Original Article

Prognostic factors in completely resected lymph-node-negative pulmonary adenocarcinoma

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Background: Lymph node involvement is one of the important prognostic factors for early-stage lung cancer. However, in lymph node-negative (N0) lung cancer the recurrent rate may be as high as 30%. We aimed to study potential prognostic factors including clinicopathological factors and epidermal growth factor receptor (EGFR) mutation status in this lung cancer population.

Methods: We retrospectively reviewed the medical records and pathological examinations of patients with completely resected N0 pulmonary adenocarcinoma treated in our institute between 2009 and 2016. We used Cobas® test to determine EGFR mutation status. Recurrence-free survival (RFS) was analyzed by univariable and multivariable Cox regression analyses.

Results: We recruited 220 patients with median duration of follow up 5 years. Majority of these patients were in stage I (80%) and did not receive adjuvant therapy (86%). There were 53% with EGFR mutations which comprised of exon 19 deletion 51% and L858R 43%. Recurrence occurred in 64 out of 220 patients (29%). The median time to recurrence was 2.1 years. Statistically significant prognostic factors in both univariate and multivariate analyses included tumor size ≥4 centimeter (cm) (HR: 1.94; 95% CI: 1.03–3.67), visceral pleural invasion (HR: 2.53; 95% CI: 1.34–4.79), tumor necrosis (HR: 2.45; 95% CI: 1.13–5.31) and bronchial resection margin <2 cm (HR: 1.96; 95% CI: 1.10–3.51). However, presence of sensitizing EGFR mutation was not found to be a significant prognostic factor (HR: 1.20; 95% CI: 0.66–2.18; P=0.56).

Conclusions: In N0 surgically resected lung adenocarcinoma, there were significant pathological prognostic factors including tumor 4 cm or more, visceral pleural invasion, tumor necrosis and bronchial resection margin less than 2 cm. Mutation of EGFR is not a significant prognostic factor to determine the risk of recurrence in this population and their risks shall be determined by the other poor prognostic factors.

Keywords: Early-stage lung cancer; lymph node-negative; prognostic factors; recurrence; EGFR mutation

Submitted Nov 25, 2021. Accepted for publication May 09, 2022.
doi: 10.21037/tcr-21-2633
View this article at: https://dx.doi.org/10.21037/tcr-21-2633

Introduction

Lung cancer is the most common leading cause of cancer-related mortality in the worldwide including Thailand (1). In early-stage non-small cell lung cancer (NSCLC), surgery is the essential curative treatment modality. After complete surgical resection, the most important prognostic factor is lymph node involvement (2). However, in patients without lymph node metastasis the recurrent rate may be as high as 30% (3). Previous studies identified several important clinicopathological prognostic risks including smoking (4), tumor size (5), solid type histology (6,7), visceral pleural invasion (5,8), tumor necrosis (9,10), and presence of lymphatic or vascular invasion (5,8,11). Only tumor size more than 4 centimeter (cm) has been shown to gain a survival benefit from adjuvant chemotherapy in lymph-node negative patients (12).

Nowadays, molecular factors play a role in the treatment of advanced stage NSCLC. In East Asian populations, epidermal growth factor receptor (EGFR) mutation is the most common driver mutation in pulmonary adenocarcinoma (13). In advanced stage, EGFR mutation is not only a predictive factor for a good response to targeted therapy but also a prognostic factor for improved survival outcomes (14). Patient who has tumor harboring EGFR sensitizing mutation treated with EGFR tyrosine kinase inhibitor (TKI) may have an average survival exceeding 3 years (15). Nevertheless, the prognostic role of EGFR mutation in early-stage lung NSCLC remains uncertain (16-18).

We conducted this retrospective study to identify the clinicopathological prognostic factors and to determine the value of the sensitizing EGFR mutations predicting recurrence in patients who had completely resected lymph node-negative pulmonary adenocarcinoma with adequate follow up time. We presented the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2633/rc).

Methods

Study population

We retrospectively reviewed charts of 220 patients diagnosed with completely resected lymph node-negative pulmonary adenocarcinoma and treated at King Chulalongkorn Memorial Hospital between 2009 and 2016. Standard anatomical resection (lobectomy, bi-lobectomy or pneumonectomy) with systematic mediastinal lymph node dissection or sampling was performed in all patients. The patients who had pathologically confirmed pulmonary adenocarcinoma and original pathological stage 0, I, II (Tis-T3N0M0) according to the American Joint Committee on Cancer staging system for lung cancer version 7 (AJCC 7th edition) (19) were included. We performed additional re-classification with the AJCC 8th edition definition (20) (stage 0, I, II, IIIA) for analytic purposes.

For metastatic evaluation, standard laboratory tests and computerized tomographic (CT) scans of the thorax and the upper abdomen were obtained for all patients. Brain imaging was obtained at the discretion of treating physicians. Patients who received adjuvant systemic treatment or radiation were eligible in this study. Patients were excluded from this study if they had any evidence of metastasis; had evidence of residual tumor at the resection margin; or died within 30 days after surgery (post-operative mortality).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (No. 214/61) and informed consent for this retrospective analysis was waived.

Study variables

Medical records containing demographic data, smoking status, type of surgery, adjuvant treatment, time to recurrence, and pattern and site of recurrence were reviewed. Smoking status at the time of diagnosis was defined into (I) non-smokers: fewer than 100 cigarettes lifetime, (II) former or light smokers: quit smoking at least 15 years with a total of ≤10 pack-years of smoking history and (III) heavy smokers: over 10 pack-years of smoking history and quit within 15 years prior (14). We employed the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score with six points, ranging from 0 (fully active) to 5 (dead) in assessing patient physical condition (21).

All pathologic specimens were re-assessed by only pathologist (P.C.) who was blinded to the other data. Tumor size was defined by maximal diameter. Bronchial resection margin (BRM) was defined by the distance from the border of tumor to the bronchial resection line and number of removed lymph node were all determined from the gross appearance in surgical specimen. Adenocarcinoma subtypes and histologic grading were assessed according to the 2015

World Health Organization classification (22). Pleural invasion level 1 (PL1) and pleural invasion level 2 (PL2) were defined as tumor invades into the visceral pleura and through the visceral pleura respectively (19). The presence of lymphovascular invasion was defined by presence of cancer cells within the lumen of lymphatic or vascular vessels. Tumor necrosis score was defined as following: scored 0, no necrosis; 1, 1 focus of necrosis per low power field (LPF), each focus <10% per LPF; 2, >1 focus of necrosis each occupying <10% or 1 focus of necrosis occupying 10% to <30% per LPF; 3, single or multiple areas of necrosis >30% per LPF (9).

For the EGFR mutation analysis, we used Cobas® DNA sample preparation kit (Roche, USA) and the Cobas® EGFR Mutation Test v2 (Roche, USA) according to the manufacturer instruction. The assay can detect EGFR specific mutations including G719A/C/S in exon 18, deletions in exon 19, S768I, T790M, and insertions in exon 20, L858R and L861Q in exon 21.

Endpoints

The primary objective of this study focused on assessing the prognostic value of sensitizing EGFR mutations and other clinicopathological factors for predicting recurrence-free survival (RFS) which was defined as the interval between the time of the diagnosis and the time of tumor recurrence evidenced by either imaging, cytopathologic examination, or death. Locoregional tumor recurrence was defined as evidence of tumor within the same lobe, the hilum, or the mediastinal lymph nodes, and distant recurrence by evidence of tumor in another lobe or elsewhere outside the hemithorax. The secondary outcomes included incidence, pattern of tumor recurrence and prevalence of EGFR mutation in the studied population.

Sample size calculations

Six risk factors for recurrence in lung cancer were smoking (4), tumor size (5), lymphovascular invasion (11), tumor grading (23), visceral pleural invasion (8) and EGFR mutation (16). The estimated recurrence rate of completely resected lymph node-negative pulmonary adenocarcinoma was approximately 30% (3). For each of the six candidate factors, our study targeted having a minimum of 10 recurrent events per factor as, suggested by Peduzzi *et al.* (24). A minimum sample size of 200 was required based on this assumed prevalence. Missing data was estimated at 10%, so the target sample size was 220 patients.

We used phone follow-up and retrieved patient's living status from Thai Civil registration to determine the survival of the patients who lost to follow up from the clinic.

Statistical analysis

Differences between the recurrent and non-recurrent group were analyzed by Chi-square and Student's *t*-test for categorical and continuous data, respectively. For measuring association among RFS, sensitizing EGFR mutations and the other clinicopathological factors, we applied a univariable Cox regression analysis to calculate the unadjusted hazard ratios. We then carried out multivariable Cox regression analysis to identify the independent prognostic factors for tumor recurrence. P values of less than 0.05 were considered statistically significant. The differences of RFS and overall survival between two groups with and without the significant factor were analyzed by two-sided log-rank test and survival curves performed by the Kaplan-Meier methods. We used SPSS version 22.0 (IBM Corp., US) for all statistical analyses.

Results

Patient characteristics

A total of 220 eligible patients were identified. The mean age of patients was 65.2 years. The majority of patients were female (61.8%), never smokers (67.7%) and stage I (80%) according to AJCC 8th staging. EGFR mutation was found in 111 out of 210 patients (52.9%). The most common mutations were exon 19 deletion (51.4%) and L858R (43.2%). The surgical procedures consisted of 215 lobectomies (97.7%), 3 bi-lobectomies (1.4%), and 2 wedge resections (0.9%). Only 13.2% of patients received adjuvant systemic treatment and 1.4% received adjuvant radiation. In patients with recurrence, we found higher proportion of heavy smokers, tumors larger than 4 cm, high histologic grade, bronchial resection margin less than 2 cm, presence of lymphovascular invasion, visceral pleural invasion and tumor necrosis. In contrast, there was no significant difference in EGFR status and surgical procedure associated with recurrent status. Patients with recurrence received significantly more adjuvant chemotherapy and radiation compared with patients who had no recurrence (*Table 1*).

We observed that the EGFR mutant subgroup had more female, never smokers, tumor less than 4 cm, low

Table 1 Clinicopathological characteristics and treatment modalities between recurrent and non-recurrent group

Characteristics	All (N=220)	No recurrence (N=156)	Recurrence (N=64)	P value
Age at diagnosis (years), n (%)				
<65	102 (46.4)	72 (46.2)	30 (46.9)	0.92
≥65	118 (53.6)	84 (53.8)	34 (53.1)	
Sex, n (%)				0.16
Male	84 (38.2)	55 (35.3)	29 (45.3)	
Female	136 (61.8)	101 (64.7)	35 (54.7)	
Smoking status, n (%)				0.031
Never	149 (67.7)	111 (71.2)	38 (59.4)	
Light	33 (15.0)	24 (15.4)	9 (14.1)	
Heavy	23 (10.5)	11 (7.0)	11 (17.2)	
Missing	15 (6.8)	10 (6.4)	6 (9.3)	
ECOG PS, n (%)				0.203
0/1	217 (98.6)	155 (99.4)	62 (96.9)	
2	3 (1.4)	1 (0.6)	2 (3.1)	
AJCC 7th staging, n (%)				<0.001
0	12 (5.5)	12 (7.7)	0	
IA	110 (50.0)	90 (57.7)	20 (31.3)	
IB	78 (35.5)	45 (28.8)	33 (51.6)	
IIA	12 (5.5)	4 (2.6)	8 (12.5)	
IIB	8 (3.5)	5 (3.2)	3 (4.7)	
AJCC 8th staging, n (%)				<0.001
0	12 (5.4)	12 (7.7)	0	
IA	142 (64.5)	111 (71.2)	31 (48.4)	
IB	34 (15.5)	20 (12.8)	14 (21.9)	
IIA	16 (7.3)	6 (3.8)	10 (15.6)	
IIB	11 (5)	5 (3.2)	6 (9.4)	
IIIA	5 (2.3)	2 (1.3)	3 (4.7)	
Tumor size (cm), n (%)				<0.001
<4	179 (81.4)	138 (88.5)	41 (64.1)	
≥4	41 (18.6)	18 (11.5)	23 (35.9)	
Adenocarcinoma subtype, n (%)				0.002
AIS	13 (5.9)	13 (8.3)	0	
MIA	29 (13.2)	28 (17.9)	1 (1.6)	
Lepidic	66 (30.0)	49 (31.4)	17 (26.5)	
Acinar	74 (33.6)	45 (28.9)	29 (45.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All (N=220)	No recurrence (N=156)	Recurrence (N=64)	P value
Papillary	7 (3.2)	4 (2.6)	3 (4.7)	
Micropapillary	8 (3.6)	4 (2.6)	4 (6.3)	
Colloid	1 (0.5)	1 (0.6)	0	
Solid	20 (9.1)	12 (7.7)	8 (12.5)	
Missing	2 (0.9)	0	2 (3.1)	
Histologic grade, n (%)				<0.001
Grade 1	111 (50.5)	93 (59.6)	18 (28.1)	
Grade 2	78 (35.5)	46 (29.5)	32 (50.0)	
Grade 3	30 (13.5)	17 (10.9)	13 (20.3)	
Missing	1 (0.5)	0	1 (1.6)	
Tumor cell type, n (%)				0.44
Non mucinous	197 (89.6)	141 (90.4)	56 (87.5)	
Mucinous	16 (7.2)	13 (8.3)	3 (4.7)	
Mixed	4 (1.8)	2 (1.3)	2 (3.1)	
Missing	3 (1.4)	0	3 (4.7)	
Lymphovascular invasion, n (%)				<0.001
No	155 (70.5)	122 (78.2)	33 (51.6)	
Yes	63 (28.6)	34 (21.8)	29 (45.3)	
Missing	2 (0.9)	0	2 (3.1)	
Visceral pleural invasion, n (%)				<0.001
No	161 (73.5)	129 (82.7)	32 (50.0)	
Into (PL1)	37 (16.9)	19 (12.2)	18 (28.1)	
Through (PL2)	21 (9.6)	8 (5.1)	13 (20.3)	
Missing	1 (0.5)	0	1 (1.6)	
Level of tumor necrosis, n (%)				<0.001
No	163 (74.0)	134 (85.9)	29 (45.3)	
1+	29 (13.2)	13 (8.3)	16 (25.0)	
2+	12 (5.5)	5 (3.2)	7 (10.9)	
3+	12 (5.5)	4 (2.6)	8 (12.5)	
Missing	4 (1.8)	0	4 (6.3)	
EGFR testing, n (%)				
Wild type	99 (47.1)	67 (45.6)	32 (50.0)	0.49
EGFR mutation	111 (52.9)	80 (54.4)	31 (48.4)	
Exon 19 deletion	57 (51.4)	41 (51.2)	16 (51.6)	0.44
L858R	48 (43.2)	35 (43.7)	13 (41.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All (N=220)	No recurrence (N=156)	Recurrence (N=64)	P value
G719X	3 (2.7)	1 (1.3)	2 (6.5)	
L861Q	3 (2.7)	3 (3.8)	0	
Missing	10 (4.5)	9 (5.8)	1 (1.6)	
Type of surgery, n (%)				0.28
Lobectomy	215 (97.7)	154 (98.8)	61 (95.3)	
Bilobectomy	3 (1.4)	1 (0.6)	2 (3.1)	
Wedge resection	2 (0.9)	1 (0.6)	1 (1.6)	
Number of mediastinal LN removal, n (%)				
<3 LN	55 (25.0)	37 (23.7)	18 (28.1)	0.31
≥3 LN	160 (72.7)	119 (76.3)	41 (64.1)	
Missing	5 (2.3)	0	5 (7.8)	
Bronchial resection margin (cm)				0.001
<2	60 (27.3)	33 (21.2)	27 (42.2)	
≥2	154 (70.0)	121 (77.6)	33 (51.6)	
Missing	6 (2.7)	2 (1.2)	4 (6.2)	
Adjuvant systemic treatment				0.002
No adjuvant	191 (86.8)	143 (91.7)	48 (75.0)	
Adjuvant chemotherapy	26 (11.8)	11 (7.1)	15 (23.4)	
Adjuvant CCRT with consolidation CMT[†]	1 (0.5)	0	1 (1.6)	
Adjuvant EGFR TKI	2 (0.9)	2 (1.2)	0	
Adjuvant radiation				0.025
No radiation	217 (98.6)	156 (100.0)	61 (95.3)	
Adjuvant radiation	2 (0.9)	0	2 (3.1)	
Adjuvant CCRT with consolidation CMT[†]	1 (0.5)	0	1 (1.6)	

[†], the patient was treated with adjuvant concurrent chemoradiation with consolidation chemotherapy because of closed margin. ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; PS, performance status; AIS, adenocarcinoma in situ; MIA, Microinvasive adenocarcinoma; PL, level of pleural invasion; EGFR, epidermal growth factor receptor; LN, lymph node; CMT, chemotherapy; CCRT, concurrent chemoradiation; TKIs, tyrosine kinase inhibitors.

histologic grade, and presence of tumor necrosis. There was no statistically significant difference among other clinicopathological characteristics (Table S1).

Recurrence and prognostic factors

At the time of data cutoff, the median follow-up time was 5 years [inter quartile range (IQR), 3.5–6.7 years]. Of 220 patients, 64 (29.1%) had recurrent disease. The median time to recurrence was 2.1 years (IQR, 1.1–3.6 years). The rate of locoregional, distant and both types of recurrence were 26.6%, 67.2%, and 6.2%, respectively. Common sites of distant relapse were lung (67.2%), pleura (23.4%) and lymph node (18.8%). There was no statistically significant difference in pattern of relapse and time to recurrence according to EGFR status (Table S2).

Fifty two out of 220 patients (23.6%) died during the study period. A total of 36 patients (69.2%) who died were

Table 2 Results of univariate and multivariate analysis for recurrence-free survival

Covariate	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (≥65 *vs.* <65 years)	0.97	0.59–1.58	0.89	NA	NA	NA
Male *vs.* female	1.53	0.94–2.51	0.09	1.81	0.81–4.02	0.15
Smoking status						
Light *vs.* never	1.19	0.57–2.45	0.65	0.39	0.13–1.18	0.09
Heavy *vs.* never	2.61	1.36–5.00	0.004	1.33	0.52–3.42	0.56
ECOG PS						
1 *vs.* 0	1.60	0.95–2.69	0.08	1.33	0.74–2.42	0.35
2 *vs.* 0	4.73	1.10–20.29	0.04	0.98	0.19–5.12	0.98
Tumor size (≥4 *vs.* <4 cm)	3.41	2.02–5.75	<0.001	1.94	1.03–3.67	0.04
Adenocarcinoma subtype (solid *vs.* non-solid)	1.91	0.91–4.03	0.09	1.36	0.38–4.82	0.64
Histologic grading						
Grade 1	1			1		
Grade 2	3.12	1.75–5.57	<0.001	1.35	0.65–2.83	0.42
Grade 3	3.25	1.59–6.63	0.001	0.81	0.24–2.73	0.73
Lymphovascular invasion (yes *vs.* no)	2.86	1.73–4.75	<0.001	1.16	0.60-2.21	0.67
Visceral pleural invasion (yes *vs.* no)	3.48	2.11–5.72	<0.001	2.53	1.34–4.79	0.004
Tumor necrosis (yes *vs.* no)	4.58	2.75–7.62	<0.001	2.45	1.13–5.31	0.023
EGFR mutation (yes *vs.* no)	0.95	0.55–1.65	0.85	1.20	0.66–2.18	0.56
Bronchial resection margin (<2 *vs.* ≥2 cm)	2.34	1.41–3.90	0.001	1.96	1.10–3.51	0.023

HR, hazard ratio; CI, confidence interval; NA, not applicable; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

from the recurrent group with 16 patients (30.8%) from the non-recurrent group. Cancer-related deaths accounted for 34 of 36 (94.4%) in the recurrent group, while no cancer deaths were reported in the non-recurrent group.

Univariate analysis for RFS revealed heavy smokers, poor performance status (ECOG 2), tumor size ≥4 cm, histologic grade ≥2, lymphovascular invasion, visceral pleural invasion, presence of tumor necrosis, and bronchial resection margin <2 cm were statistically significant prognostic factors for tumor recurrence. However, in the multivariate analysis, tumor size ≥4 cm, visceral pleural invasion, presence of tumor necrosis, and bronchial resection margin <2 cm remained to be statistically significant, while heavy smokers, poor performance status, histologic grade ≥2 and lymphovascular invasion lost their significance. Sensitizing EGFR mutation was not a significant prognostic factor in both univariate and multivariate analyses (*Table 2*).

When we took all the significant prognostic factors (tumor size ≥4 cm, visceral pleural invasion, tumor necrosis, and bronchial resection margin <2 cm) from the multivariate analysis and categorized patients by the number of observed factors for each patient to 5 groups (between 0 and 4 factors), we found a statistical difference between the recurrent and non-recurrent group. Every patient who had four significant prognostic factors had recurrent disease (Table S3).

Moreover, the Cox regression analysis showed that an increasing number of significant factors were strongly associated with higher risk of recurrence. When excluding patients who received adjuvant treatment, this subgroup of patients showed similar outcomes compared to whole population (*Table 3*).

Results from the two-sided log-rank test showed that patients with one of the significant prognostic factors (tumor

Table 3 Correlation of the number of significant factors and recurrence free survival in Cox regression analysis

Number of significant factors	All patients (N=216)			Patients who did not receive adjuvant treatment (N=187)		
	HR	95% CI	P value	HR	95% CI	P value
0 factor	1	–	–	1	–	–
1 factor	5.12	2.1–12.4	<0.0001	3.74	1.4–9.7	0.006
2 factors	7.76	3.3–18.3	<0.0001	7.42	3.1–18.0	<0.0001
3 factors	15.0	5.4–41.5	<0.0001	15.70	5.5–45.0	<0.0001
4 factors	50.88	17.2–150.2	<0.0001	36.4	9.2–144.3	<0.0001

HR, hazard ratio; CI, confidence interval.

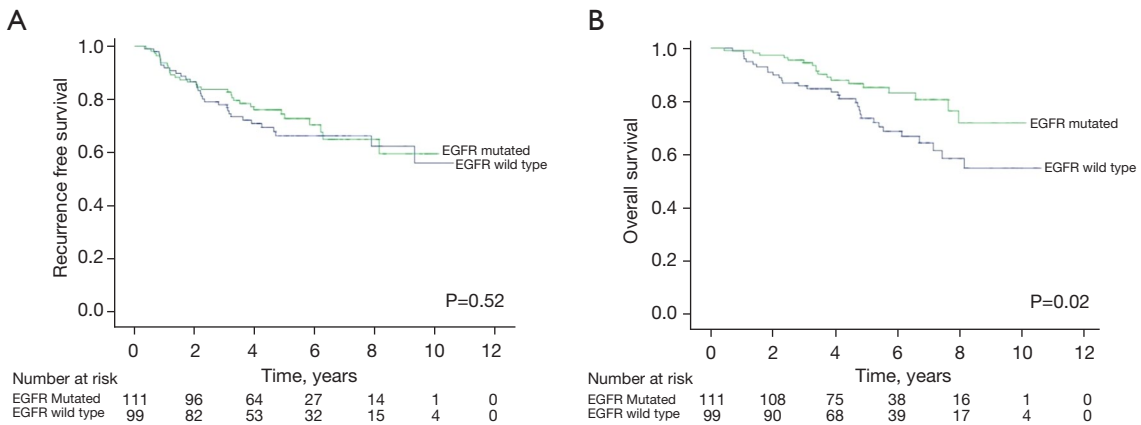

Figure 1 Kaplan-Meier estimates RFS and OS by EGFR status. (A) RFS: 5-year RFS in EGFR mutated *vs.* EGFR wild type 72.9% *vs.* 66.4%; P=0.52 and (B) OS: 5-year OS in EGFR mutated *vs.* EGFR wild type 85.2% *vs.* 73.7%; P=0.02. RFS, recurrence free survival; OS, overall survival; EGFR, epidermal growth factor receptor.

size ≥4 cm, visceral pleural invasion, tumor necrosis, and bronchial resection margin <2 cm) had worse outcomes in both 5-year RFS and overall survival (OS) than patients without these factors. While 5-year RFS between sensitizing EGFR mutation and wild type patients were not statistically different, the 5-year OS in sensitizing EGFR mutation group was statistically longer (Table S4). The survival curves for the RFS and OS between sensitizing EGFR mutation and wild type patients were shown in *Figure 1*.

Discussion

Recent studies have attempted to identify potential prognostic factors in resectable lung cancer. In addition to lymph node metastasis, several clinicopathological factors including smoking (4), tumor size (5), solid type histology (6,7), visceral pleural invasion (5,8), tumor necrosis (9,10), and presence of lymphatic or vascular invasion (5,8,11) reported as the poor prognostic risks for tumor recurrence after complete surgical resection. Our study reported similar consistent poor prognostic factors including tumor size, visceral pleural invasion, presence of tumor necrosis but not the histological subtype and the presence of lymphatic or vascular invasion. In addition, we found the bronchial resection margin <2 cm is a new prognostic factor in our population. These 4 prognostic factors could be incorporated into a model of incremental risk for likelihood of recurrence associated with cumulative prognostic factors.

Prognostic factor study in early-stage lung cancer may be confounded by the heterogeneity of the studied population and inadequate surgery which lead to different outcomes. Our study had selected relatively early stage (80% stage I), pure adenocarcinoma, homogenously diagnosed and treated lung cancer population (single institution and 85.9%

without adjuvant therapy), which may help lessen a few biases. Moreover, surgery quality was adequate evidenced by the mean number of lymph node removed equal to ten. With the above factors, we believe that our study has addressed the prognostic factors in early-stage lung adenocarcinoma.

Several analyses have shown conflicting results regarding EGFR mutation as a prognostic factor in early-stage lung cancer (16-18). Prior meta-analysis study of 4,872 patients showed similar disease-free survival between EGFR wild type and mutation (25). A recent large study from Japan involved 5,780 patients revealed that EGFR mutation lung cancer, 41.7% of all population, had a better recurrence free survival and overall survival compared to those of wildtype EGFR (26). These conflicting results may stem from different stages, surgery, adjuvant treatments and variabilities of EGFR mutation testing. Though our study population was much smaller, our well define group of very early-stage lung adenocarcinoma without lymph node metastasis indicated that EGFR mutation is not an independent prognostic factor for recurrence. The incidence and type of EGFR mutation in our study were similar to the earlier report of advanced stage lung adenocarcinoma in Thai population (27). From our data, overall survival may not be a suitable endpoint when analyzing outcomes between EGFR mutation and wildtype subgroup due to interference from the subsequent treatment with an effective EGFR inhibitor. Most of patients with EGFR mutation, 21 out of 31 patients (68%), received EGFR TKI upon recurrence which help improving the overall survival of these patients.

Though our study population could be considered as a relatively good prognosis group by the fact that there was no lymph node involvement, we found a moderately high incidence of recurrent disease in the overall population (29.1%) similar to a previous report (3). The above findings urge us that additional risk assessment is clearly needed to identify patient at risk for recurrence. With multivariate analyses, we have demonstrated the risk factors for tumor recurrence including tumor size ≥4 cm, visceral pleural invasion, tumor necrosis and bronchial resection margin <2 cm. When analyzing by the Cox regression analyses of these four factors, patients who had all four factors had 50 times higher risk of recurrence than the patients without any of these factors. Substantiated by several studies indicate that tumor size (5), visceral pleural invasion (8) and tumor necrosis (10) are the important prognostic factors, we believe that these four prognostic factors will be helpful in identifying patient at risk for recurrence and may be suitable for adjuvant therapy consideration.

In this study we found the distance of bronchial resection margin is a new prognostic factor consistent with prior recommendation of acceptable bronchial margin of 2 cm for pulmonary adenocarcinoma (28). Few studies have shown that the bronchial resection margin had no significant impact on survival outcome in resected NSCLC (29,30). These discrepancies may be due to different studied population. Our study population were all without lymph node involvement. Thus, an adequate surgical resection margin may significantly contribute to the survival outcomes.

There were few limitations in our study. First, we could not perform EGFR mutation testing and pathological review in every patient due to unavailability or inadequate quality of tissue samples. Second, there was missing data of the patients who lost to follow up. We tried to overcome this latter problem by telephone and checked with Thai Civil registration for the last living status of these patients. However, there were relatively low number of missing data (3.6%) and invalid tissue samples (4.5%) which might not severely affect the overall outcome.

Conclusions

We have demonstrated four important prognostic factors for surgically resected and lymph node negative lung adenocarcinoma including tumor size ≥4 cm, visceral pleural invasion, tumor necrosis and the distance of bronchial resection margin <2 cm. Mutation of EGFR is not a significant prognostic factor to determine the risk of recurrence in this population and their risks shall be determined by the other poor prognostic factors. Future study addressing the utility of these prognostic factors in a prospective manner is warranted.

Acknowledgments

We would like to thank Micheal Ullman for polishing our manuscript.

Funding: This research was supported by the Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University (Grant No. RA61/114 to VS) and Chulalongkorn Academic Advancement into Its 2nd Century (CUAASC) Project to VS and CV.

Footnote

Reporting Checklist: The authors have completed the

STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2633/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2633/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2633/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2633/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (No. 214/61) and informed consent for this retrospective analysis was waived.

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Cite this article as: Pakvisal N, Chantranuwat P, Vinayanuwattikun C, Sitthideatphaiboon P, Teerapakpinyo C, Shuangshoti S, Benjacholamas V, Pornpattanarak N, Sriuranpong V. Prognostic factors in completely resected lymph-node-negative pulmonary adenocarcinoma. Transl Cancer Res 2022;11(7):2238-2248. doi: 10.21037/tcr-21-2633

Supplementary

Table S1 Clinicopathological characteristics between EGFR wild type and mutated group

Characteristics	All[†] (N=210)	EGFR wild type (N=99)	EGFR mutant (N=111)	P value
Age at diagnosis, n (%)				0.23
<65 years	99 (47.1%)	51 (51.5%)	48 (43.2%)	
≥65 years	111 (52.9%)	48 (48.5%)	63 (56.8%)	
Sex, n (%)				0.019
Male	78 (37.1%)	45 (45.5%)	33 (29.7%)	
Female	132 (62.9%)	54 (54.5%)	78 (70.3%)	
Smoking status, n (%)				0.002
Never	144 (73.8%)	57 (62%)	87 (84.5%)	
Light	30 (15.4%)	20 (21.7%)	10 (9.7%)	
Heavy	21 (10.8%)	15 (16.3%)	6 (5.8%)	
ECOG, n (%)				0.55
0	94 (44.8%)	41 (41.4%)	53 (47.7%)	
1	113 (53.8%)	57 (57.6%)	56 (50.5%)	
2	3 (1.4%)	1 (1.0%)	2 (1.8%)	
AJCC 8th staging, n (%)				0.006
0	11 (5.2%)	1 (1.0%)	10 (9%)	
IA	136 (64.8%)	63 (63.6%)	73 (65.8%)	
IB	33 (15.7%)	14 (14.1%)	19 (17.1%)	
IIA	16 (7.6%)	12 (12.1%)	4 (3.6%)	
IIB	10 (4.8%)	5 (5.1%)	5 (4.5%)	
IIIA	4 (1.9%)	4 (4.1%)	0	
Tumor size, n (%)				0.029
<4 cm	172 (81.9%)	75 (75.8%)	97 (87.4%)	
≥4 cm	38 (18.1%)	24 (24.2%)	14 (12.6%)	
Histologic grade, n (%)				0.007
Grade 1	106 (50.5%)	40 (40.4%)	66 (59.5%)	
Grade 2	75 (35.7%)	39 (39.4%)	36 (32.4%)	
Grade 3	29 (13.8%)	20 (20.2%)	9 (8.1%)	
Lymphovascular invasion, n (%)				0.29
No	146 (70.2%)	66 (66.7%)	80 (73.4%)	
Yes	62 (29.8%)	33 (33.3%)	29 (26.6%)	
Visceral pleural invasion, n (%)				0.59
No	152 (72.7%)	73 (74.5%)	79 (71.2%)	
Yes	57 (27.3%)	25 (25.5%)	32 (28.8%)	
Tumor necrosis, n (%)				<0.001
No	155 (74.9%)	63 (64.3%)	92 (84.4%)	
Yes	52 (25.1%)	35 (35.7%)	17 (15.6%)	
Bronchial resection margin, n (%)				0.79
<2 cm	58 (28.3%)	28 (29.2%)	30 (27.5%)	
≥2 cm	147 (71.7%)	68 (70.8%)	79 (72.5%)	

[†], not include 10 of 220 patients who had no result of EGFR mutation. EGFR, epidermal growth factor receptor.

https://dx.doi.org/10.21037/tcr-21-2633

Table S2 Pattern of relapse and time to recurrence between EGFR wild type and mutated group

	All of recurrence† (N=63)	EGFR wild type (N=32)	EGFR mutant (N=31)	P value
Pattern of relapse, n (%)				0.53
Locoregional	16 (25.4%)	7 (21.9%)	9 (29%)	
Distant	43 (68.3%)	22 (68.8%)	21 (67.7%)	
Both locoregional and distant	4 (6.3%)	3 (9.4%)	1(3.2%)	
Intracranial relapse, n (%)	11 (17.5%)	7 (21.9%)	4 (12.9%)	0.35
Median time to recurrence, year (IQR)	2.13 (1.16–3.53)	2.20 (1.23–3.19)	2.06 (1.09–3.87)	0.45

†, not include 1 of 64 recurrent patients who had no result of EGFR mutation. EGFR, epidermal growth factor receptor; IQR, inter quartile range.

Table S3 Number of significant factors between recurrence and non-recurrence

Number of significant factors	All† (N=216)	No recurrence (N=156)	Recurrence (N=60)	P value
0 factor, n (%)	94 (100.0)	87 (92.6)	7 (7.4)	<0.001
1 factor, n (%)	59 (100.0)	42 (71.2)	17 (28.8)	
2 factors, n (%)	45 (100.0)	24 (53.3)	21 (46.7)	
3 factors, n (%)	11 (100.0)	3 (27.3)	8 (72.7)	
4 factors, n (%)	7 (100.0)	0	7 (100.0)	

†, not include 4 of 220 patients who had missing data of four significant factors.

Table S4 Five-year recurrence free survival and overall survival of significant prognostic factors and EGFR status

Covariate	5-year RFS	P value	5-year OS	P value
Tumor size <4 cm	76.8%	<0.001	82.5%	0.002
Tumor size ≥4 cm	44.5%		61.9%	
No visceral pleural invasion	80.2%	<0.001	84.5%	0.003
Visceral pleural invasion	45.7%		63.1%	
≥2 cm of bronchial resection margin	78.0%	0.001	82.1%	0.01
<2 cm of bronchial resection margin	56.4%		69.8%	
No tumor necrosis	82.7%	<0.001	86.1%	<0.001
Tumor necrosis	39.6%		56.8%	
Sensitizing EGFR mutation	72.9%	0.52	85.2%	0.02
EGFR wild type	66.4%		73.7%	

EGFR, epidermal growth factor receptor; RFS, recurrence free survival; OS, overall survival.

https://dx.doi.org/10.21037/tcr-21-2633