Original Article

Factors associated with the prognosis and long-term survival of patients with metastatic lung adenocarcinoma: a retrospective analysis

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Background: Outcome of patients with advanced non-small cell lung cancer (NSCLC) treated with platinum-based doublet chemotherapy is usually poor, with overall survival ranges from 8–13 months. However, the overall survival is improved to 21–28 months in the era of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). This study aimed to explore the prognostic factors to predict long-term survival in the era of EGFR TKI.

Methods: A total 1,030 patients were studied who had been diagnosed with metastatic adenocarcinoma of lung from January 2005 to December 2009 at Linkou Chang Gung Memorial Hospital. Long-term survivors (LTS) were defined as patients who survived five years or more after the initial diagnosis of stage IV disease. Data on patient age, gender, smoking status, performance status at diagnosis, TNM stage, metastatic pattern, number of metastases, and organs with tumor involvement, *EGFR* gene mutation status, types of treatment received, EGFR TKI treatment and longest EGFR TKI duration were retrospectively obtained from medical charts. We calculated the odds ratio (OR) of long-term survival from collected clinical parameters to predict long-term survival.

Results: In this large retrospective study, we reported a five-year survival of 5.0% among patients with metastatic adenocarcinoma of lung. A total 52 LTS and 978 non-LTS were identified. Patients had more contralateral or pleural/pericardial metastases in the LTS group than in the non-LTS group (51.9% *vs.* 19.0%, P<0.001), while less extrathoracic spread than in the non-LTS group (42.3% *vs.* 79.6%, P<0.001). The mutation of the *EGFR* gene was more frequent in the LTS group than in the non-LTS group (19.2% *vs.* 7.1%, P=0.006).

Conclusions: In conclusion, our results suggest that an age younger than 60 years, absence of extrathoracic spread and EGFR TKI treatment duration of more than one year play an important role in the long-term for survivors who survive for more than 5 years.

Keywords: Advanced lung adenocarcinoma; long-term survival; epithelial growth factor receptor gene (*EGFR* gene)

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Introduction

Lung cancer is the most common and deadliest cancer worldwide (1). During the era of platinum-based combination chemotherapy patients diagnosed with advanced non-small cell lung cancer (NSCLC) experienced poor outcomes, with a typical expected lifetime of around 8 to 13 additional months (2-8). Driver mutations in the epidermal growth factor receptor (*EGFR*) gene have been found in a subset of lung adenocarcinomas and define cancers in which tumor cell survival is exquisitely dependent on EGFR pathway signaling (9). Furthermore, patients with advanced NSCLC harboring oncogenic driver mutation had better survival outcome as comparing to patients without driver mutation (10,11). In Asia-Pacific region, EGFR exon 18–21 mutation is the most common type of oncogenic mutation in lung adenocarcinoma, with incidence rate of 55% (12). Tyrosine kinase inhibitors (TKIs) targeting EGFR had been shown to improve progression-free survival in patients with advanced NSCLC harboring sensitive EGFR mutation status in first line setting (13-20). The overall survival had improved to 21–28 months in the era of EGFR TKI.

Despite the overall poor prognosis, a small subgroup of patients with advanced NSCLC would survive more than 5 years from the literature (21-23). Treatment with EGFR TKI is reported to be significant long-term survival factor in one study (23). In rare cases, survival for more than 10 years has been reported in patients with advanced NSCLC who had been treated with chemotherapy or EGFR TKI (24). As the development of TKI in NSCLC, the true impact of *EGFR* gene and TKI in long term survival remains uncertain. This study aimed to explore the prognostic factors of long-term survival in patients with advanced NSCLC in the era of EGFR TKI.

Methods

Patient selection

There were 1,081 patients with stage IV lung adenocarcinoma included for this study. All the diagnosis was made with pathologic proof between 2005–2009 at our institute. We excluded patients with tumor histology type other than adenocarcinoma (N=1,692), received subsequent treatment at other hospital (N=37), incompatible clinical stage (N=9), malignancy other than primary lung cancer (N=5) were excluded. A total 1,030 patients were included for final analysis. All the diagnoses were made based on either cytology or histopathology. Long-term survivors (LTS) were defined as patients who survived five years or more after the initial diagnosis of stage IV disease. Survival time was defined from the diagnosis of advanced disease to death of any cause or last follow-up date. Patients who did not survive more than five years were defined as non-LTS group. All patients were diagnosed with stage IV cancer as defined by the American Joint Committee on Cancer (AJCC) 7th edition of cancer staging (25). All clinical information and histopathologic features were collected from electric medical records retrospectively. The study was approved by the institutional review board (approval number 201800208B0), in compliance with the Helsinki Declaration (1996).

Data collection

Data on patient age, gender, smoking status, performance status at diagnosis, TNM stage, metastatic pattern, number of metastases, and organs with tumor involvement, EGFR exon 18–21 gene mutation status, types of treatment received, EGFR TKI treatment and longest EGFR TKI duration were retrospectively obtained from medical charts. Extrathoracic involvement was defined as having metastasis to any of the following organ sites at diagnosis: adrenal gland, bone, central nervous system, cutaneous soft tissue, liver, non-regional lymph nodes, peritoneum, skin and spleen.

Statistical analysis

Basic demographic data were summarized as the n (%) for categorical variables and medians with ranges or 95% confidence interval (CI) for continuous variables. We calculated the odds ratio (OR) of long-term survival from collected clinical parameters to predict long-term survival. A binary logistic regression model was used for multivariate analysis. All statistical assessments were two-sided. Survival time was analyzed using the Kaplan-Meier method. Log-rank tests were used to determine significant differences between the survival curves. All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). A P value less than 0.05 was considered significant.

Results

A total 52 LTS and 978 non-LTS were identified during

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Table 1 Basic demographic data for patients

Variable	Long-term survival group (n=52)	Non-long-term survival group (n=978)	P value
Gender (M:F)	42:58	53:47	0.139
Age (median)	57 [28–82]	64 [30–95]	0.006
Performance status (PS)			
ECOG 0–1	50 (96.0%)	664 (67.9%)	<0.001
Smoking status:			
Never or light smoker*	43 (82.7%)	681 (69.6%)	0.126
Metastatic pattern			
Lung, pleura or pericardium (M1a disease)	30 (57.7%)	200 (20.4%)	<0.001
Any extrathoracic organ (M1b disease)	22 (42.3%)	778 (79.6%)	<0.001
Metastatic site (at baseline)			
Lung or pleura	47 (90.4%)	695 (71.1%)	0.001
Bone	11 (21.1%)	577 (59.0%)	<0.001
Central nervous system	6 (11.5%)	219 (22.4%)	0.065
Liver	2 (3.8%)	165 (16.9%)	0.013
Adrenal	0 (0%)	112 (11.5%)	0.01
Lymph nodes (non-regional)	5 (9.6%)	87 (8.9%)	0.859
Other organs	0 (0%)	59 (6.0%)	0.068
Any extrathoracic organ	22 (42.3%)	778 (79.6%)	<0.001
Involved organ system			
1 or 2 organ systems	51 (98.1%)	656 (67.1%)	<0.001
≥3 organ systems	1 (1.9%)	322 (32.9%)	

*, less than 20 pack-year cigarette smoking; ECOG, Eastern Cooperative Oncology Group.

a five-year retrieval period (Jan 2005 to Dec 2009). The median survival time was 86.6 months for the LTS patient group (95% CI: 75.9–97.3 months) and 7.0 months in the non-LTS group (95% CI: 6.16–7.85). The basic characteristics of the two groups are listed in *Table 1*. Patients in the LTS group had a significantly better performance status when comparing with the non-LTS group [Eastern Cooperative Oncology Group (ECOG); 0–1 96.0% *vs.* 67.9%, P<0.001]. Smoking status was not significantly different between the two groups (82.7% *vs.* 69.9%, P=0.126). The outcome and the Kaplan-Meier survival curve of two groups are shown in *Figure 1*.

Regarding the metastatic pattern, patients had more contralateral or pleural/pericardial metastases in the LTS group than in the non-LTS group (51.9% *vs.* 19.0%, P<0.001), while less extrathoracic spread than in the non-LTS group (42.3% *vs.* 79.6%, P<0.001). The metastatic patterns are also shown in *Table 1*. The number of involved organs was significantly lesser in the LTS group than in the non-LTS group (three or more organs 1.9% *vs.* 32.9%, P<0.001). The metastatic sites at baseline shown in *Table 1* also had significant differences in the two groups. Commonly involved organ sites in the LTS group included the lung and pleura (90.4% *vs.* 71.1%, P=0.001), bone (21.1% *vs.* 59.0%, P<0.001), liver (3.8% *vs.* 16.9%, P=0.013), and adrenal gland (0% *vs.* 11.5%, P=0.010) when comparing with the non-LTS group.

The EGFR mutation of tumor and treatment type is summarized in *Table 2*. The mutation of the *EGFR* gene was identified more frequently in the LTS group

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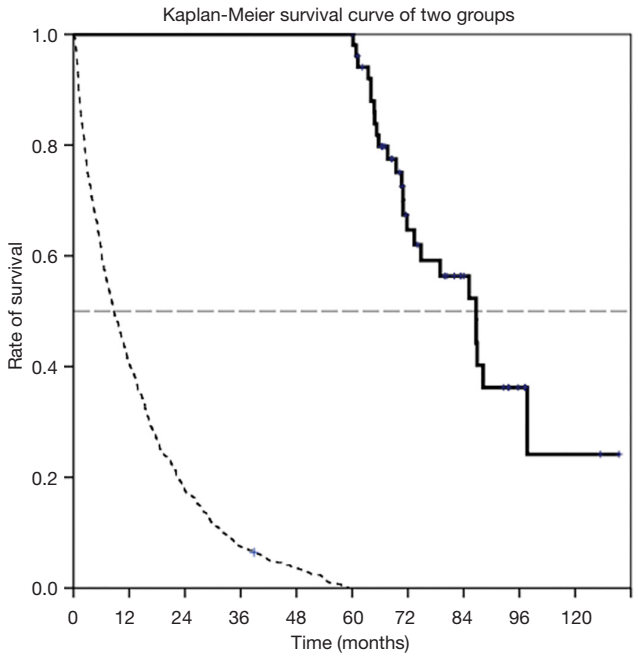

Figure 1 Overall survival of the two groups. Solid line indicates the long-term survival (LTS) group; dotted line indicates the non-LTS group.

than in the non-LTS group (19.2% *vs.* 7.1%, P=0.006). Specific EGFR mutations included in-frame deletion in exon 19, L858R in exon 21, L861Q in exon 21, and insertion in exon 19. Patients in the LTS group received significantly more treatments than the non-LTS group, including metastasectomy (30.8% *vs.* 11.6%, P<0.001), any chemotherapy (88.5% *vs.* 64.0%, P<0.001) and EGFR TKI therapy (94.2% *vs.* 54.9%, P<0.001).

The ORs associated with long-term survival are listed in *Table 3*. Significant factors associated with long-term survival identified in our series were age younger than 60 years (OR 2.34, 95% CI: 1.32–4.15, P=0.003), performance status ECOG 0–1 (OR 11.75, 95% CI: 2.84–48.59, P<0.001), absence of extrathoracic spread (OR 5.31, 95% CI: 3.00–9.40, P<0.001), underwent metastasectomy (OR 3.40, 95% CI: 1.83–6.33, P<0.001), use of any chemotherapy (OR 4.31, 95% CI: 1.82–10.20, P<0.001), use of EGFR TKI (OR 1.72, 95% CI: 1.57–1.87, P<0.001), and longest EGFR TKI duration more than 1 year (OR 107.2, 95% CI: 51.46–223.3, P<0.001). In multivariate analysis using binary logistical regression model, significant factors associated with long-term survival were age younger than 60 years (adjusted OR 2.35, 95% CI: 1.02–5.41, P=0.044), absence of extrathoracic spread (adjusted OR 3.64, 95% CI: 1.60–8.31, P=0.002) and longest EGFR TKI duration more than 1 year (adjusted OR 61.9, 95% CI: 25.32–151.4, P<0.001). The forest plot of OR was shown in *Figure 2*.

Discussion

To our knowledge, this is the largest retrospective study to report long-term survival (more than five years) of patients with advanced NSCLC in the era of EGFR TKI. In this study, we reported a five-year survival of 5.0% (52/1,030) in patients diagnosed with metastatic lung adenocarcinoma. Wang *et al*. (22) reported a five-year survival of 6.6% in 846 patients with stage IIIA-IV NSCLC in the era of chemotherapy. Ozkaya *et al*. (21) and Kaira *et al*. (23) also reported five-year survival rates of 2.8% (total number =141) and 8.0% (total number =124), respectively, in patients with stage IIIB-IV NSCLC.

In recent studies focusing on long-term survival of advanced NSCLC, treatment of EGFR TKI was reported as a significant factor to LTS in several retrospective studies (23,26). In this study, we identified three significant prognostic factors associated with LTS, which were age 60 years old or younger, absence of extrathoracic spread (M1a disease) and longest TKI duration more than one year. Among patients with all these three clinical factors in this study, the five-year survival rate was 100% (14 of 14). These findings suggested that disease pattern and the response to treatment play a major role of having long-term survival. Besides systemic therapy, patients with oligometastases disease might be amenable to a curative surgery or localized therapy (27), which also played a role in achieving long-term survival. Other factors associated with long-term survival (more than five years) from other retrospective studies are summarized in *Table 4*.

Among phase III trials comparing single-agent EGFR TKI to standard platinum-based doublet chemotherapy in treating patients with advanced NSCLC as first-line setting, the median overall survival was reported between 19.3 to 30.5 months (13-20,28). However, a subgroup of patients had achieved longer clinical benefit from EGFR TKI. In a recently reported study, the medicine Afatinib has been reported to provide a significantly higher 24-month progression-free survival rate than the medicine Gefitinib in first-line setting (17.6% *vs.* 7.6%) (29), indicating that a different TKI might have an effect on the clinical outcome. However, only a small part of patients in this study had tests of tumor *EGFR* gene mutation, with an overall majority (90.2%) having had unknown EGFR mutation status. This

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Table 2 *EGFR* gene mutation and types of treatment

Variable	Long-term survival group (n=52)	Non-long-term survival group (n=978)	P value
EGFR exon 18–21 status			
Mutations*	10 (19.2%)	69 (7.1%)	0.006
Wild type	1 (1.9%)	21 (2.2%)	
Not checked	41 (78.8%)	888 (90.8%)	
Type of treatment			
Any metastasectomy	16 (30.8%)	113 (11.6%)	<0.001
Any chemotherapy	46 (88.5%)	626 (64.0%)	<0.001
Any EGFR TKI	49 (94.2%)	537 (54.9%)	<0.001
EGFR-TKI treatment			
Gefitinib (G)	13 (25.0%)	248 (45.1%)	<0.001
Erlotinib (E)	21 (40.4%)	221 (22.6%)	
Both G & E	15 (28.8%)	68 (7.0%)	
No TKI treatment	3 (5.8%)	441 (45.1%)	
Best response to EGFR TKI	Evaluable =49	Evaluable =388	–
Complete or partial response	29 (59.2%)	249 (64.2%)	
Duration of TKI treatment (days, range)	1,049 [67–2,954]	174 [1–1,535]	

*, specific types of EGFR mutation include: deletion in exon 19, L858R in exon 21, L861Q in exon 21, G719X in exon 18, insertion in exon 19. EGFR, epithelial growth factor receptor; TKI, tyrosine kinase inhibitor.

Table 3 Univariate and multivariate analysis of factors associated with long-term survival

Clinical parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Male gender	0.65 (0.37–1.15)	0.134	–	–
Age ≤60 y/o	2.34 (1.32–4.15)	0.003	2.35 (1.02–5.41)	0.044
ECOG performance status 0–1	11.75 (2.84–48.59)	<0.001	1.67 (0.34–8.37)	0.531
Never or light smoker	1.94 (0.93–4.03)	0.072	–	–
Involved organ system ≤2	25.03 (3.44–182.0)	<0.001	7.36 (0.89–61.22)	0.065
Absence of extrathoracic spread (M1a disease)	5.31 (3.00–9.40)	<0.001	3.64 (1.60–8.31)	0.002
Underwent metastasectomy	3.40 (1.83–6.33)	<0.001	2.02 (0.77–5.26)	0.152
Use of any chemotherapy	4.31 (1.82–10.20)	<0.001	0.77 (0.24–2.47)	0.662
Use of any EGFR TKI	1.72 (1.57–1.87)	<0.001	2.19 (0.56–8.52)	0.258
Longest TKI duration >1 year	107.2 (51.46–223.3)	<0.001	61.9 (25.32–151.4)	<0.001

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epithelial growth factor receptor; TKI, tyrosine kinase inhibitors.

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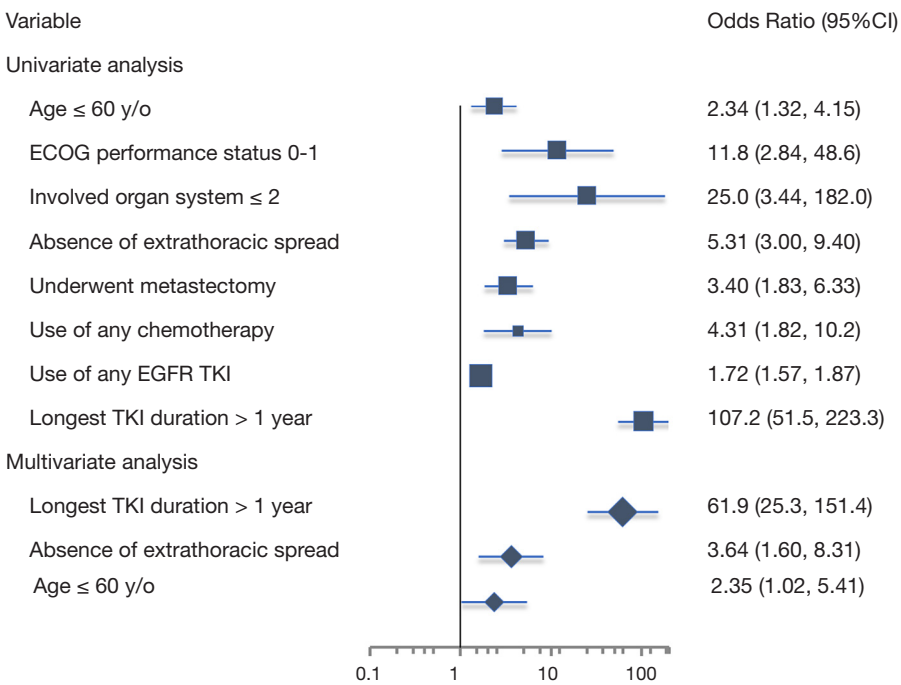

Figure 2 Univariate and multivariate analysis of patient characteristics for odds ratio of long-term survival. 95% CI, 95% confidence interval.

Table 4 Summary of long-term survival (>5 years) analysis in selected studies

Authors	Accrual year	Stage	Total patients	5y OS rate	Prognostic factors
Wang *et al*. (22)	1986–2001	IIIA–IV	846	6.60%	Resectable N2 disease, multiple lung tumors, T3N0, single site distant metastasis
Ozkaya *et al*. (21)	2001–2004	IIIB–IV	141	2.80%	NA
Kaira *et al.* (23)	2002–2003	IIIB–IV	124	8.00%	Performance status, adenocarcinoma and EGFR TKI therapy
This study	2005–2009	IV	1,030	5.00%	Age ≤60 years, absence of extrathoracic spread, longest EGFR TKI duration >1 year

NA, not applicable; EGFR, epithelial growth factor receptor; TKI, tyrosine kinase inhibitor.

is the major limitation of our study. It remains uncertain whether patients with metastatic NSCLC acquiring EGFR mutation would had a higher long-term survival rate. However, patients with evaluable disease in LTS group treated with EGFR TKI had objective response rate of 59% (29/49). In a phase III clinical trial study comparing gefitinib to carboplatin plus paclitaxel (20), the objective response rate of gefitinib was 71.2% in *EGFR* gene mutation-positive subgroup (P<0.001) and 1.1% in *EGFR* gene mutation-negative subgroup (P=0.001). Such distinct response to gefitinib suggested that LTS group in our study is very likely a group of EGFR-mutant lung adenocarcinoma.

Anaplastic lymphoma kinase (ALK) fusion oncogene is an emerging molecular target in lung adenocarcinoma (30), which accounts for 3–5% of genetic alteration (12,31,32). Patients with ALK fusion oncogene were characterized by younger age, non-smoking status and good response to several TKIs (33). Surprisingly, a retrospective study includes 14 patients with advanced NSCLC harboring ALK fusion gene reported five-year OS rate of 78.6% (34). ROS1 rearrangement is another emergent but rare molecular target (35) that respond well to crizotinib in advanced

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NSCLC (36). KRAS mutation is the major genetic alteration in lung adenocarcinoma of Western countries (37). In contrast, KRAS mutation appears to negatively affect overall survival (38,39). However, our study is also limited to identify the potential long-term survival impact of ALK, ROS1, KRAS and other oncogenic mutations.

This retrospective study has several limitations. First, only patients with adenocarcinoma histology were included in this study. Therefore, the interpretation of the results may be inappropriate to patients with squamous cell carcinoma or other histology types. Second, the overall survival outcome of non-LTS group in this study is lower than described in literature. This probably relates to poor performance status (32.1% patients with performance status ECOG ≥2), who is not fit for standard chemotherapy. Third, EGFR TKI was not reimbursed as second-line setting (regardless of EGFR mutation status) in Taiwan before 2008. Therefore, not all patients had received EGFR TKI in this study, which precludes the efficacy and response to EGFR TKI from certain patients and introduced a selection bias in this study.

Conclusions

In conclusion, our results suggest that an age younger than 60 years, absence of extrathoracic spread and EGFR TKI treatment duration of more than one year play an important role in the long-term for survivors who survive for more than 5 years.

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Footnote

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

Ethical Statement: This study was reviewed and approved by our Institutional Review Board (approval number 201800208B0), in compliance with the Helsinki Declaration (1996).

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