Analysis of prognostic factors after Surgery for Stage IA Invasive Lung Adenocarcinoma

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Research

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Abstract

Background

Lung cancer is one of the most common malignant tumors with poor prognosis. Even for stage IA, many cases relapsed after completed resection. In the era of precision medicine, it is of great significance to determine the risk factors for postoperative recurrence or death in stage IA invasive lung adenocarcinoma.

Methods

The data of patients with pathological stage IA invasive lung adenocarcinoma underwent complete resection from June 2012 to December 2016 in Fujian Provincial Hospital were collected and retrospectively analyzed. Recurrence-free survival (RFS) was estimated by the Kaplan-Meier method and compared with the log-rank test. The Cox proportional risk model was used to analyze the factors affecting the RFS.

Results

A total of 210 patients were enrolled in the study. During the follow-up period, 14 (6.7%) patients recurred. Univariate survival analysis showed that predominant pathological subtype, micropapillary/solid pattern, stage T1b and lymphovascular invasion were correlated with RFS ($P < 0.05$). Cox multivariate analysis showed that the micropapillary/solid pattern was associated with RFS ($P < 0.01$). Patients with micropapillary/solid pattern had a worse 5-year RFS rate than those without micropapillary/solid pattern (82.3% versus 96.7%, $P < 0.001$).

Conclusion

Pathological subtype is a prognostic factor for patients with pathological stage IA invasive lung adenocarcinoma. Patients with micropapillary/solid pattern have a poor prognosis. Lymphovascular invasion and stage T1b are also correlated with poor RFS. These findings may serve as reliable predictive factors for long-term prognostic, and provide theory evidence for the choice of postoperative adjuvant therapy for patients with lung adenocarcinoma in stage IA.

1. Introduction

Lung cancer is the leading cause of cancer-related death in humans worldwide[1]. Adenocarcinoma is the most common histological type of lung cancer. At present, surgical resection is the main treatment option for early-stage non-small cell lung cancer (NSCLC)[2]. Patients with pathologic stage (p-stage) I NSCLC

have a good prognosis, with a 5-year survival rate of over 70%. However, there is still a large difference between stage IA and IB. The 5-year survival rate of patients with stage IA NSCLC is more than 80%[3, 4]. Even for stage IA, the main reason for treatment failure is postoperative recurrence. In the era of precision medicine, it is of great significance to determine the risk factors for postoperative recurrence or death in stage IA invasive lung adenocarcinoma (IADC) for guiding clinical practice and designing clinical trials for high-risk patients. It can also guide the selection of adjuvant treatment for high-risk patients with early-stage lung cancer after surgery.

The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS) proposed a new classification of lung adenocarcinoma in 2011[5], which was also adopted in the 2015 World Health Organization (WHO) classification of lung tumors[6]. The main pathological subtypes of lung adenocarcinoma include lepidic, acinar, papillary, micropapillary and solid types[5, 6]. So far, there have been studies showing the effects of the new classification on postoperative survival. Micropapillary and solid predominant subtypes indicate the poor postoperative outcomes in patients with lung adenocarcinoma[7]. However, it is difficult to reflect the factors influencing the prognosis of p-stage IA IADC. Therefore, this study aimed to explore the factors influencing the prognosis of completely resected p-stage IA IADC and to provide more favorable evidence for postoperative adjuvant treatment.

2. Materials And Methods

2.1. Patients

In this study, the data of all patients who underwent complete resection for p-stage IA lung adenocarcinoma in Fujian Provincial Hospital from June 2012 to December 2016 were retrospectively reviewed. Before the operation, clinical stage was assessed by chest computed tomography (CT), upper abdomen CT or abdomen ultrasound, brain magnetic resonance imaging (MRI) or enhanced CT and whole body bone imaging with emission computed tomography (ECT) according to the 8th edition of American Joint Committee on Cancer/International Union for Cancer Control (AJCC/UICC) cancer staging manual[8]. The postoperative pathological staging determination was also based on the 8th edition of AJCC/UICC TNM Classification[8]. Patients who received preoperative neoadjuvant chemotherapy or radiotherapy were excluded, as were patients with lung adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA).

2.2. Clinicopathological characteristics

The clinicopathological characteristics of patients were collected, including age, sex, smoking history, type of resection, extent of lymph node dissection, postoperative adjuvant therapy, tumor diameter, pathological subtypes, lymphovascular invasion (LVI) and tumor epidermal growth factor receptor (EGFR) status. All resected specimens were fixed in formalin and stained with hematoxylin and eosin (H&E). Histological subtypes were classified according to the 2011 IASLC/ATS/ERS and the 2015 WHO

classification of lung adenocarcinoma. The main pathological subtypes included lepidic, acinar, papillary, micropapillary and solid subtypes, and other rare subtypes were also recorded[5]. We recorded the percentage of each histological component in 5% increments. The presence of a histological subtype is defined as the percentage of this histological component ≥ 5%. The predominant pathological subtype is defined as the subtype with the highest percentage. The extent of pulmonary resection and lymph node dissection was determined according to the experience of the surgeon and the process of surgery. The postoperative adjuvant chemotherapy was mainly dependent on the doctors' attitude, because the adjuvant chemotherapy remains controversial in stage IA NSCLC. It is not necessary for patients with stage IA NSCLC to receive adjuvant chemotherapy after surgery according to guidelines. However, previous studies showed that patients with micropapillary or solid predominant subtype may benefit from postoperative adjuvant chemotherapy, even in early-stage lung adenocarcinoma[9].

2.3. Follow-up protocol

Chest CT was the routine examination, performed every 3 months in the first year after surgery and every 6 months thereafter. Upper abdomen CT or abdomen ultrasound was also recommended as a routine exam. Brain MRI or CT was performed when neurological symptoms occurred or when brain metastasis was suspected. Whole body bone imaging with ECT was performed for suspected bone metastasis. The recurrence is defined as either local recurrence or distant metastasis. We distinguished recurrent lung cancer from multiple primary lung cancer according to the recommendation of Detterbeck et al[10, 11]. For patients who did not undergo the second surgery or biopsy, the diagnosis was determined in the light of positive imaging examinations and clinical courses of disease. After initial diagnosis of recurrence, further examinations were performed to detect other metastases. Overall survival (OS) is defined as the interval between the date of surgery and the date of death from any cause or last follow-up. Recurrence-free survival (RFS) is defined as the interval between the date of surgery and the date of initial diagnosis of recurrence or last follow-up. Survival date were collected through telephone from the date of surgery till February 2020.

2.4. Statistical analysis

The count data were expressed as percentage (%) and the measurement data were presented as mean ± standard deviation (SD). The OS and RFS rates were calculated by the Kaplan-Meier method, and comparisons between the groups were made by the log-rank test in univariate analysis. The Cox proportional hazards model was used for multivariate analysis. All of the variables with P values < 0.1 in univariate analysis were included in multivariate analysis. SPSS software version 21.0 (IBM, Armonk, NY, USA) was used for statistical analysis. GraphPad Prism software version 6.0 (GraphPad Software, La Jolla, CA, USA) was used for plotting. P values < 0.05 were considered statistically significant.

3. Results

3.1. Clinicopathological characteristics of patients

A total of 353 patients diagnosed with p-stage IA lung cancer were screened retrospectively. 210 patients diagnosed with p-stage IA IADC with complete follow-up data were enrolled in the study. (Fig. 1).

The median follow-up period of all patients was 52.0 months (ranging from 15 to 92 months). During follow-up, 6 (2.9%) patients died (3 deaths due to lung cancer from 20 to 47 months after surgery and 3 deaths unrelated to lung cancer) and 14 (6.7%) cases relapsed. For all patients, 3-year OS and RFS rates were 97.62% and 93.74% and 5-year OS and RFS rates were 94.5% and 93.1% (Fig. 2A and 2B). The clinical and pathological characteristics of 210 patients are shown in Table 1. The median age was 59 years old (ranging from 27 to 75 years). Among the 210 cases, 161 (76.7%) underwent lobectomy, 28 (13.3%) received segmentectomy, 21 (10.0%) underwent wedge resection, none of them underwent pneumonectomy. Mediastinal lymph node dissection was performed in 197 (93.8%) cases and mediastinal lymph node sampling was only performed in the other 13 (6.2%) cases. As for pathological components, there were 200 (95.2%) cases containing acinar pattern, 180 (85.7%) containing lepidic pattern, 76 (36.2%) containing papillary pattern, 37 (17.6%) containing micropapillary pattern, 19 (9.0%) containing solid pattern, 4 (1.9%) containing mucinous pattern and 2 (1.0%) containing fetal pattern. For predominant pathological subtype, 99 (47.1%) patients were acinar predominant, 85 (40.5%) were lepidic predominant, 17 (8.1%) were papillary predominant, 1 (0.5%) was micropapillary predominant, and 4 (1.9%) cases were solid predominant. LVI was present in 21 (10.0%) cases. During follow-up, 14 (6.7%) patients relapsed with a median recurrence time of 22.0 months (ranging from 6 to 42 months). Among these 14 cases, 3 of them suffered from lung cancer-specific death after surgery during the follow-up period, all of which were confirmed by pathology. The pathological characteristics of these 3 cases are shown in Table 2.

Table 1
Clinicopathological characteristics of patients. (n = 210)

Characteristic	Value
Median follow-up period(months)	52
Age, years (mean ± SD)	58.1 ± 9.5
Sex, n (%)	
Male	108(51.4)
Female	102(48.6)
Smoking history, n (%)	
Yes	46(19.5)
No	169(80.5)
Type of resection, n (%)	
Lobectomy	161(76.7)
Segmentectomy	28(13.3)
Wedge resection	21(10.0)
Mediastinal LN dissection, n (%)	
Yes	197(93.8)
No	13(6.2)
Adjuvant therapy, n (%)	
Yes	6(2.86)
No	204(97.14)
Tumor size, cm (mean ± SD)	1.5 ± 0.5
T stage, n (%)	
T1a	59(28.1)
T1b	116(55.2)
T1c	35(16.7)
Lymphovascular invasion, n (%)	
Yes	21(10.0)

SD, Standard deviation; LN, lymph node.

Characteristic	Value
No	189(90.0)
Predominant pattern, n (%)	
Lepidic predominant	85(40.5)
Acinar predominant	99(47.1)
Papillary predominant	17(8.1)
Micropapillary predominant	1(0.5)
Solid predominant	4(1.9)
Other predominant	4(1.9)
Pathological subtype pattern, n (%)	
Lepidic pattern	180(85.7)
Acinar pattern	200(95.2)
Papillary pattern	76(36.2)
Micropapillary pattern	37(17.6)
Solid pattern	19(9.0)
Micropapillary/solid pattern	52(24.8)
Other patterns	6(2.9)
EGFR status, n (%)	
Mutated	126(60.0)
Wild type	54(25.7)
Unknown	30(14.3)
SD, Standard deviation; LN, lymph node.	

Table 2
The pathological characteristics of the 3 patients died from lung cancer.

NO.	Tumor size (cm)	Pathological components	LVI	OS (months)	RFS (months)
1	1.4	Lepidic:30%; acinar:40%; micropapillary:30%	No	47	15
2	1.8	Lepidic:45%; acinar:35%; papillary:10%; micropapillary:10%	Yes	51	33
3	1.5	Acinar:30%; micropapillary:10%; solid:60%	Yes	20	18

Tumor size, maximum tumor diameter; LVI, lymphovascular invasion; OS, overall survival; RFS, recurrence-free survival.

3.2. Prognosis analysis

The patients were divided into > 59 and ≤ 59 years old according to the median age (59 years old) of 210 patients. Survival analysis by age, sex, smoking history, type of resection, extent of lymph node dissection, adjuvant therapy, pathological subtype pattern, LVI and tumor EGFR status was conducted. Since only 3 of 210 (1.4%) patients suffered from lung cancer-specific death, we just performed univariate and multivariate survival analyses for RFS in patients with p-stage IA IADC.

In univariate analysis, p-stage, LVI, major pathological subtype and micropapillary/solid pattern were correlated with RFS ($P < 0.05$), as predictors of postoperative recurrence. The RFS rate of patients with stage T1b was lower than stage T1a ($P = 0.045$), while the difference between stage T1c and stage T1a was not statistically significant ($P = 0.321$). The cases without LVI had a better prognosis than those with LVI ($P = 0.024$). The pathological components were divided into micropapillary/solid pattern and non-micropapillary/solid pattern according to the presence of micropapillary and/or solid patterns. RFS rate of patients with micropapillary/solid predominant was lower than non-micropapillary/solid predominant ($P = 0.007$). The patients without micropapillary/solid pattern had a better prognosis, compared with the patients with micropapillary/solid pattern ($P < 0.001$). However, age, sex, smoking history, extent of surgical resection, adjuvant chemotherapy and EGFR status were not significantly correlated with RFS ($P > 0.05$), as shown in Table 3.

Table 3
Univariate survival analysis of recurrence-free survival in patients with p-stage IA IADC. (n = 210)

Variables	HR	95%CI	*P* value
Age, years (> 59/≤59)	1.384	0.500-3.829	0.392
Male/Female	2.318	0.813–6.614	0.116
Smoking history (Yes/No)	1.193	0.315–4.570	0.066
Type of resection (Lobectomy/ Sublobectomy)	1.273	0.374–4.330	0.149
Mediastinal lymph node dissection (Yes/No)	0.873	0.102–7.501	0.901
Adjuvant therapy (Yes/No)	2.856	0.374–21.840	0.312
T stage			
T1a	1		
T1b	3.200	0.906–10.512	0.045
T1c	3.370	0.306–37.167	0.321
Lymphovascular invasion (Yes/No)	3.808	1.194–12.145	0.024
Predominant pattern			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	7.872	1.758–35.240	0.007
Micropapillary/solid pattern (Yes/No)	6.115	2.049–18.254	< 0.001
EGFR (Mutated / Wild type)	0.614	0.181–2.081	0.433
HR, Hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor.			

The variables with *P* values < 0.1 in univariate survival analysis, which include smoking history, T stage, LVI, major pathological subtype and the micropapillary/solid pattern were included in Cox multivariate analysis. We found that micropapillary/solid pattern was independently associated with RFS in patients with p-stage IA IADC ($P < 0.05$). However, smoking history, LVI, T stage and major pathological subtype were not significantly correlated with the RFS ($P > 0.05$), as shown in Table 4.

Table 4
Cox multivariate survival analysis of recurrence-free survival in patients with p-stage IA IADC. (n = 210)

Variables	HR	95%CI	*P* value
Smoking history (Yes/No)	0.887	0.245–3.213	0.856
T stage			
T1a	1		
T1b	3.204	0.395–25.979	0.275
T1c	1.602	0.135–19.053	0.709
Lymphovascular invasion (Yes/No)	2.656	0.807–8.747	0.108
Predominant pattern			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	3.329	0.668–16.589	0.142
Micropapillary/solid pattern (Yes/No)	4.167	1.278–13.584	0.018
HR, Hazard ratio; CI, confidence interval.			

According to the result of Cox multivariate analysis, all patients were subdivided into two groups: patients without micropapillary/solid pattern (group 1) and patients with micropapillary/solid pattern (group 2). The Kaplan-Meier plot for RFS of these two groups showed that patients in the group with micropapillary/solid pattern had a higher likelihood of recurrence ($P < 0.001$). The 5-year RFS rate of patients with micropapillary/solid pattern was worse than those without micropapillary/solid pattern (82.3% versus 96.7%, $P < 0.001$), as shown in Fig. 3.

Discussion

In this study, we retrospectively investigated the clinicopathological characteristics and postoperative prognosis of 210 patients with p-stage IA lung adenocarcinoma, according to the 8th edition of the AJCC/UICC TNM classification. Univariate and multivariate analyses confirmed that micropapillary/solid pattern was independent predictor of RFS in patients with p-stage IA IADC after complete resection of lung cancer.

So far, a number of studies have been conducted on the survival and prognosis of patients with lung adenocarcinoma based on the 2011 IASLC/ATS/ERS classification and the 2015 WHO classification of lung adenocarcinoma. Most of these studies have reached the same conclusion that lung adenocarcinoma with micropapillary and solid predominant subtypes have poorer prognosis than other common subtypes[12, 13]. However, few studies have confirmed the prognosis predictive value of pathological subtypes in p-stage IA lung adenocarcinoma. Previous studies on the postoperative prognosis of early stage lung adenocarcinoma mainly focused on stage I or IB. Hung et al[14] reported the

prognosis predictive value of micropapillary/solid patterns in lung adenocarcinoma with tumor diameter ≤ 3 cm and lymph node negative. However, the study also included visceral pleural invasion, which is a known risk factor for poor prognosis in stage I lung adenocarcinoma[15]. What is more, some studies investigated the prognosis in patients with clinical stage IA lung cancer[16]. These studies included patients diagnosed as clinical stage IA before surgery but found pleural invasion and even lymph node metastasis after resection, which may lead to the decline of RFS and OS rates. There is another special type of stage IA lung adenocarcinoma, that is MIA, which has a good prognosis as AIS[17]. The inclusion of MIA may affect the outcome of prognostic analysis, especially for stage IA1.Therefore, this study excluded cases with pleural invasion, lymph node metastasis and MIA, focusing on patients with p-stage IA IADC.

This study showed that micropapillary/solid pattern was related to the RFS of patients with p-stage IA IADC. In both of the univariate and multivariate survival analyses, the differences were statistically significant ($P < 0.05$), meaning that micropapillary/solid pattern was an independent risk factor for poor prognosis of p-stage IA IADC. Stage IA lung adenocarcinomas without micropapillary/solid pattern had a better prognosis after complete resection. In terms of the univariate analysis for main pathological subtype, patients without micropapillary/solid pattern have higher RFS rate ($P < 0.01$), meaning the predominant pathological subtype of lung adenocarcinoma was associated with prognosis. However, there was no significant difference in multivariate analysis *(*$P > 0.05$). It may be due to the small proportion of patients with micropapillary/solid predominant subtype in this study, which affected our judgment on the prognosis predictive value of predominant pathological subtype. Further studies with larger sample sizes are still needed to verify the validity.

In addition to pathological subtypes, this study showed that, LVI was another prognostic factor ($P < 0.05$) in univariate Kaplan-Meier survival analysis of RFS. In a study of 306 patients, Samejima et al[18] found that LVI was a prognostic factor for p-stage IA1-2 lung adenocarcinoma. Patients with LVI had worse 5-year OS and 5-year RFS rates than those without LVI in stage IA1-2 lung adenocarcinoma. However, LVI could not be used to predict the prognosis of p-stage IA3 lung adenocarcinoma, which may be related to the low proportion of patients with stage IA3 included in that study. Therefore, LVI may also be an important factor for the prognosis of early-stage lung cancer.

In the univariate analysis, T stage was also associated with the prognosis of p-stage IA lung adenocarcinoma in this study. Patients with p-stage T1b had a worse prognosis than those with stage T1a ($P < 0.05$). However, there was no significant difference in 5-year RFS rates between stage T1c and T1a ($P > 0.05$), probably due to the small number of patients in p-stage T1c and few of them relapsed in our study. Secondly, segmentectomy is allowed for some early-stage lung cancers ≤ 2 cm according to preoperative assessment[19]. Moreover, lobectomy was generally selected for tumor > 2 cm which may also lead to this result of p-stage T1c. In the multivariate analysis, there was no statistically significant difference among the 5-year RFS rates of stage T1a, T1b and T1c ($P > 0.05$). We believe that stage T1c IADC is more invasive than T1a and T1b IADC, but the prognosis is affected by multiple factors.

Pathological T stage may not be an independent risk factor for recurrence of completely resected p-stage IA lung adenocarcinoma, but it needs to be further verified by more studies.

According to current guidelines, adjuvant chemotherapy is not recommended for p-stage IA lung adenocarcinoma after complete resection[19]. However, Wang et al[20] found that postoperative adjuvant chemotherapy was a favorable prognostic factor for p-stage IA IADC with micropapillary predominant subtype. Patients with p-stage IA micropapillary predominant adenocarcinoma could benefit from postoperative adjuvant chemotherapy. The use of adjuvant chemotherapy in this study was depended on surgeon's preference and experience. We seldom recommended patients with p-stage IA lung adenocarcinoma to perform adjuvant chemotherapy after surgery. Therefore, the sample size of this study was too small to evaluate the effect of adjuvant chemotherapy on early-stage lung adenocarcinoma. Multicenter clinical trials are needed to illuminate the value of postoperative adjuvant chemotherapy or immunotherapy for completely resected stage IA lung adenocarcinoma with high-risk factors.

In this study, the 5-year OS rate was 94.5% and the 5-year RFS rate was 93.1%, which were higher than the data reported previously. The possible reasons included: 1) the mean age of patients in this study was young; 2) the proportion of lepidic and acinar predominant subtypes were high, and the number of patients with micropapillary/solid predominant was small. As a result, the number of patients with postoperative recurrence was small in our study, which may affect the result. What is more, there are several other limitations in this study. Firstly, as a retrospective study, patient selection bias and potential selection bias between surgical procedures were inevitable. Secondly, only patients with p-stage IA IADC were selected as subjects and the overall prognosis of them was good. Therefore, prospective randomized control studies are needed to confirm these findings in the future.

Conclusions

In conclusion, we confirm that, pathological subtype is associated with the prognosis of p-stage IA lung adenocarcinoma. The presence of micropapillary/solid components is an independent risk factor for poor prognosis. Lymphovascular invasion and stage T1b also indicate poor RFS. The study provides useful evidence for clinical treatment selection and prognosis evaluation of these patients. These findings offer favorable evidence for the clinical treatment and survival prognostic of patients with p-stage IA IADC after completed resection. The study has an important reference value and guiding significance for early identification of high-risk patients with early-stage lung cancer after surgery to achieve precision treatment.

Declarations

Ethical approval and consent to participate

Ethical approval was not sought as we used routinely collected clinical data retrospectively.

Consent for publication

The consent to publish was obtained from patients, or their legal guardian.

Data Availability Statement

The data sets supporting the results of this article are included within the article. Some detail data during the study are available from the corresponding author by request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wenshu Chen: methodology, project administration, writing – review & editing;

Yun Ding: data curation, formal analysis, writing – original draft;

Peilin You: data curation, formal analysis, investigation;

Pengjie Tu: investigation, resources, software; supervision;

Jianyuan Huang: data curation, investigation;

Xiaojie Pan: methodology, project administration, writing – review & editing

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Figures

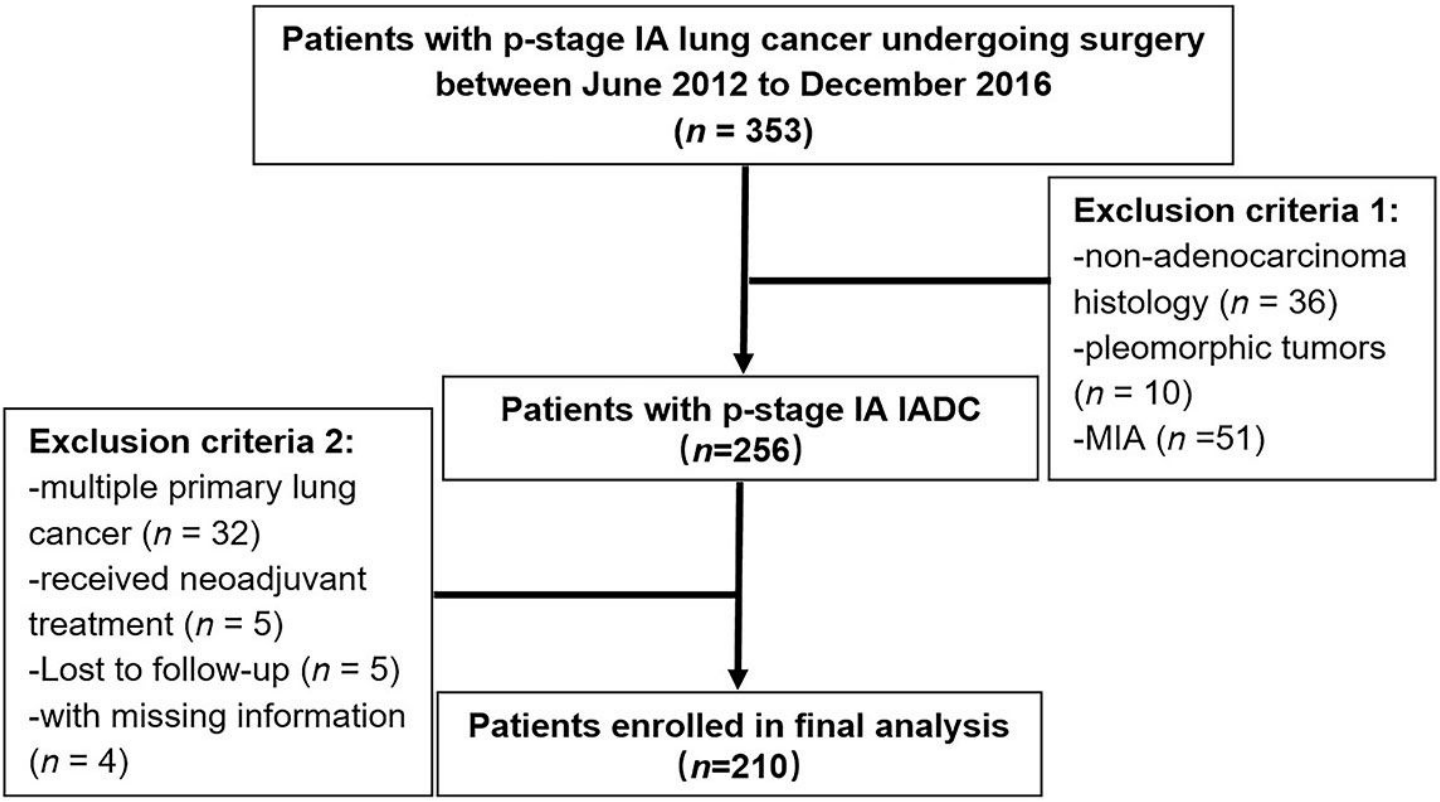

Figure 1

The study flow this chart to screen eligible patients diagnosed with p-stage IA IADC. p-stage, pathological stage; MIA, minimally invasive adenocarcinoma; IADC, invasive lung adenocarcinoma.

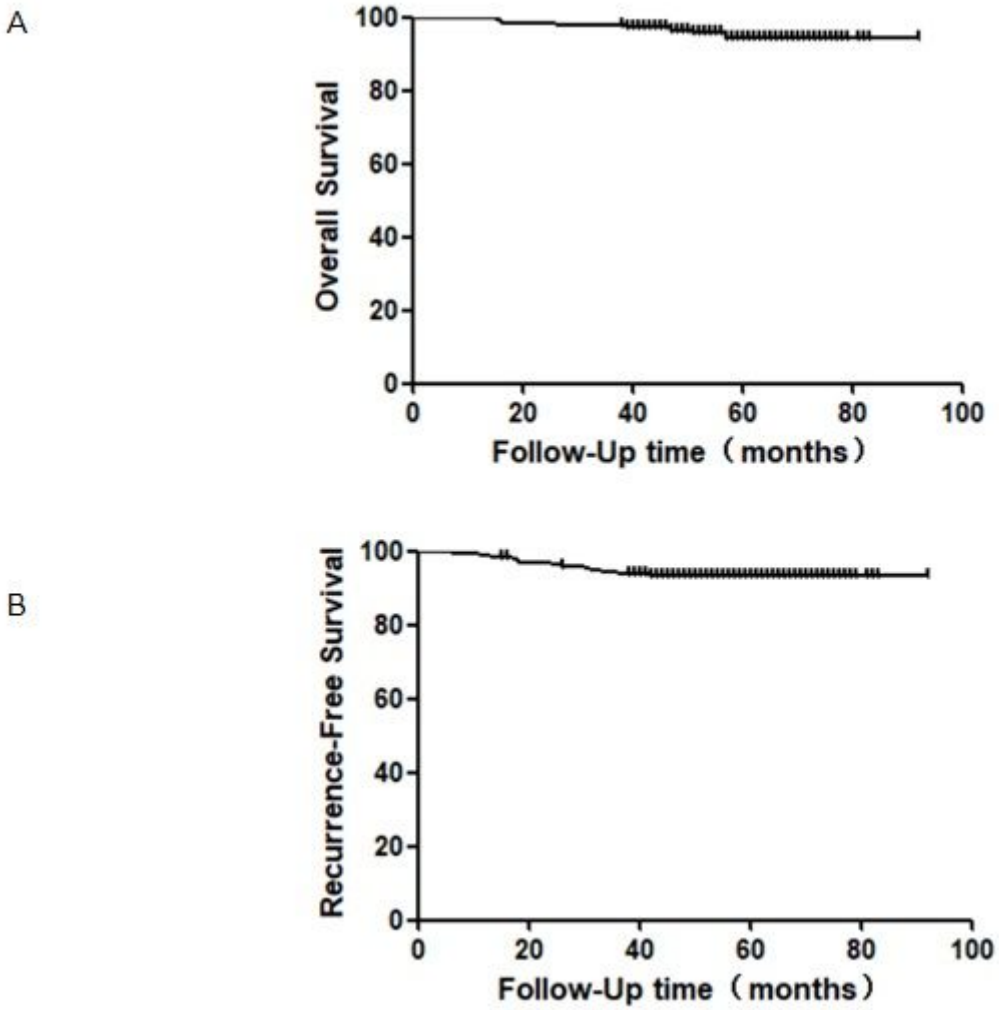

Figure 2

The study flow this chart to screen eligible patients diagnosed with p-stage IA IADC. p-stage, pathological stage; MIA, minimally invasive adenocarcinoma; IADC, invasive lung adenocarcinoma.

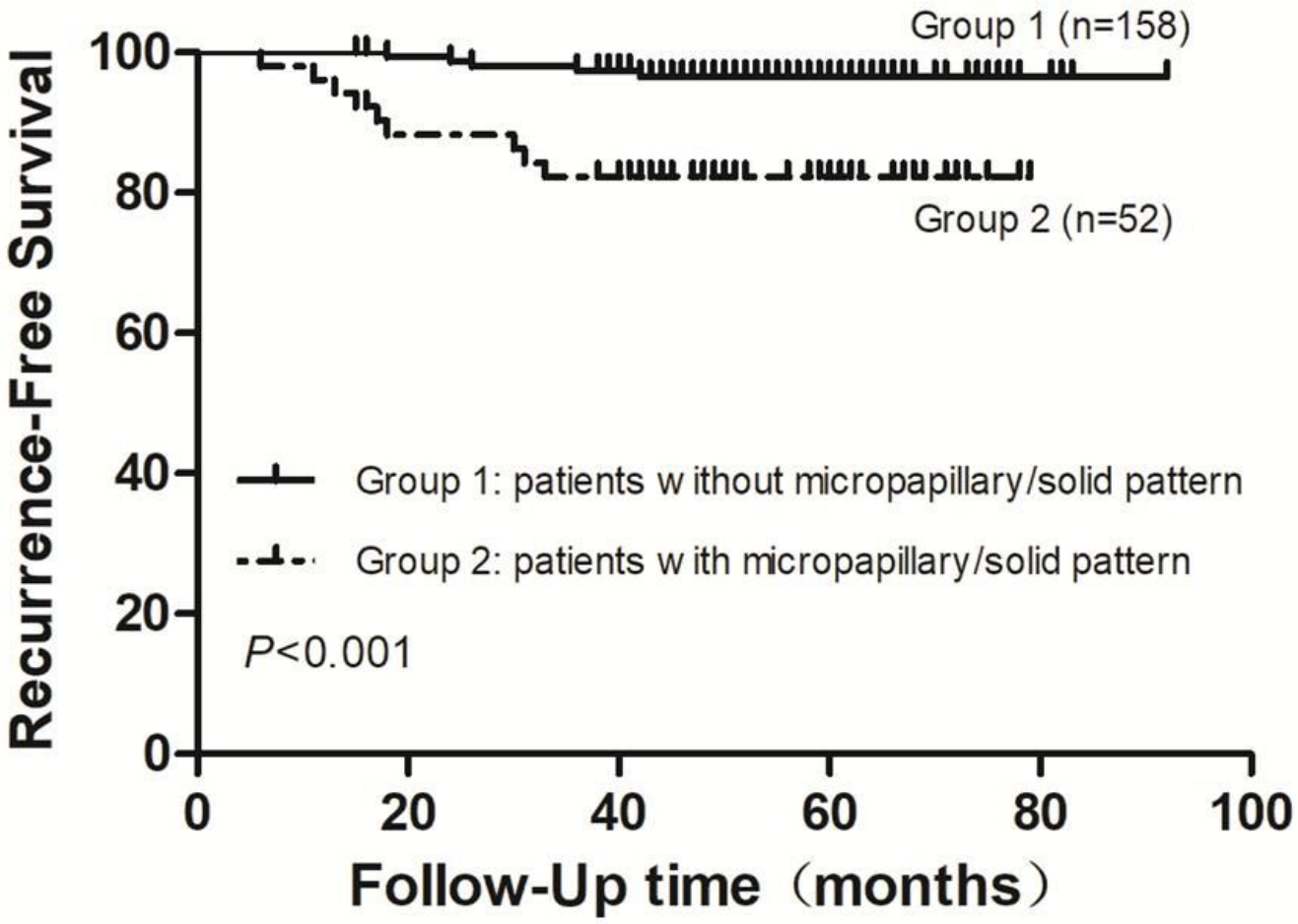

Figure 3

Recurrence-free survival curves for patients without micropapillary/solid pattern (group 1, n=158) and with micropapillary/solid pattern (group 2, n=52). There was a significant difference between two groups.