 78.31		
IV	3	33 (1)	−20.0 to 86.68			3	33 (1)	−20.0 to 86.68		
Lymph node metastasis				9.515	.004				1.072	.220
0	86	73 (63)	63.90 to 2.61			27	44 (12)	25.70 to 63.19		
>0	25	40 (10)	20.80 to 59.20			31	58 (18)	40.69 to 75.44		
VPI				0.198	1.000				0.042	.526
No	109	66 (72)	57.17 to 74.94			36	53 (19)	36.47 to 69.19		
Yes	2	50 (1)	−19.3 to 100			22	50 (11)	29.11 to 70.89		
STAS				1.512	.262				0.006	.579
No	81	69 (56)	59.08 to 79.20			21	52 (11)	31.02 to 73.74		
Yes	30	57 (17)	38.93 to 74.40			37	51 (19)	35.25 to 7.46		

[a] Statistically significant.

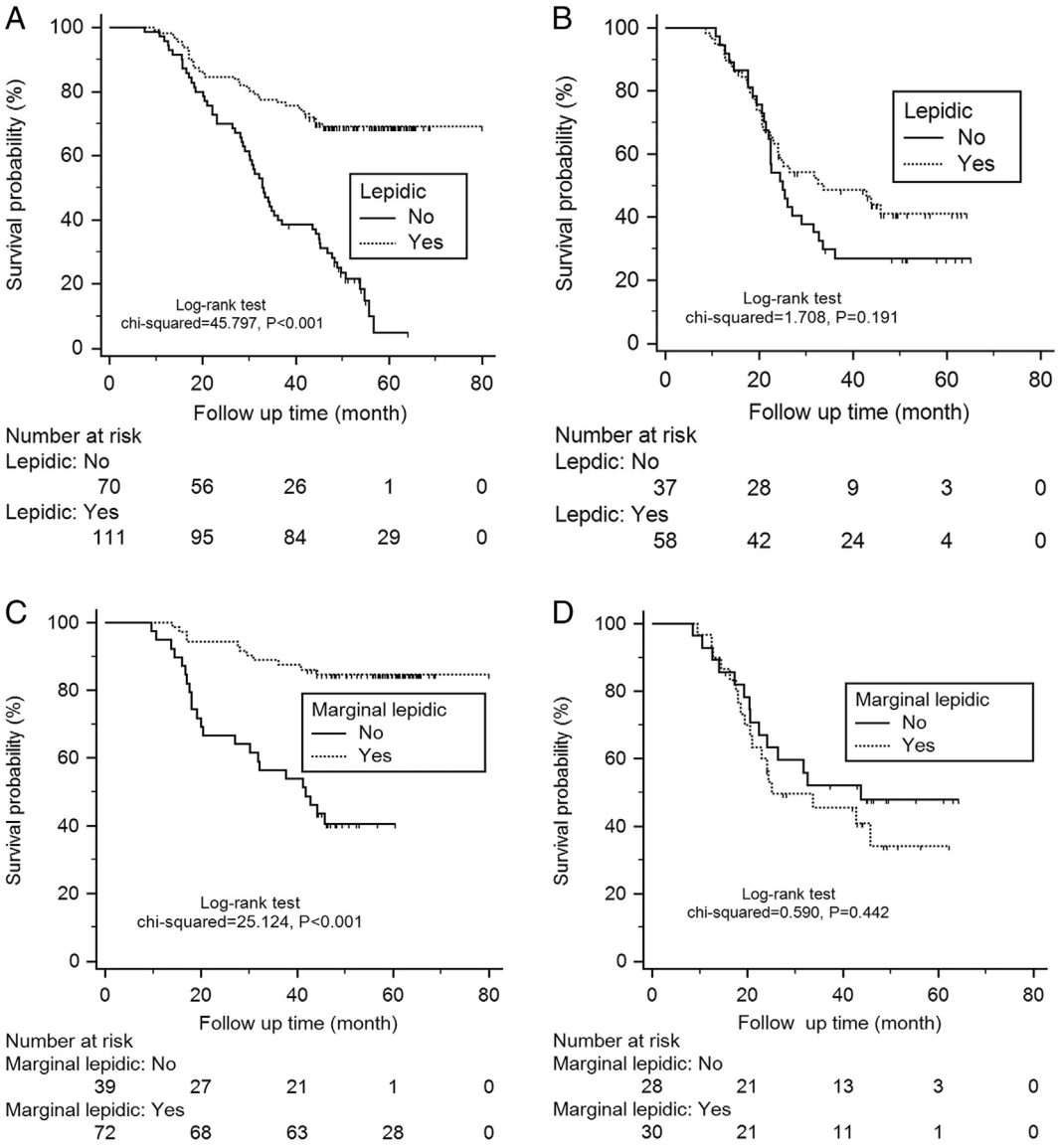

Fig. 2 Overall survival of patients with lung adenocarcinoma of 3 cm or less (A) and greater than 3 cm (B) stratified by lepidic component. Overall survival of patients with lung adenocarcinoma of 3 cm or less (C) and greater than 3 cm (D) stratified by marginal lepidic component.

28.828 [$P < .001$] and $\chi^2 = 33.125$ [$P < .001$], respectively). In the lepidic subtype, the percentage of patients without lymph node metastasis increased ($\chi^2 = 33.593$, $P < .001$), and there was no statistical difference in patient age ($P = .189$), sex ($P = .679$), smoking habits ($P = .359$), pulmonary VPI ($P = 1.000$), or tumor spread through air spaces ($P = .986$). There was no statistical difference in the clinicopathological characteristics among the group with tumors of greater than 3 cm.

The clinicopathological characteristics of patients with marginal and nonmarginal lepidic components are provided in Table 2. In the group with tumors of 3 cm or less, there was a statistically significant difference between those with the marginal lepidic pattern and those with the nonmarginal lepidic feature with respect to histologic subtype, TNM stage, and lymph node metastasis ($\chi^2 = 11.256$ [$P = .022$], $\chi^2 = 13.147$ [$P = .002$], and $\chi^2 = 9.515$ [$P = .004$], respectively).

Table 3 The Schoenfeld residual test for the assumptions on the proportional hazards of lepidic components and clinicopathological characteristics of tumors ≤3 cm

Variable	χ^2	P
Age	1.47	.226
Sex	0.46	.4959
Smoking	0.71	.3982
Histologic subtype	8.16	.0043 [a]
TNM	9.47	.0021 [a]
Lymph node metastasis	0.62	.4328
VPI	0.43	.5128
STAS	0.87	.35
Lepidic	4.21	.0401 [a]
Global test	30.27	.0004 [a]

[a] Statistically significant.

Table 4 The Schoenfeld residual test for the assumptions on the proportional hazards of the marginal lepidic and clinicopathological characteristics in tumors ≤3 cm

Variable	χ^2	P
Age	3.36	.0667
Sex	0.61	.4353
Smoking	0.99	.3203
Histologic subtype	0.13	.7215
TNM	0.09	.7642
Lymph node metastasis	1.24	.2648
VPI	0.76	.3823
STAS	1.52	.2178
Marginal lepidic	0.32	.5739
Global test	7.02	.6352

There was no statistical difference in age (P = .842), sex (P = .225), smoking habits (P = .678), and pulmonary VPI (P = 1.000). In the group with tumors of greater than 3 cm, there was no statistical difference among any of the clinicopathological characteristics.

3.3. Survival analyses

Kaplan-Meier analysis showed that the lepidic component in tumor tissue suggested a better prognosis than its absence in the group with tumors of 3 cm or less (χ^2 = 45.797, P < .001; Fig. 2A). In the group with tumors of greater than 3 cm, the prognosis was not statistically different for patients with or without a lepidic component (χ^2 = 1.708, P = .191; Fig. 2B). When tumors were 3 cm or less, the prognosis was better in those with the marginal lepidic than in those with non-marginal lepidic pattern (χ^2 = 25.124, P < .001; Fig. 2C). When tumors were greater than 3 cm, the distribution of the lepidic component had no effect on prognosis (χ^2 = 0.590, P = .442; Fig. 2D).

Table 3 generalizes the Schoenfeld residual test for the assumptions of the proportional hazards from the lepidic components and clinicopathological characteristics in the group with tumors of 3 cm or less showing P < .05 for the lepidic components and global test. Therefore, it was not necessary to use these factors to validate the Cox model results. However, because of the P > .05 for the marginal lepidic feature and global test, the assumptions about the proportional hazards of the marginal lepidic pattern and clinicopathological characteristics were established for the group with tumors of 3 cm or less (Table 4).

Table 5 summarizes the results of the univariate and multivariate analyses of the effect of clinicopathological characteristics on overall survival. In the group with tumors of 3 cm or less, multivariate analysis was performed for age, sex, smoking habits, histologic subtype, TNM stage, lymph node metastasis, pulmonary VPI, tumor spread through air spaces, and the marginal lepidic pattern. The histologic subtypes (P < .001) and the marginal lepidic pattern (P = .003) proved to be independent prognostic factors. In Table 5, most histologic subtypes were associated with a bad prognosis; however, the marginal lepidic feature indicates a good prognosis.

4. Discussion

According to the 2011 IASLC/ATS/ERS classification, acinar, papillary, micropapillary, and solid subtypes are invasive components of these tumors, which is different from the lepidic component [4]. The percentage of the invasive components is positively related to the invasion and progression of

Table 5 Univariate and multivariate analyses of factors associated with overall survival

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age	0.797 (0.403 to 1.578)	.515	0.973 (0.363 to 2.611)	.957
Sex	0.663 (0.339 to 1.300)	.232	1.073 (0.465 to 2.477)	.868
Smoking	1.091 (0.546 to 2.179)	.805	1.008 (0.426 to 2.387)	.986
Histologic subtype		<.001 [a]		<.001 [a]
Acinar	2.4×10^{-5} (9.2×10^{-98} to 6.2×10^{87})	.922	0.003 (2.4×10^{-12} to ~2.8×10^{6})	.575
Papillary	7.298 (1.932 to 27.560)	.003 [a]	7.166 (1.762 to 29.146)	.006 [a]
Micropapillary	24.718 (5.708 to 107.030)	<.001 [a]	10.094 (1.325 to 6.881)	.026 [a]
Solid	114.93 (27.414 to 481.832)	<.001 [a]	168.089 (22.689 to 1245.263)	<.001 [a]
TNM		<.001 [a]		.995
II	10.176 (4.295 to 24.108)	<.001 [a]	0.625 (4.5×10^{-59} to 6×10^{57})	.995
III	21.208 (8.023 to 56.063)	<.001 [a]	0.620 (4.4×10^{-5}9 to 8.6×10^{57})	.994
IV	48.400 (11.456 to 04.492)	<.001 [a]	1.302 (0.19 to 8.944)	.788
Lymph node metastasis	8.705 (4.320 to 17.541)	<.001 [a]	0.866 (6.3×10^{-59} to 1.2×10^{58})	.998
VPI	4.776 (1.119 to 20.386)	.035 [a]	5.377 (0.598 to 48.314)	.133
STAS	5.439 (2.730 to 10.840)	<.001 [a]	1.777 (0.469 to 6.727)	.398
Marginal lepidic	0.192 (0.093 to 0.394)	<.001 [a]	0.275 (0.117 to 0.644)	.003 [a]

[a] Statistically significant.

tumors. In contrast, the lepidic growth pattern, as a noninvasive component, might be a significant prognostic factor. Many studies have reported that only the lepidic and micropapillary components correlate with disease recurrence [7,8,17,18] and that the lepidic component in invasive lung adenocarcinoma is associated with a good prognosis [19]. All of the above studies emphasized the important role of the lepidic component in the diagnosis of a histologic subtype of lung adenocarcinoma and heterogeneity evaluation, which is consistent with our study results. However, we were not clear about which part of the lepidic component was valuable. Further research showed that when tumors were 3 cm or less, the marginal lepidic pattern was associated with a better prognosis than adenocarcinoma without the structure; therefore, the marginal lepidic feature might be an independent prognostic factor in invasive lung adenocarcinoma.

In the analyses of the marginal lepidic pattern and the clinicopathological characteristics, we found that when tumors were 3 cm or less, the marginal lepidic feature was associated with a histologic subtype of lung adenocarcinoma, TNM stage, and lymph node metastasis (P = .022, P = .002, and P = .004, respectively). When tumors were greater than 3 cm, the distribution of the lepidic component was not correlated with the clinicopathological characteristics of invasive lung adenocarcinoma.

Common invasive lung adenocarcinoma is histologically heterogeneous and has 5 distinct growth patterns—lepidic, acinar, papillary, micropapillary, and solid [11]. In our study, all patients were known to have invasive lung adenocarcinoma, which provided the possibility of the presence of the lepidic component at the tumor margin. We found that the marginal lepidic subtype was related to a histologic subtype of invasive lung adenocarcinoma in the group with tumors of 3 cm or less. The major histologic subtypes affect the prognosis and survival of the patients, yet the prognostic value of the current lung adenocarcinoma classification is not limited to the predominant growth patterns. In Table 2, the histologic subtypes represent the predominant growth patterns, whereas the marginal lepidic pattern refers to the nondominant pattern. The more favorable outcome associated with the nondominant lepidic pattern further emphasizes the importance of histologic subtyping and the assessment of tumor heterogeneity in the diagnosis of lung adenocarcinoma [19].

Previous studies proved the implication of lymph node metastasis in new classifications [18,20-24]. When the micropapillary component was present in the tumor, metastasis to the lymph nodes was common [18,21]; therefore, the micropapillary-predominant or solid-predominant component was associated with a high potential for lymph node metastasis [22,24]. Zhang et al [23] reported that metastasis to the lymph nodes was not common in adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic-predominant adenocarcinoma.

Tumor size is one of the most important factors in the prognosis of lung cancer, which makes it one of the key elements in TNM staging [25]. The evidence that the prognosis is better predicted after adjusting the tumor size descriptor using the pathology results of the invasive size in adenocarcinomas with the lepidic component is based primarily on data from small tumors (≤3 cm) with a lepidic component [26]. In addition, previous data demonstrated that the presence of the lepidic component decreases the incidence of lymph node and distant metastasis [23]; therefore, the lepidic component might be associated with TNM stage. We concluded from our study that the marginal lepidic pattern is correlated with TNM stage and lymph node metastasis.

A recent study showed that the probability of the lepidic component was higher in patients with no smoking history [27]. We found no correlation between smoking habits and the marginal lepidic feature in the group with tumors of 3 cm or less. Pulmonary visceral pleura invasion is regarded as an important prognostic factor [28-31] and is more common in solid and micropapillary subtypes than in the lepidic subtype [28-31]. The previous study found that tumor spread through air spaces occurred less often in lepidic-predominant adenocarcinoma [32], which might be because the noninvasive lepidic component affects the biological behavior of lung cancer. In our study, no statistical difference was found among the marginal lepidic pattern, pulmonary pleura invasion, and tumor spread through air spaces.

Our multivariate analysis revealed that the histologic subtype of lung adenocarcinoma is a cooperative variable and that the marginal lepidic pattern has an effect on patient prognosis. In 2011, Yoshizawa et al [33] reported that the IASLC/ATS/ERS classification system determined the prognosis of the histologic subtype that showed a significant difference in stage I lung adenocarcinoma. Russell et al [34] found that the histologic subtype according to the IASLC/ATS/ERS classification was closely related to 5-year survival in stage I-III lung adenocarcinoma, and that histologic subtype was an independent prognostic factor.

Histologic subtype has been proposed as a potential screening method for lung cancer patients at high risk of recurrence [35]. Many studies have proved that the major driver genes of lung adenocarcinoma are potential targets for specific treatment. To a great extent, tissue phenotype is dependent on gene phenotype, and a change in the genes is closely related to histologic morphology. A recent study found that lepidic-predominant lung adenocarcinoma is associated with a mutation in the epidermal growth factor receptor gene. Moon et al [36] said that having a low percentage of the lepidic component in lung adenocarcinoma was a risk factor for recurrence. Another study showed that the percentage of the lepidic component in lung adenocarcinoma is negatively correlated with the risk of recurrence [9]. A previous study showed that the predominant histologic subtype of invasive lung adenocarcinoma determines the prognosis; however, the prognosis of lung adenocarcinoma was not limited to the predominant subtype. The nonpredominant important lepidic component was also related to prognosis [19]. In our study, we found that the lepidic component was an independent prognostic factor and

that the marginal lepidic pattern was even more valuable as a prognostic factor.

Previous studies have shown that the 5-year recurrence-free survival rate of patients with the lepidic component was 100% [9,37]. Other studies have found that the lepidic-predominant lung adenocarcinoma has a better prognosis and that the 5-year recurrence-free survival rate is 85.7% to 100% [38]. A nonpredominant lepidic component in lung adenocarcinoma also suggests a good prognosis [19]. Our study showed that when tumors were 3 cm or less, the marginal lepidic resulted in a better prognosis than the nonmarginal lepidic ($\chi^2 = 25.124$, $P < .001$), which suggested that patients with the marginal lepidic had a better 5-year survival rate in tumors of 3 cm or less.

4.1. Study limitations

Our study had some limitations. First, as a retrospective study from a single institution, our sample was small. A larger sample is needed for further study to improve the reliability of the results. Second, we did not collect treatment information after recurrence, which might cause bias of the overall survival analysis. Third, we did not explore the association between the histologic subtype of lung adenocarcinoma and gene mutation or investigate the mechanism by which the marginal lepidic pattern seems to be an independent prognostic factor in invasive lung adenocarcinoma and why it suggests a better prognosis from the viewpoint of gene mutation.

4.2. Conclusions

Our study found that the marginal lepidic pattern is a significant histologic feature in invasive lung adenocarcinoma and suggests a better prognosis than other histologic subtypes.

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