

Prognostic factors in curatively resected pathological stage I lung adenocarcinoma

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Background: Patients with pathological stage I (p I) lung adenocarcinoma show variabilities in prognosis even after complete resection. The factors resulting in heterogeneities of prognosis remain controversy. The aim of this study was to identify the risk factors affecting recurrence/metastasis and survival in patients with curatively resected p I lung adenocarcinoma.

Methods: A total of 252 patients with p I lung adenocarcinoma underwent curative resection between January 1st, 2009 to September 30th, 2011 were retrospectively reviewed to analyze the associations of recurrence and survival with the following clinicopathological variables: gender, age, cigarette smoking, family cancer history, tumor size, TNM stage, tumor differentiation, visceral pleural invasion, bronchial involvement, lymphovascular invasion, postoperative adjuvant treatment, pathological subtypes and micropapillary pattern.

Results: Among those 252 patients, 48 had local recurrence or distant metastasis, the rest 204 patients had no relapse until the last follow-up. Cox univariate survival analysis revealed that tumor size ($P<0.001$), TNM stage [disease-free survival (DFS), $P<0.001$; overall survival (OS), $P=0.004$], tumor differentiation ($P<0.001$), bronchial involvement ($P<0.001$), lymphovascular invasion (DFS, $P=0.021$; OS, $P=0.001$) and micropapillary pattern (DFS, $P<0.001$; OS, $P=0.003$) were significantly associated with DFS and OS, while cigarette smoking ($P=0.029$) and pathological subtypes ($P=0.041$) were found to be risk factors for DFS either. In multivariate analysis, tumor differentiation ($P<0.001$) was an independent risk factor for both DFS and OS, TNM stage ($P=0.007$), bronchial involvement ($P=0.004$) and micropapillary pattern ($P=0.001$) only for DFS, while tumor size ($P=0.009$) and lymphovascular invasion ($P=0.010$) were found to be independent risk factors only for OS.

Conclusions: Tumor size, TNM stage, tumor differentiation, bronchial involvement, lymphovascular invasion and micropapillary pattern could be considered as risk factors for predicting local recurrence or distant metastasis and survival in curatively resected p I lung adenocarcinoma patients.

Keywords: Lung adenocarcinoma; prognosis; recurrence; metastasis; survival

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Introduction

Lung cancer is increasing rapidly in recent years and has become the leading cause of cancer-related death in China (1). Currently, the standard treatment for stage I non-small cell lung cancer (NSCLC) is still surgery, however, 20% of patients with pathological stage I (p I) NSCLC still have local recurrence or distant metastasis (2). Up to now, the risk factors resulting in treatment failure after surgery in those with p I NSCLC have not been well elucidated, and the clinicopathological features placing patients at particularly high risks of tumor recurrence have not been definitely studied. The aim of this study was to identify the risk factors of local recurrence and distant metastasis in patients with curatively resected p I lung adenocarcinoma.

Methods

Study design and patients

From January 1st, 2009 to September 30th, 2011, 265 consecutive patients underwent complete resections for p I lung adenocarcinoma at our hospital, 13 of those lost follow-up and were excluded. Eventually, 252 patients were eligible for analysis, including gender, age, smoking cigarette, family cancer history, tumor size, TNM stage, tumor differentiation, visceral invasion, bronchial involvement, lymphovascular invasion, postoperative adjuvant chemotherapy, pathological subtype and micropapillary pattern. The survival statuses were confirmed through telephone call. The association of the above parameters with recurrence and survival was retrospectively analyzed. This study was approved by the ethical committee of Cancer Hospital, Chinese Academy of Medical Sciences (No. NCC2014ST-07). Last follow-up was conducted in December 7th, 2015. The follow-up interval was 49 to 78 months.

We defined “p I” lung adenocarcinoma cases as those patients who underwent anatomical lobectomy and had p IA to IB adenocarcinoma including stage T1aN0M0, T1bN0M0 and T2aN0M0 and final cancer staging was confirmed by reviewing the official pathological reports according to 7th edition of TNM classification. All patients with pathologically reported N1 or M1 were excluded, regardless of their T stage. The patients receiving preoperative radiation or chemotherapy, or underwent incomplete resections (R1–R2), or died of postoperative complications were also excluded in this study. All patients received precise preoperative evaluation including computed tomographic scans, head magnetic resonance imaging (MRI)

and bone scan prior to surgical resection.

The H & E staining slides of all the 252 patients were reviewed again by two experienced pathologists separately and the subtypes were determined according to the 8th American Joint Committee on Cancer (AJCC)/International Union for Cancer Control (UICC) lung cancer staging system. Elastic stainings were added in suspicious visceral invasion cases.

Methods

The demographic features including gender, age, smoking cigarette, family cancer history were reviewed. The correlation of prognosis with pathological factors such as the tumor size, TNM stage, grade of differentiation, invasion of visceral pleura, bronchial involvement, the lymphovascular invasion and pathological subtype as well as micropapillary pattern were analyzed. Micropapillary components were assessed and calculated in percentage, only 0% micropapillary components were considered as micropapillary pattern negative, more than 0% components were considered as micropapillary pattern positive. Surgery-related factor as postoperative adjuvant chemotherapy was also reviewed. DFS period was calculated from the date of surgery to the date of surgical treatment failure (defined as local recurrence or distant metastasis were confirmed by images or pathology of biopsy). OS period was defined as the time from date of surgery to the date of death or the date of last follow-up (2015-12-7).

Statistical analysis

SPSS (V22.0, SPSS) was used for statistical analysis. Chi-square test was used to analyze the relationship between groups. DFS and OS curves were estimated using the Kaplan-Meier method. Significance was assessed using the log rank test. A P value of <0.05 was considered statistically significant. Possible prognostic predictors of DFS and OS were analyzed using Cox univariate and multivariate proportional hazards regression.

Results

The demographic features and recurrence of the patients (n=252) were listed in *Table 1*, with 48 recurrence cases and 27 death cases. Recurrence and metastasis were found to be significant differences with smoking cigarette (P=0.026), tumor size (P<0.001), TNM stage (P<0.001), tumor differentiation (P<0.001), bronchial involvement (P<0.001), lymphovascular invasion (P=0.011), pathological subtype

($P < 0.001$) and micropapillary pattern ($P < 0.001$). The 1-, 3- and 5-year DFS and OS of this series were 91.3%, 81.0%, 77.0%, and 99.2%, 91.7%, 81.0% respectively. Kaplan-Meier analysis revealed that tumor size (Figure 1; $P < 0.001$), TNM stage (Figure 2; $P = 0.002$ for DFS, $P = 0.004$ for OS), tumor differentiation (Figure 3; $P < 0.001$), bronchial involvement (Figure 4; $P < 0.001$), lymphovascular invasion (Figure 5; $P < 0.001$), pathological subtype (Figure 6; $P < 0.001$) and micropapillary pattern (Figure 7; $P < 0.001$ for DFS, $P = 0.001$ for OS) were significant factors affecting DFS and OS.

Of the 252 patients, 48 patients had local recurrences or distant metastases (Table 2), which were confirmed by repeated images or by pathological/cytological results of biopsies. Six (12.5%) patients had only local recurrences, while the other 42 (87.5%) patients had distant metastases and 9 of those (18.8%) had \geq two sites of metastases. The common sites of metastases were contralateral lung (18.8%), brain (16.7%) and bone (12.5%).

Univariate analysis of the factors affecting survival was shown in Table 3. The results revealed that cigarette smoking ($P = 0.029$), tumor size ($P < 0.001$), TNM stage ($P < 0.001$), tumor differentiation ($P < 0.001$), bronchial involvement ($P < 0.001$), lymphovascular invasion ($P = 0.021$), pathological subtype ($P = 0.041$) and micropapillary pattern ($P < 0.001$) were the statistically significant predictors for DFS, while tumor size ($P < 0.001$), TNM stage ($P = 0.004$), tumor differentiation ($P < 0.001$), bronchial involvement ($P < 0.001$), lymphovascular invasion ($P = 0.001$) and micropapillary pattern ($P = 0.003$) were statistically significant predictors for OS.

Tumor size, TNM stage, tumor differentiation, bronchial involvement, lymphovascular invasion and micropapillary pattern were significantly associated with DFS and OS. Multivariate analysis of the 6 factors affecting survival was shown in Table 4. The results showed that TNM stage ($P = 0.007$), tumor differentiation ($P < 0.001$), bronchial involvement ($P = 0.004$) and micropapillary pattern ($P = 0.001$) were found to be statistically significant factors for DFS. While, tumor size ($P = 0.009$), tumor differentiation ($P < 0.001$) and lymphovascular invasion ($P = 0.010$) were statistically significant predictors for OS.

Discussion

Although the TNM staging system has been the gold standard parameter used for predicting the survival and determining whether adjuvant treatment should be

given or not after curative resection of advanced stage NSCLC for the past several decades. For p I NSCLC, TNM staging seems to be a weak predictor not only for recurrence but also for long term survival (3). However, some other clinicopathological factors were found to be also predictive for prognosis in addition to the TNM staging (4). These clinicopathological risk factors associated with the development of local recurrence or distant metastasis after curatively surgical resection could also be used for pick out the patients at high risks who may need close follow-up and aggressive postoperative adjuvant therapy (5). Although these clinicopathological factors may be helpful, actually, they are not well definitely identified and usually used subjectively in our routine clinical practice (6). Therefore, a retrospective analysis was conducted in order to elucidate the correlation between various clinicopathological factors and outcomes in 252 p I lung adenocarcinoma patients who received curative lung resection. The results of this study indicated that tumor size, TNM stage, tumor differentiation, bronchial involvement, lymphovascular invasion and micropapillary pattern not only significantly correlated with recurrence but also with survival, especially the DFS.

Tumor differentiation was useful in defining the aggressiveness of malignant tumors and was reported to be significantly associated with disease recurrence and short DFS according to the results reported by Choi *et al.* (7). This study also showed the similar results that poor tumor differentiation significantly affected the DFS and OS.

The presence of lymphovascular invasion was generally regarded as an unfavorable prognostic predictor. Kiankhooy *et al.* (8) reported that the presence of lymphovascular invasion was a significant risk factor for early recurrence (< 2 years) in early-stage lung cancers (T1a to T2b) despite a R0 resection and absence of nodal involvement. Higgins *et al.* (9) reported that lymphovascular invasion was associated with the presence of regional lymph node (LN) involvement and was strongly associated with increased risk of developing distant metastases and death in adenocarcinoma. Hamanaka *et al.* (10) pointed that pleural invasion, blood vessel invasion and lymphatic vessel invasion were all independent factors for recurrence. In this study, univariate analysis also showed that lymphovascular invasion was an independent predictor for survival.

In Huang's meta-analysis, visceral pleural invasion was reported as an independent predictor and associated with increased risk of recurrence and metastases in stage I NSCLC (11). Lakha *et al.* and Schuchert *et al.* reported

Table 1 Demographic features and recurrence of 252 patients with complete resected p I stage NSCLC

Variables	Patient number	Recurrence		P value	5-year DFS (%)
		Yes (%)	No (%)		
Gender				0.088	
Male	114	27 (23.7)	87 (76.3)		71.9
Female	138	21 (15.2)	117 (84.8)		77.5
Age (years)				0.239	
≤65	185	32 (17.3)	153 (82.7)		75.7
>65	67	16 (23.9)	51 (76.1)		73.1
Smoking cigarette				0.026	
smoker	91	24 (26.4)	67 (73.6)		68.1
Non-smoker	161	24 (14.9)	137 (85.1)		78.9
Family cancer history				0.765	
Yes	64	13 (20.3)	51 (79.7)		67.2
No	188	35 (18.6)	153 (81.4)		77.7
Tumor size (cm)				<0.001	
≤2	130	11 (8.5)	119 (91.5)		83.1
2.1–5.0	122	37 (30.3)	85 (69.7)		66.4
TNM stage				<0.001	
IA	131	12 (9.2)	119 (90.8)		80.9
IB	121	36 (29.8)	85 (70.2)		68.6
Tumor differentiation				<0.001	
Well	60	0 (0)	60 (100.0)		86.7
Moderately	150	29 (19.3)	121 (80.7)		76.7
Poorly	42	19 (45.2)	23 (54.8)		52.4
Visceral pleural invasion				0.184	
Yes	177	38 (21.5)	139 (78.5)		73.4
No	75	10 (13.3)	65 (86.7)		78.7
Bronchial involvement				<0.001	
Yes	45	22 (48.9)	23 (51.1)		48.9
No	207	26 (12.6)	181 (87.4)		80.7
Lymphovascular invasion				0.011	
Yes	13	6 (46.2)	7 (53.8)		53.8
No	239	42 (17.6)	197 (82.4)		76.2
Postoperative adjuvant chemotherapy				0.366	
Yes	101	22 (21.8)	79 (78.2)		76.2
No	151	26 (17.2)	125 (82.8)		74.2

Table 1 (continued)

Table 1 (continued)

Variables	Patient number	Recurrence			5-year DFS (%)
		Yes (%)	No (%)	P value	
Pathological subtype					<0.001
Lepidic	21	0 (0)	21 (100.0)		95.2
Papillary	35	2 (5.7)	33 (94.3)		88.6
Acinar	138	31 (22.5)	107 (77.5)		71.7
Solid	32	13 (40.6)	19 (59.4)		59.4
Others	26	2 (7.7)	24 (92.3)		76.9
Micropapillary pattern					<0.001
Negative	186	23 (12.4)	163 (87.6)		80.6
Positive	66	25 (71.4)	41 (28.6)		43.9

p I, pathological stage I; NSCLC, non-small cell lung cancer; DFS, disease-free survival.

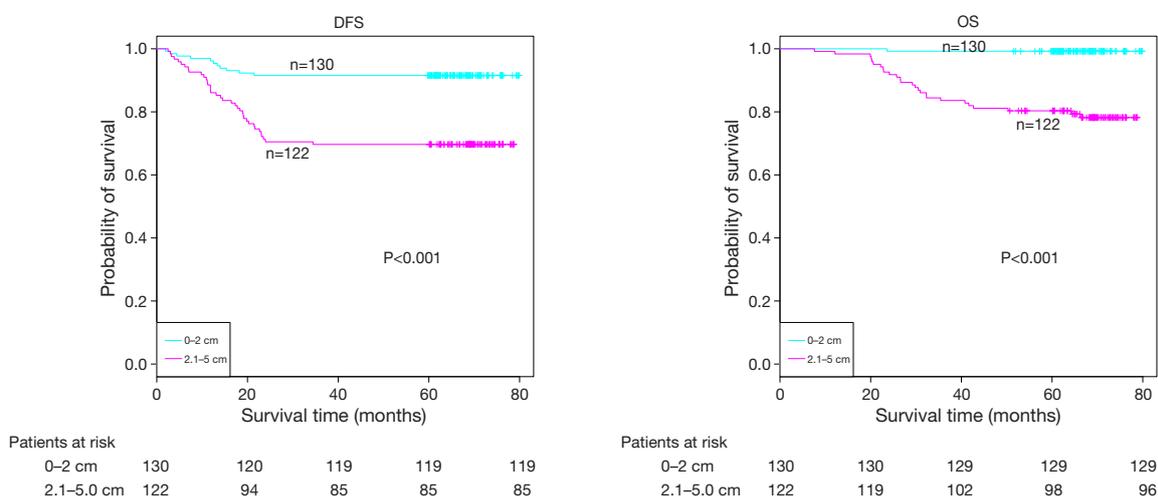


Figure 1 DFS and OS estimated by Kaplan-Meier in patients with tumor ≤2 cm and 2.1–5.0 cm (P<0.001, log-rank test). DFS, disease-free survival; OS, overall survival.

similar results (12,13). But in this study, visceral pleural invasion was not associated with recurrence or survival. Hung’s report showed that visceral pleural invasion did not influence OS and DFS in patients with resected stage I NSCLC with a diameter of 3 cm or less (14). In our data, 213 patients (84.5%) with 3 cm or less tumor size, that might explain our results.

The heterogeneity of stage I lung adenocarcinoma might be correlated with complicated pathological morphology. Lung adenocarcinoma consisted of several pathological subtypes, which contributed to clinical, radiological,

pathological and molecular level of heterogeneity (15,16). In 2011, new histopathological classification of lung adenocarcinoma was proposed by IASLC/ATS/ERS and divided into three groups according to the prognosis. The prognosis of the lepidic predominant adenocarcinoma was good, the acinar and papillary predominant adenocarcinoma were moderate, and solid and micropapillary adenocarcinoma were poor (17). The results of this series showed that pathological subtypes likely affected recurrence and metastasis, but no statistically significant difference was revealed in univariate and multivariate analysis, which may

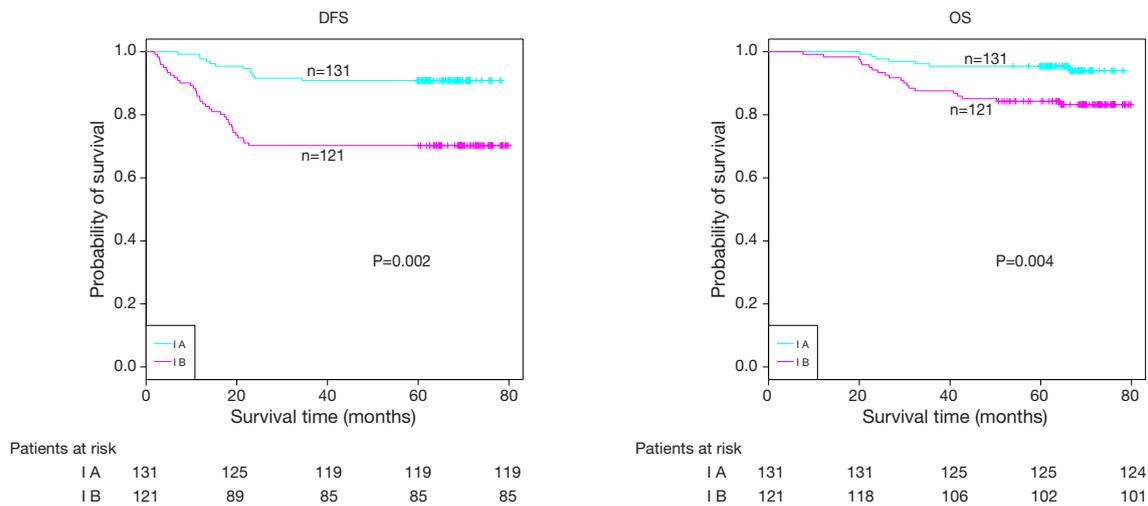


Figure 2 DFS (P=0.002, log-rank test) and OS (P=0.004, log-rank test) estimated by Kaplan-Meier in stage IA and IB patients. DFS, disease-free survival; OS, overall survival.

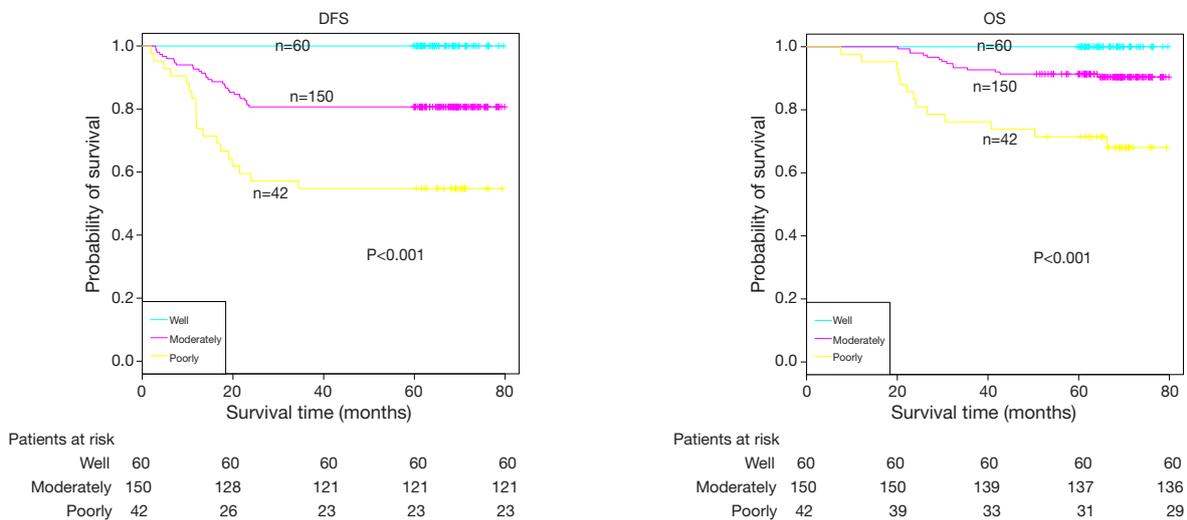


Figure 3 DFS and OS estimated by Kaplan-Meier in patients with different grades of tumor differentiation (P<0.001, log-rank test). DFS, disease-free survival; OS, overall survival.

be caused by this limited example and it could not deny the prognosis-predictive value of new adenocarcinoma classification system and large enough examples are still needed to demonstrate its significance.

Micropapillary component was reported as one of the risk factors of poor prognosis in most of the articles. Warth *et al.* (18) analyzed 487 lung adenocarcinoma patients and found that OS differed significantly among five subtypes. The OS, DFS and disease-specific survival (DSS) of solid and micropapillary predominant were much worse than

that of other adenocarcinomas. Kamiya *et al.* (19) reported that components, 383 patients with lung adenocarcinoma were classified as none (0%), focal (<10%), moderate (<50%), or extensive (≥50%) based on the proportion of micropapillary pattern area in the tumors. The 5-year and 10-year OS rates of the micropapillary pattern-positive group were significantly poor than that of micropapillary pattern-negative group, and as the micropapillary pattern proportion increased, the prognosis became worse and worse. Zhang *et al.* (20) reported similar result as Kamiya

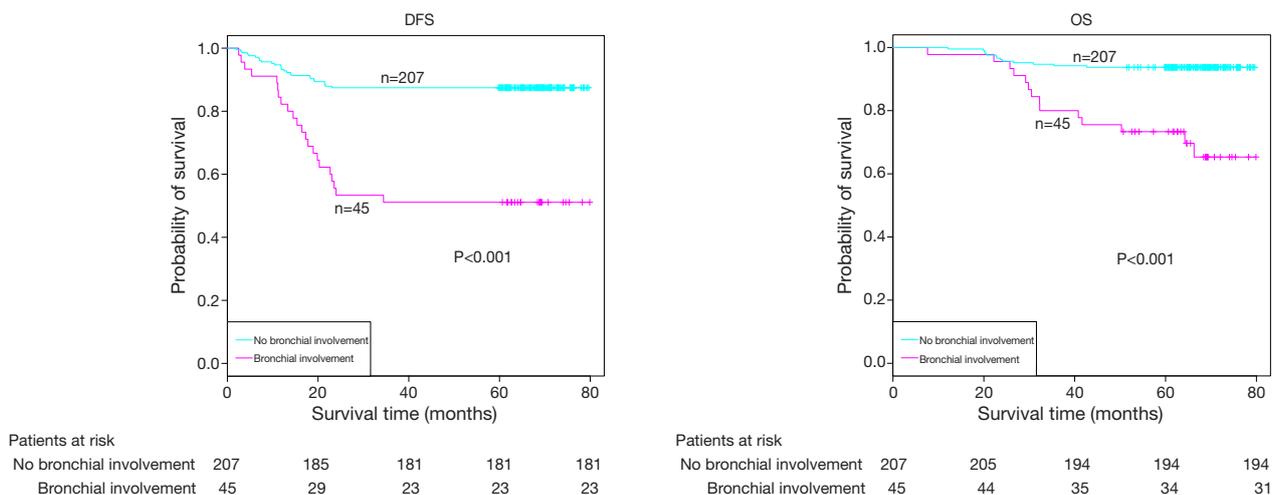


Figure 4 DFS and OS estimated by Kaplan-Meier in patients with or without bronchial involvement (P<0.001, log-rank test). DFS, disease-free survival; OS, overall survival.

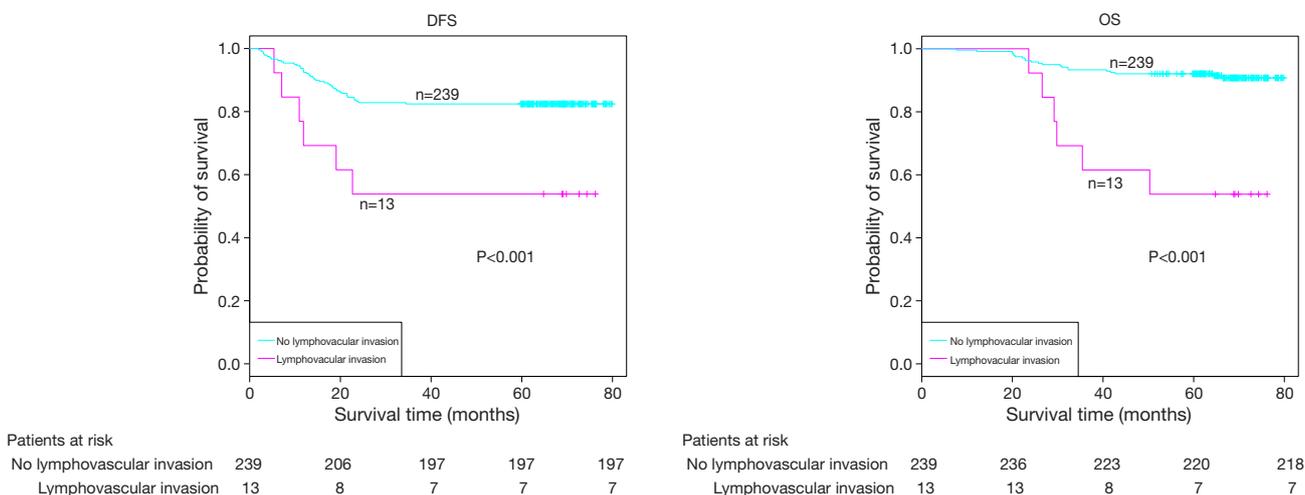


Figure 5 DFS and OS estimated by Kaplan-Meier in patients with or without lymphovascular invasion (P<0.001, log-rank test). DFS, disease-free survival; OS, overall survival.

et al. reported based of analysis of 886 adenocarcinomas. All the above studies demonstrated that micropapillary pattern was a risk factor for lung adenocarcinoma, but no comparison between early stage and advanced stage lung adenocarcinoma was reported. Up to now, few literatures reported the influence of micropapillary pattern on the prognosis in early lung adenocarcinoma.

The prognosis of the patients with positive micropapillary pattern was compared with that of negative micropapillary pattern in this series, regardless of its proportion. We found that micropapillary pattern was a statistically significant predictor

of recurrence, metastasis and prognosis. This was consistent with the results reported in several literatures (20-22). Lee *et al.* (23) reported that 525 lung adenocarcinoma patients were classified into three subgroups according to the presence and proportion of micropapillary subtype: (I) ≥5% of the micropapillary pattern (n=114); (II) <5% of the micropapillary pattern (n=115); and (III) absence (<1%) of the micropapillary pattern (n=296). He found that even a small proportion of micropapillary pattern (<5%) had a significant prognostic impact on OS. Therefore, the p I lung adenocarcinoma patients with micropapillary pattern

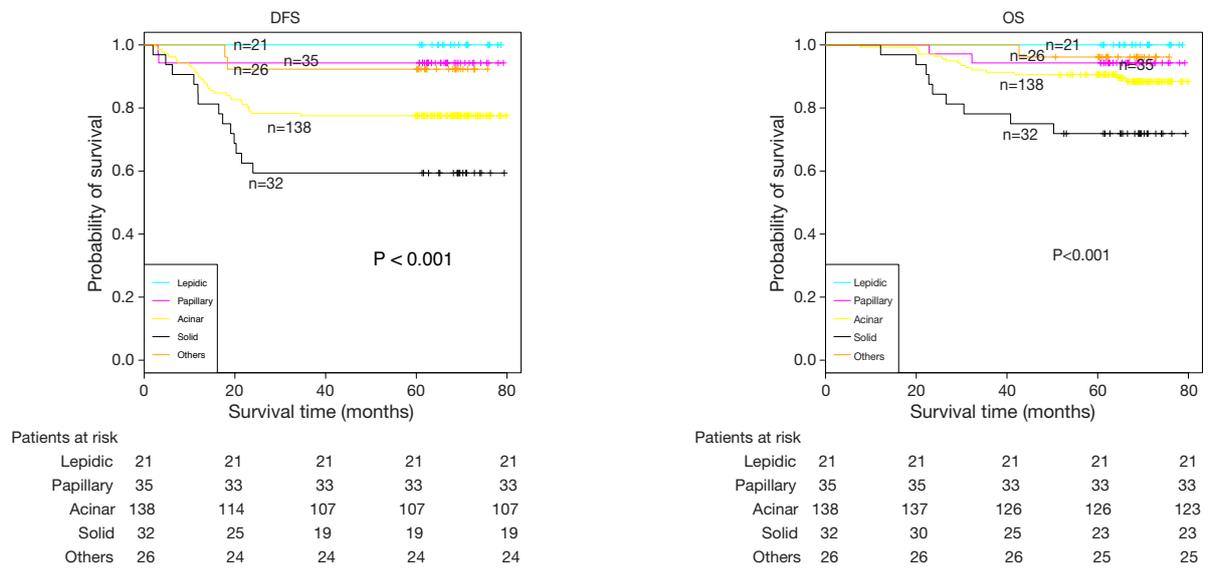


Figure 6 DFS and OS estimated by Kaplan-Meier in patients with different pathological subtypes (P<0.001, log-rank test). DFS, disease-free survival; OS, overall survival.

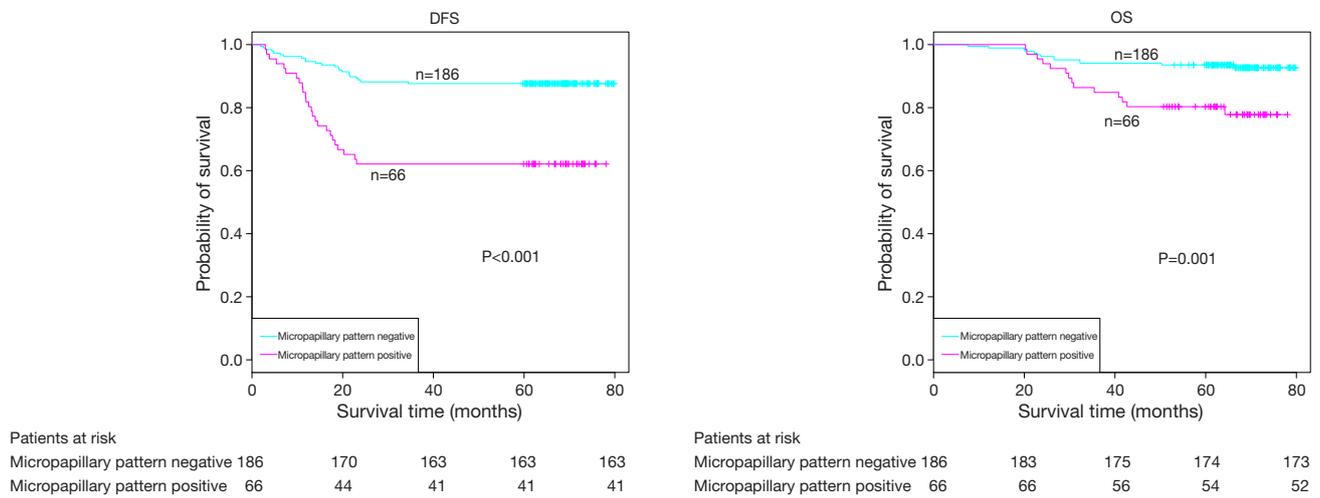


Figure 7 DFS (P<0.001, log-rank test) and OS (P=0.001, log-rank test) estimated by Kaplan-Meier in patients with or without micropapillary pattern. DFS, disease-free survival; OS, overall survival.

might need a closer follow-up and more aggressive adjuvant therapy in order to improve the prognosis.

This was a small cohort retrospective study in a single center and some limitations might be existed due to the flaws made during the operations which were completed by different surgeons and the pathological findings which were reported by different pathologists. Therefore, in order to clarify all above discussed factors that might affecting the

recurrence and survival, further research using molecular biomarkers to stratify the subgroups are still needed.

In conclusion, tumor size, TNM stage, tumor differentiation, bronchial involvement, lymphovascular invasion and micropapillary pattern could be considered as risk factors for predicting local recurrence or distant metastasis and survival in curatively resected p I lung adenocarcinoma patients. The new pathological classification

Table 2 Locations of 48 patients with local recurrence or distant metastasis

Recurrence location	Patient number	%
Local	6	12.5
Recurrence	2	4.2
Regional lymph nodes	4	8.3
Distant	42	87.5
Pleura	3	6.3
Contralateral lung	9	18.8
Distant lymph nodes	5	10.4
Chest wall	1	2.1
Bone	6	12.5
Brain	8	16.7
Adrenal gland	1	2.1
≥ two lesions	9	18.8

system in lung adenocarcinoma had an important clinical significance for prediction of prognosis and adjuvant therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the ethical committee of Cancer Hospital, Chinese Academy of Medical Sciences (No. NCC2014ST-07).

Table 3 Univariate analysis of the factors affecting survival

Variables	DFS		OS	
	P value	95% CI	P value	95% CI
Gender	0.085	0.34–1.07	0.121	0.25–1.18
Age	0.284	0.99–1.05	0.161	0.99–1.08
Smoking cigarette	0.029	0.30–0.94	0.241	0.37–1.27
Family cancer history	0.860	0.50–1.79	0.606	0.59–2.45
Tumor size	<0.001	2.03–7.82	<0.001	4.09–222
TNM stage	<0.001	1.98–7.32	0.004	1.37–7.65
Tumor differentiation	<0.001	2.43–6.33	<0.001	2.51–9.45
Visceral invasion	0.091	0.28–1.13	0.639	0.35–1.93
Bronchial involvement	<0.001	0.12–0.38	<0.001	0.09–0.39
Lymphovascular invasion	0.021	0.13–0.74	0.001	0.07–0.41
Postoperative adjuvant chemotherapy	0.365	0.43–1.35	0.969	0.46–2.12
Pathological subtype	0.041	1.01–1.74	0.100	0.94–1.96
Micropapillary pattern	<0.001	2.07–6.45	0.003	1.52–6.87

DFS, disease-free survival; OS, overall survival; CI, confidence interval.

Table 4 Multivariate analysis of the factors affecting survival

Variables	DFS		OS	
	P value	95% CI	P value	95% CI
Tumor size	0.336	0.68–3.12	0.009	1.93–11.5
TNM stage	0.007	1.31–5.39	0.415	0.59–3.56
Tumor differentiation	<0.001	2.34–7.10	<0.001	2.28–10.7
Bronchial involvement	0.004	0.22–0.75	0.178	0.26–1.29
Lymphovascular invasion	0.091	0.20–1.12	0.010	0.12–0.75
Micropapillary pattern	0.001	1.49–4.91	0.056	0.98–4.84

DFS, disease-free survival; OS, overall survival; CI, confidence interval.

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