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ORIGINAL ARTICLE

Validation of stage groupings in the eighth edition of the tumor node metastasis classification for lung adenocarcinoma

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Keywords
EGFR gene mutation; lung adenocarcinoma; thoracic surgery; TNM classification.

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Abstract

Background: The purpose of this study was to validate stage groupings in the 8th edition of the tumor node metastasis (TNM) classification for lung adenocarcinoma and explore the non-anatomic factors that influence the prognosis of lung adenocarcinoma patients in China.

Methods: We retrospectively analyzed the data of 291 lung adenocarcinoma patients at our department between 2008 and 2013. Logrank tests and Cox regression models were used to analyze survival among adjacent stage groupings. Kaplan–Meier curves were used to estimate overall survival (OS).

Results: There were significant differences in OS in adjacent stage groupings in early stages in the 8th edition. There were also significant differences between patients treated with radical surgery and limited resection ($P = 0.027$). Lepidic predominant adenocarcinoma (LPA) had better survival rates than acinar predominant (APA), papillary predominant, and solid predominant with mucin production adenocarcinoma (SPA) ($P = 0.008$). Survival rates of micropapillary predominant adenocarcinoma were lower than the others ($P = 0.003$). *EGFR* mutations were closely associated with lepidic predominant (65%, $P = 0.56$) but less commonly associated with solid predominant with mucin production adenocarcinoma (24%, $P = 0.02$). There was no significant difference in survival between *EGFR* gene mutation-positive and negative groups ($P = 0.402$).

Conclusion: The 8th edition TNM may be more accurate and applicable than the 7th edition for Chinese lung adenocarcinoma patients who have undergone surgical treatment. Stage IV patients may gain survival improvement from radical surgery.

Introduction

The function of the tumor node metastasis (TNM) classification system is to describe the anatomical extent of malignant tumors. On 1 January 2017, the 8th edition of the TNM classification was released. This edition was developed based on the new International Association for Lung Cancer Study (IASLC) database, which collected information from 94 708 patients diagnosed with lung cancer between 1999 and 2010. Although patients from Asia comprised a large proportion of the database, most were from Japan and had been diagnosed with lung cancer before 2004.[1] China has the highest incidence of lung cancer in the world.[2] The clinical characteristics of Chinese patients differ from Japanese patients. A study reported that Chinese patients had a lower mean age with larger tumor sizes and higher TNM staging.[3] The number of adenocarcinoma cases has recently exceeded squamous cell carcinoma, and it has become the most common histological type of lung cancer in China, as well as in other developed countries.[4,5] Validation of the stage groupings in the 8th edition of the TNM classification aimed at patients with lung

adenocarcinoma in China is urgently needed, particularly because lung adenocarcinoma research has made significant clinical, radiologic, and pathologic advances, including molecular biology, in recent years.[6] Some non-anatomical elements, such as pathological classification and *EGFR* gene mutation status, are reported to influence lung adenocarcinoma prognosis. Although 23 non-anatomical elements are described in the new IASLC database,[1] pathological classification of lung adenocarcinoma and *EGFR* gene mutation status are not included. Thus, we combined these factors with other basic non-anatomical elements (e.g. age, gender) to determine valuable elements of patient survival from the 8th edition TNM classification.

Methods

The Ethical Review Committee of Tianjin Medical University General Hospital approved this study. All biological samples were obtained with patients' written informed consent. The Laboratory Animal Ethics Committee of Tianjin Medical University approved all procedures and experimental protocols. All methods were performed in accordance with the relevant guidelines.

Patients

We collected the medical records of 377 patients diagnosed with lung adenocarcinoma who underwent surgical treatment at the Department of Lung Cancer Surgery at Tianjin Medical University General Hospital between January 2008 and June 2013. Patients administered preoperative chemoradiation therapy or who died within 30 days of the preoperative period were excluded. Patients lost to follow-up were also excluded. A total of 291 patients were included in this study. After reviewing medical records and pathological data, patients were reclassified based on the 8th edition TNM classification for lung cancer.

Surgical approaches

Surgical approaches included lobectomy, sleeve lobectomy, wedge resection, segmentectomy, and pneumonectomy. The stage IV patients all had oligometastatic lung cancer. Our institution recommends surgery for advanced lung cancer. Radical surgical treatments, such as lobectomy, sleeve lobectomy, and pneumonectomy, are performed if the primary tumor can be completely resected and is followed by chemoradiation therapy. Metastatic nodules in the diaphragm and chest wall of the contralateral lung lobe are resected by wedge resection or segmentectomy if possible. Pleurodesis and pleural nodule cauterization are used for the pleura, pericardial nodules, and malignant effusions. Partial resection of the great vessels (with artificial vessel replacement), pericardial, and atrium is performed if computed tomography shows tumor invasion or obvious symptoms are exhibited (e.g. superior vena cava syndrome). Stage IV patients who undergo limited resection, such as wedge resection or segmentectomy, are administered chemoradiation therapy after confirmation of pathological type. Radiotherapy is administered to treat brain and bone metastases.

Pathological classification and *EGFR* gene mutation testing

The International Multidisciplinary Classification of Lung Adenocarcinoma (IMCLA, sponsored by the American Thoracic Society, IASLC, and the European Respiratory Society in 2011) was used to confirm pathological classification.[6] Preinvasive lesions consisted of atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA). Invasive adenocarcinomas were divided into lepidic predominant adenocarcinoma (LPA), acinar predominant (APA), papillary predominant (PPA), mucin production adenocarcinoma (MPA) and solid predominant with mucin production adenocarcinoma (SPA). Several variants of invasive adenocarcinomas (VIA) were also included: invasive mucinous adenocarcinoma (IMA), colloid adenocarcinoma, enteric adenocarcinoma, and fetal adenocarcinoma. *EGFR* gene mutation testing was conducted by SurExam Bio-Tech Co., Ltd. (Guangzhou China) in 162 patients using gene chip technology.

Statistical analysis

Overall survival (OS) was defined as the interval from the date of surgery to the date of death from any cause. Kaplan–Meier curves were used to estimate OS in the different groups. Significant differences among the survival curves were compared using the logrank test. Cox regression analyses were used to calculate hazard ratios (HRs) between adjacent stage groupings and were adjusted by baseline factors (age, gender, pathological subtype, smoking history) and surgical procedure. Chi-square tests were used to analyze the distributions of gene mutations in different subtypes. All methods were two-sided, and $P < 0.05$ was considered a statistically significant difference. SPSS version 20 (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

The study cohort of 291 patients consisted of 156 (53.6%) men and 135 (46.4%) women, at a median age of 62 (interquartile range [IQR] 56–68) years. The median follow-up

duration was 53.3 (IQR 20.7–69.8) months. Lobectomy was performed in 229 (78.7%) patients. Of the 162 patients tested, 73 patients had an *EGFR* gene mutation. Patient characteristics are summarized in Table 1. No patients in this study cohort were classified as stage IIIC according to the 8th edition of the TNM classification. Changes in stage groupings are provided in Table 2. Several stages were increased (IB, IIA, IIB and IIIA) from the 7th edition TNM classification.

Patient survival based on the tumor node metastasis (TNM) classification

Survival curves from the 7th and 8th editions of the TNM classification are shown in Figure 1 with results of the log-rank test. There were no significant survival differences between adjacent stage groupings from the 7th and 8th editions. The five-year survival rates (5-YSR) of our study and the IASLC database are shown in Figure 2. The 5-YSR for stage IV patients was 33.8%, which was higher than in the IASLC database.

Comparison of different surgical procedures in stage IV

Of the patients with stage IV lung adenocarcinoma, 30 underwent radical surgery (e.g. lobectomy, pneumonectomy, sleeve lobectomy); 6 underwent partial resection of the great vessels, pericardial and atrium; and 16 patients underwent limited resection (wedge resection and segmentectomy). Survival curves of the different resections and metastasis situations are shown in Figure 3. The median survival time (MST) of the patients who underwent radical surgery was 58.8 months, which was much longer than in patients in other groups (16.7 months). Comparison between the two groups showed significant differences ($P = 0.027$).

Table 1 Patient characteristics

Variable ($n = 291$)	Value
Age (years)	
Median (IQR)	62 (56–68)
Gender	
Male	156 (53.6%)
Female	135 (46.4%)
Smoking history	
Positive	124 (42.6%)
Negative	167 (57.4%)
Tumor diameter (cm)	
Median (IQR)	3.0 (2.0–4.5)
Surgical procedure	
Lobectomy	229 (78.7%)
Sleeve lobectomy	20 (6.9%)
Wedge resection	33 (11.3%)
Segmentectomy	6 (2.1%)
Pneumonectomy	3 (1.0%)
EGFR gene mutation status	
Positive	73/162 (45.1%)
Negative	89/162 (54.9%)
Follow-up time (months)	
Median (IQR)	53.3 (20.7–69.8)

IQR, interquartile range.

Comparison between adjacent stages of TNM classification

The results of Cox regression models are shown in Table 3. The models were adjusted for age (≥ 60 years vs. < 60 years), gender (female vs. male), smoking history (positive vs. negative), and pathological classification. Surgical method was also included. In the 8th edition TNM classification, differences in adjacent stages between stage IA1–IIA were significant (IA1 vs. IA2: HR 0.131, 95% confidence interval [CI] 0.018–0.982, $P = 0.048$; IA2 vs. IA3: HR 0.172, 95% CI 0.068–0.432, $P < 0.001$; IA3 vs. IB: HR 0.290, 95% CI 0.115–0.730, $P = 0.009$; IB vs. IIA: HR 0.187, 95% CI 0.093–0.375, $P < 0.001$). In the 7th edition TNM classification, comparison between the adjacent stage groupings in stage IA–IIB showed significant differences (IA vs. IB: HR 0.214, 95% CI 0.108–0.424, $P < 0.001$; IB vs. IIA: HR 0.236, 95% CI 0.128–0.437, $P < 0.001$; IIA vs. IIB: HR 0.472, 95% CI 0.231–0.963, $P = 0.039$). Comparisons of other adjacent stage groupings between the 7th and 8th editions of the TNM classification showed no significant differences, but the HRs were all < 1. Changes to stage groupings occurred in stage IB, IIA (all patients were upgraded to IIB in the 8th edition), IIB and IIIA from the 7th edition. We compared survival between patients with and without stage migration at each stage by Cox regression models adjusted for age, gender, smoking history, and pathological classification. The comparison in stage IB showed a significant difference (IB# vs. IIA#: HR 0.265, 95% CI 0.074–0.950; $P = 0.042$). Comparison of the other groups showed no significant differences (IIB# vs. IIIA#: HR 2.817, 95% CI 0.828–9.581, $P = 0.097$; IIIA# vs. IIIB#: HR 0.750, 95% CI 0.364–1.546, $P = 0.436$).

Comparison between *EGFR* gene mutation positive and negative groups

Of the 162 patients who were tested, 73 had an *EGFR* gene mutation. Comparison of survival in *EGFR* gene mutation positive and negative groups is shown in Figure 4. There were no significant differences ($P = 0.402$). The MST of the patients in the two groups were similar, but there was a

Table 2 Changes to stage between the 7th and 8th editions of the TNM classification

		7th TNM classification							
		IA	IB	IIA	IIB	IIIA	IIIB	IV	Total (*n* %)
8th TNM classification	IA1	7	0	0	0	0	0	0	7 (2.4)
	IA2	21	0	0	0	0	0	0	21 (7.2)
	IA3	22	0	0	0	0	0	0	22 (7.6)
	IB	0	56	0	0	0	0	0	56 (19.2)
	IIA	0	9	0	0	0	0	0	9 (3.1)
	IIB	0	0	26	7	0	0	0	33 (11.3)
	IIIA	0	0	0	12	51	0	0	63 (21.6)
	IIIB	0	0	0	0	17	17	0	34 (11.7)
	IVA	0	0	0	0	0	0	45	45 (15.5)
	IVB	0	0	0	0	0	0	1	1 (0.3)
	Total (*n* %)	50 (17.2)	65 (22.3)	26 (9.0)	19 (6.5)	68 (23.4)	17 (6.8)	46 (15.8)	291 (100)

TNM, tumor node metastasis.

distinct difference in survival time when the survival rate was 75% (STs 75%).

Comparison between different histological subtypes

We confirmed the pathological classification of patients according to the IMCLA. Survival curves of patients based on pathological classification are shown in Figure 5. Relationships between pathological and TNM classification are shown in Figure 6. LPA mainly occurred in stage I and had the highest *EGFR* mutation frequency (65%, $P = 0.56$). SPA was mainly distributed in stage IIIA–IV (in the 7th and 8th TNM classifications). The frequency of *EGFR* mutation in SPA was lower than in other subtypes (24%, $P = 0.02$). Results of the logrank test (excluding VIA) and the frequency of *EGFR*, *KRAS*, and *ALK* mutations in different pathological subtypes are shown in Figure 5. LPA had better survival rates than APA, PPA, and SPA. MPA exhibited the worst survival rates.

Discussion

The TNM classification system is widely used worldwide in clinical practice to describe the anatomical extent of malignant tumors. It is a valuable resource for predicting patient survival and guiding treatment. The 8th edition of the TNM classification was released last year, and a large number of patients from Asia were included in the new IASLC database. However, these cases were mainly from Japan prior to 2004, thus the data may not be applicable to estimate lung cancer rates in China. Moreover the most common histological type of lung cancer in China is adenocarcinoma. Several specific non-anatomical elements, such as pathological classification, which have been shown to affect the prognosis of patients with adenocarcinoma,

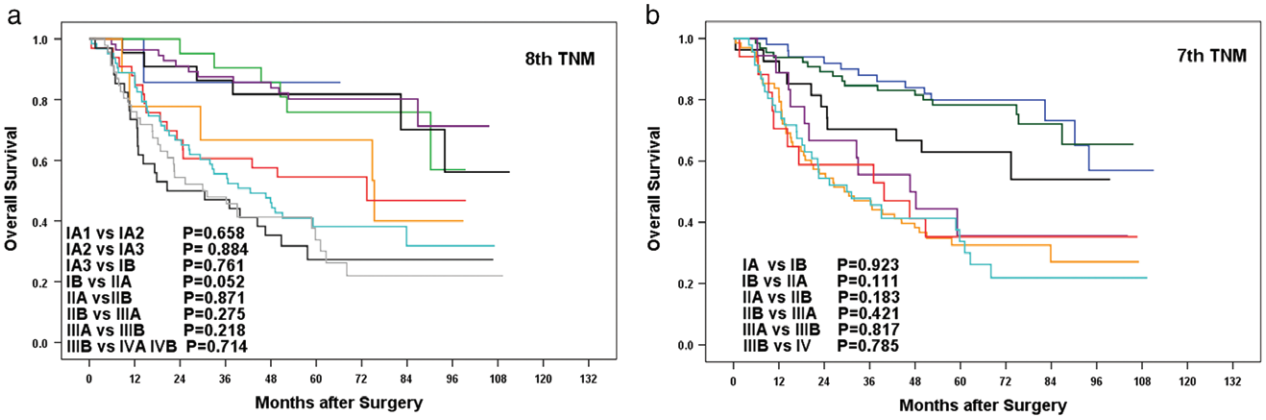


Figure 1 Overall Kaplan–Meier survival curves for patients according to the (**a**) 8th and (**b**) 7th editions of the tumor node metastasis (TNM) classification. 8th TNM: (——) IA1 (*n* = 7), (——) IA2 (*n* = 21), (——) IA3 (*n* = 22), (——) IB (*n* = 56), (——) IIA (*n* = 9), (——) IIB (*n* = 33), (——) IIIA (*n* = 63), (——) IIIB (*n* = 34), (——) IVA IVB (*n* = 46); 7th TNM: (——) IA (*n* = 50), (——) IB (*n* = 65), (——) IIA (*n* = 26), (——) IIB (*n* = 19), (——) IIIA (*n* = 68), (——) IIIB (*n* = 17), (——) IV (*n* = 46).

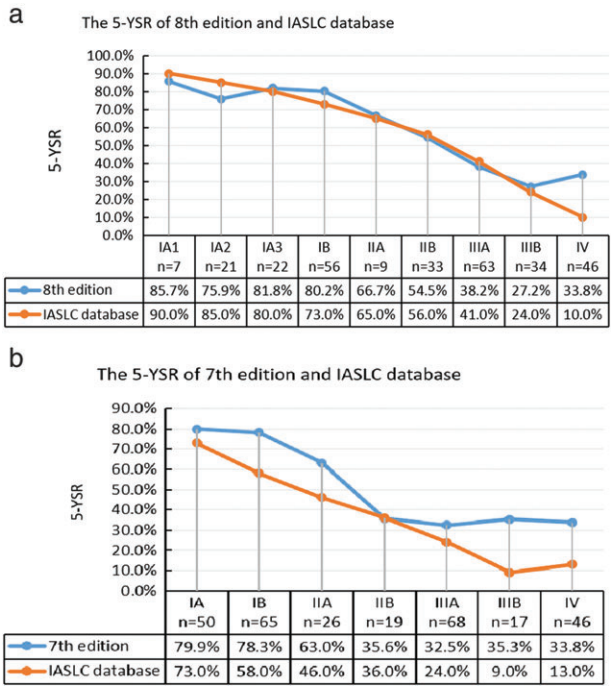


Figure 2 The five-year survival rates (5-YSRs) of our study and the International Association for Lung Cancer Study (IASLC) database using the (**a**) 8th and (**b**) 7th editions.

are not included in the database. This study evaluated the applicability of the 8th edition TNM classification for Chinese patients with lung adenocarcinoma.

Survival curves from the 7th and 8th editions of the TNM classification did not show obvious separation, and there were no significant differences between adjacent stage groupings. In the Cox regression models, survival rates of adjacent stage groupings (8th edition: IA1–IIA; 7th edition: IA–IIB) after adjusting for non-anatomic elements showed significant differences. The 5-YSR of patients decreased as stages were upgraded in the 8th edition of the TNM classification, although patients with stage IIB–IV had similar 5-YSR, which did not match the results in the IASLC database of the 7th edition. Furthermore, in stage IB (7th edition), patients that were not restaged as a result of the different editions showed better survival than patients who were restaged. These findings demonstrate that the 8th edition may be more applicable than the 7th edition for Chinese patients with lung adenocarcinoma. This is attributed to the larger cohort and the greater proportion of Asian patients included in IASLC database of the new edition classification.

The 5-YSRs of patients in the present study were similar to 5-YSRs in the IASLC database, except for stage IV in the 8th edition TNM classification. The 5-YSR for patients in stage IV was much higher than in the IASLC database. We attribute this to selection bias because 42 (91.3%) patients with stage IV were in the M1a (metastasis component descriptors) stage, and the radical surgery group consisted of oligometastatic lung cancer patients who had undergone radical surgery, as recommended at our institution. However, according to National Comprehensive Cancer Network (NCCN) guidelines,[7] definitive local therapy (parenchymal sparing resection [preferred], radiation, or ablation) is recommended, if possible, for patients with multiple lung cancers (N0-1) limited to the chest. For multiple lung cancers (N2–3), systemic therapy is recommended.

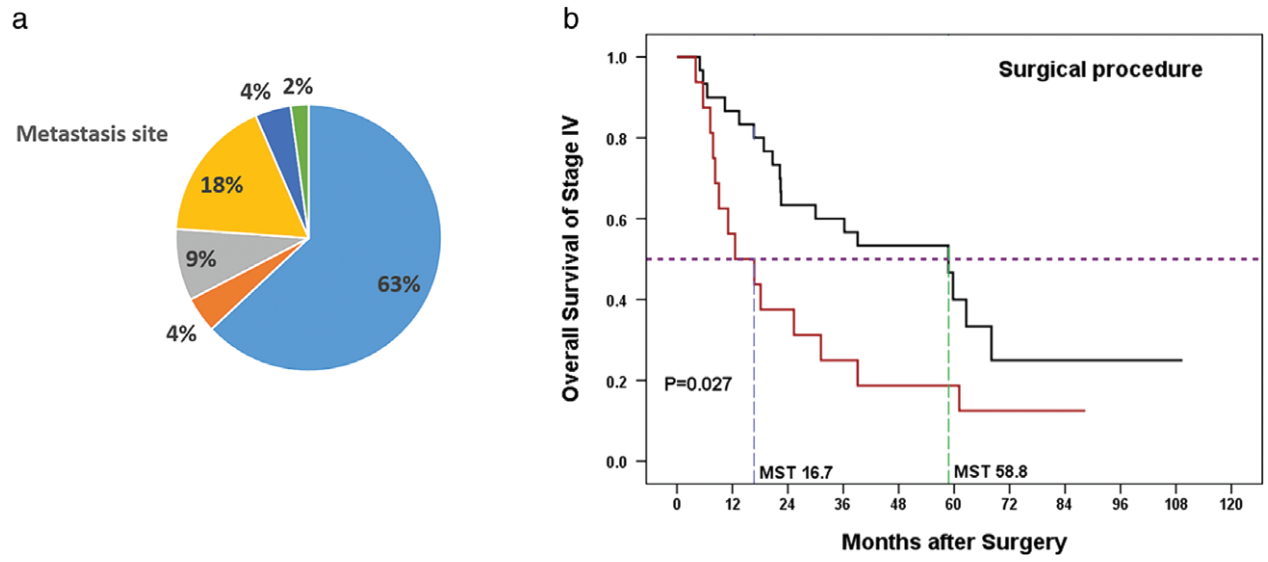


Figure 3 (**a**) Metastasis situation: survival curves of patients regarding extent of resection. (**b**) Results of the logrank test and median survival time (MST) of the two groups. (■) Pleural or pericardial nodules/malignant effusion (n = 29), (■) contralateral lung (solitary nodule) (n = 4), (■) ribs (n = 2), (■) brain (n = 2), (■) diaphragm/chest wall nodules (n = 8), and (■) brain and bone (n = 1). Surgical procedure: (——) radical surgery (n = 30) and (——) limited resection (n = 16).

Table 3 Results of Cox regression model analysis for stage groupings in the 7th and 8th editions of the TNM classification†

	8th edition			7th edition		
Comparison of adjacent stages (OS)	HR	95% CI	*P*	HR	95% CI	*P*
IA1 versus IA2	0.131	0.018–0.982	0.048	—	—	—
IA2 versus IA3	0.172	0.068–0.432	< 0.001	—	—	—
IA3 versus IB	0.290	0.115–0.730	0.009	—	—	—
IA versus IB	—	—	—	0.214	0.108–0.424	< 0.001
IB versus IIA	0.187	0.093–0.375	< 0.001	0.236	0.128–0.437	< 0.001
IIA versus IIB	0.601	0.228–1.587	0.304	0.472	0.231–0.963	0.039
IIB versus IIIA	0.648	0.344–1.222	0.180	0.902	0.444–1.832	0.775
IIIA versus IIIB	0.871	0.527–1.439	0.590	0.981	0.605–1.592	0.939
IIIB versus IV	—	—	—	0.665	0.310–1.427	0.295
IIIB versus IVA and IVB	0.995	0.547–1.807	0.986	—	—	—

†Adjusted for age, gender, smoking history, pathological classification, and surgical method. CI, confidence interval; HR, hazard ratio; OS, overall survival; TNM, tumor node metastasis.

Local therapy (e.g. pleurodesis, ambulatory small catheter drainage, pericardial window) can be performed in patients with pleural or pericardial effusion in stage M1a. Some studies have reported that radical resection for lung cancer (T4) invading the great vessels or carina is only beneficial in selected N0–N1 patients.[8,9] Zhou *et al.* reviewed 349 stage IIIA and IIIB patients with great vessel or carina invasion who underwent partial resection of the great vessels with artificial vessel replacement and reported a 5-YSR > 30%.[10] The prognosis of locally advanced lung cancer could be improved by radical treatments. In the present study (60.9% patients were N2 stage), radical surgery might have improved the outcomes of therapy after treatment in selected stage IV adenocarcinoma patients. Although our method is not recommended by IASLC, the high 5-YSRs achieved in our stage IV patients indicate that our method may be superior; however further investigation is required to confirm our results.

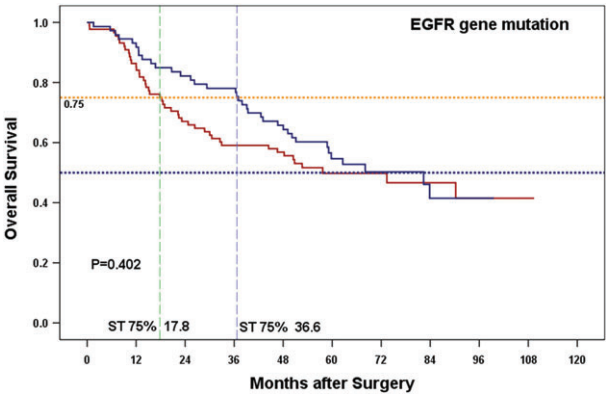


Figure 4 Survival curves of *EGFR* gene mutation positive and negative groups, results of the logrank test and the survival time when the survival rate is 75% (ST 75%) in the two groups. *EGFR* gene mutation (——) negative (n = 89) and (——) positive (n = 73).

The histological subtypes of adenocarcinoma also affect patient prognosis. Patients with AIS or MIA have nearly 100% postoperative five-year disease-free survival if completely resected.[6,11,12] In invasive adenocarcinoma, patients with LPA have the best survival, followed by APA and PPA, while patients with SPA and MPA show the worst survival rates.[13–16] In addition, MPA is associated with a high risk of lymph node metastasis and recurrence.[17] Patient survival rates in the present study were similar to the results of previous studies, except for SPA, which had a survival rate similar to APA and PPA. Moreover, the higher proportion of MPA in a cohort, the higher the rate of local recurrence after limited lung resection.[18] The advanced lung adenocarcinoma patients in our study with high-risk histological subtypes (e.g. SPA, MPA) achieved longer OS than patients with intermediate grade histological subtypes (e.g. LPA, APA), which is likely the result of better responses to chemotherapy.[19] We infer that radical surgery combined with systemic therapy (e.g. adjuvant chemotherapy) may improve the survival of patients with advanced lung adenocarcinoma with SPA or MPA. This might explain why patients with stage IV who underwent radical surgery had better survival rates than patients who underwent limited resection.

The frequency of *EGFR* mutations in Asians is higher than in Caucasians.[20] EGFR-TKIs (tyrosine kinase inhibitors) can prolong progression-free survival in patients with an *EGFR* gene mutation and is recommended as first-line treatment in such patients.[7,21] However, our results did not indicate a significant survival advantage in patients with *EGFR* gene mutations. Furthermore, other studies have also reported that EGFR-TKIs do not improve patient survival.[22–24] Although most patients with *EGFR* mutations have prominent and permanent responses to EGFR-TKIs (gefitinib or erlotinib), these patients always develop resistance to *EGFR* inhibitors within 12 months (median time to disease progression).[25,26] Approximately 50% of acquired

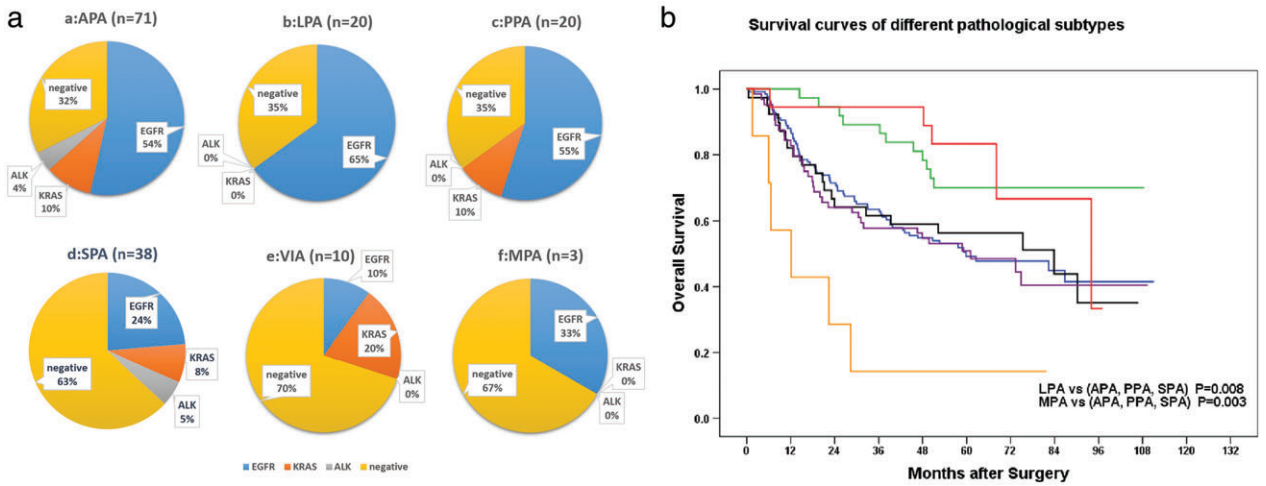
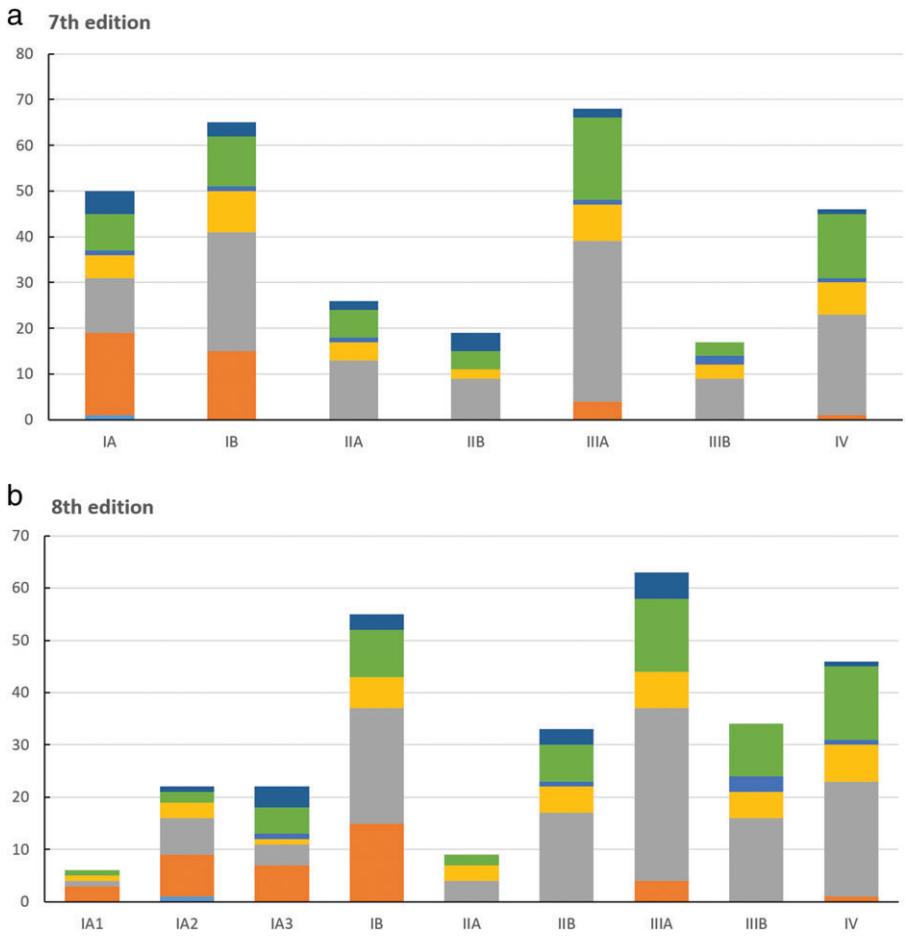


Figure 5 (**a**) The frequency of *EGFR*, *KRAS*, and *ALK* mutations in different pathological subtypes. (**b**) Survival curves of patients based on pathological classification and results of the logrank test. (■) *EGFR*, (■) *KRAS*, (■) *ALK* and (■) negative. (——) Acinar predominant adenocarcinoma (APA, n = 126), (——) lepidic predominant adenocarcinoma (LPA, n = 38), (——) papillary predominant adenocarcinoma (PPA, n = 38), (——) solid predominant with mucin production adenocarcinoma (SPA, n = 64), (——) mucin production adenocarcinoma (MPA, n = 7) and (——) variants of invasive adenocarcinomas (VIA, n = 17).

Figure 6 Distribution of pathological classification in the (**a**) 7th and (**b**) 8th editions of the tumor node metastasis (TNM) classification. (■) Minimally invasive adenocarcinoma (MIA), (■) lepidic predominant adenocarcinoma (LPA), (■) acinar predominant adenocarcinoma (APA), (■) papillary predominant adenocarcinoma (PPA), (■) mucin production adenocarcinoma (MPA), (■) solid predominant with mucin production adenocarcinoma (SPA) and (■) variants of invasive adenocarcinomas (VIA).



resistance to *EGFR* inhibitors is the result of mutation at T790M.[27] According to the survival curves in Figure 3, the *EGFR* mutation-positive group had a better OS rate in the middle part of the curve than the negative group, but the two curves ultimately overlapped. This may have been caused by acquired resistance to EGFR inhibitors, even though the new generation of EGFR inhibitors (e.g. osimertinib) have been shown to be effective for both *EGFR*-TKI-sensitizing and T790M resistance mutations.[28] However, these inhibitors did not prevent acquired resistance in our study because of the complexity of targeted drug resistance mechanisms, which require further investigation.[29] We look forward to the development of an efficient subsequent therapy to overcome acquired resistance to third generation EGFR-TKIs. Regardless of the type of targeted therapy, a US study reported that *EGFR* gene mutations were positive prognostic markers in resected stage I (7th edition) non-small cell lung cancer.[30] Tumor genotype is an important factor in lung adenocarcinoma. Thus, the IMCLA recommends molecular testing of small biopsy and cytology specimens because it may help to understand histologic type and *EGFR* mutation status.[6]

In our study, the *EGFR* mutation frequency in LPA was 65%, but was not significantly different compared to the *EGFR* mutation frequency in other pathologic types, possibly, because of the limited number of patients. This may infer that the LPA survival advantage results not only from the TNM classification, but also from the high *EGFR* mutation frequency. The frequency of *EGFR* mutations in SPA was lower compared to other types, which may indirectly lead to a poor prognosis. Further research is required to determine the connections between gene mutation and pathological subtype.

There are several limitations to this study. First, the number of patients and residential locations sampled were limited. Second, as a retrospective study, selection and information bias is inevitable. All cases were patients who had undergone surgical treatment; therefore, the survival results may not adequately represent lung adenocarcinoma in China. Third, only a small number of patients were sampled in stage IIA (8th edition), although this was not solely the result of selection bias because only T2bN0M0 (8th edition) patients are classified as stage IIA. Finally, several other non-anatomical elements (e.g. performance status) were not included.

Our results imply that the 8th edition may be more applicable to Chinese patients with lung adenocarcinoma who undergo surgical treatment than the 7th edition. In stage IV, radical surgery combined with systemic therapy (e.g. adjuvant chemotherapy) may improve outcomes in selected patients. Our results require validation with more data from multicenter studies. Histological subtypes and *EGFR* mutation status have an effect on the survival of patients with lung adenocarcinoma.

In conclusion, lung cancer prognosis is determined by multiple factors. Multidisciplinary team cooperation is necessary to evaluate lung cancer stage, implement treatment, and predict survival.

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Disclosure

No authors report any conflict of interest.

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