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Original Article

Factors Associated with Postoperative Recurrence in Stage I to IIIA Non–Small Cell Lung Cancer with Epidermal Growth Factor Receptor Mutation: Analysis of Korean National Population Data

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Purpose Recent development in perioperative treatment of resectable non–small cell lung cancer (NSCLC) have changed the landscape of early lung cancer management. The ADAURA trial has demonstrated the efficacy of adjuvant osimertinib treatment in resectable NSCLC patients; however, studies are required to show which subgroup of patients are at a high risk of relapse and require adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor treatment. This study evaluated risk factors for postoperative relapse among patients who underwent complete resection.

Materials and Methods Data were obtained from the Korean Association for Lung Cancer Registry (KALC-R), a database created using a retrospective sampling survey by the Korean Central Cancer Registry (KCCR) and the Lung Cancer Registration Committee.

Results A total of 3,176 patients who underwent curative resection was evaluated. The mean observation time was approximately 35.4 months. Among stage I to IIIA NSCLC patients, the *EGFR*-mutant subgroup included 867 patients, and 75.2%, 11.2%, and 11.8% were classified as stage I, stage II, and stage III, respectively. Within the *EGFR*-mutant subgroup, 44 (5.1%) and 121 (14.0%) patients showed early and late recurrence, respectively. Multivariate analysis on association with postoperative relapse among the *EGFR*-mutant subgroup showed that age, pathologic N and TNM stages, pleural invasion status, and surgery type were independent significant factors.

Conclusion Among the population that underwent complete resection for early NSCLC with *EGFR* mutation, patients with advanced stage, pleural invasion, or limited resection are more likely to show postoperative relapse.

Key words Recurrence, Non-small-cell lung carcinoma, ErbB receptors

Introduction

The treatment of choice in stage I to IIIA lung cancer is surgery. Despite curative resection, the 5 years postoperative recurrence-free survival (RFS) rates were 87.8% for patients with stage I, 54.7% for those with stage II, and 33.4% for those with stage III in non–small cell lung cancer (NSCLC) [1]. After curative resection in patients with stage II to IIIA NSCLC, adjuvant cisplatin-based chemotherapy is recommended [2]. Also, among patients with stage IB NSCLC, adjuvant systemic therapy is recommended in high-risk groups. According to the recent study in stage IB (American Joint Commission on Cancer [AJCC] 8th) NSCLC patients, adjuvant chemotherapy is beneficial in patients with high-risk factors, reducing recurrence rate and risk of mortality (hazards ratio, 0.408 and 0.176, respectively) [3]. According to the National Comprehensive Cancer Network (NCCN) guidelines, high-risk groups include patients with poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural involvement, and unknown lymph node status.

Recent advances in perioperative treatment of resectable NSCLC have changed the landscape of early lung cancer management [4]. The ADAURA trial has shown significant efficacy of adjuvant osimertinib treatment in resectable NSCLC patients [5]. Among patients with resected, epidermal growth factor receptor (*EGFR*)–mutant, stage II to IIIA NSCLC, the 5-year overall survival (OS) was 85% in the osimertinib group, while only 73% in the placebo group [5]. It is undeniable that adjuvant treatment is effective in decreasing the chance of postoperative relapse and improving postoperative survival in *EGFR*-mutant patients who underwent

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complete resection for stage I to IIIA NSCLC.

However, osimertinib treatment for adjuvant purposes is not often covered by insurance or reimbursed in many countries, and financial burden is significant for most patients considering that there is no consensus regarding when to discontinue the adjuvant treatment [6]. Furthermore, both the prevalence and clinical characteristics of *EGFR*-mutant NSCLC patients vary according to region and race [7-9]. More clinical data are required to show which *EGFR*-mutant patient subgroups are at high risk of postoperative relapse and would benefit from adjuvant EGFR tyrosine kinase inhibitor (TKI) treatment.

This study evaluated risk factors for postoperative recurrence among patients who underwent complete resection using national Korean cancer data, with a focus among *EGFR*-mutant patients.

Materials and Methods

1. Patient selection

Data were obtained from the Korean Association for Lung Cancer Registry, a database created using a retrospective sampling survey by the Korean Central Cancer Registry (KCCR) and the Lung Cancer Registration Committee [10]. During the 2014-2017 period, the KCCR registered patients newly diagnosed with NSCLC. Among a total of 9,860 NSCLC patients, 3,364 underwent curative resection. Among them, 188 patients who were diagnosed as clinical stage IV or unknown stage were excluded. Finally, a total of 3,176 patients was enrolled in this study (Fig. 1). All patients were confirmed as having undergone operation for curative resection. Patients were staged according to the AJCC 7th edition TNM classification. Registered patients were followed for approximately 5 years after operation. All data in this study were obtained from the registered database with no additional review of individual data.

2. Definition of pleural invasion

According to a modified Hammar classification for pathologic assessment of visceral pleural invasion, PL0 is defined as no pleural invasion [11]. PL1 is defined as invasion beyond the elastic layer of the visceral pleura. PL2 is defined as invasion to the surface of the visceral pleura, and PL3 is defined as invasion to the parietal pleura.

3. Definition of early recurrence

Patients who showed postoperative relapse within one year of resection were classified as early recurrence patients.

4. Statistical analysis

Continuous variables are shown as mean±standard deviation, and categorical variables are shown as percentages. Risk factors for mortality were analyzed using Cox proportional hazards model. All statistical analyses were performed using SPSS ver. 20.0 (IBM Corp., Armonk, NY).

Results

1. Clinical characteristics of enrolled patients

A total of 3,176 patients who underwent curative resection was evaluated (S1 Table). The proportion of patients with smoking history was 56.0%. Approximately 81.5% of enrolled patients had good performance status (Eastern Cooperative Oncology Group [ECOG] 0-1). According to pathologic stage, 67.2%, 17.0%, and 12.9% of the patients were classified as stage I, stage II, and stage III, respectively. Regarding pathologic type, 70.7% were adenocarcinoma. Among the stage I to IIIA NSCLC patients, the *EGFR*-mutant subgroup included 867 patients.

Among the overall 3,176 patients, postoperative recurrence after curative resection occurred in 545 patients (17.1%). Median RFS was 31.73 months. Among 2,133 patients with *EGFR* results, the duration of OS was significantly shorter for *EGFR*-wild type patients than *EGFR*-mutant patients (S2A Fig.). However, the RFS showed no significant difference between *EGFR*-wild type and mutant patients (S2B Fig.).

2. Clinical characteristics of *EGFR*-mutant patients

The 867 patients with *EGFR*-mutant NSCLC who underwent curative surgery were analyzed (Table 1). Female sex and never-smokers were more prevalent than male sex and ever-smokers, respectively. Of these patients, 75.2%, 11.2%, and 11.8% were classified as stage I, stage II, and stage III, respectively. Among them, 94.3% were adenocarcinoma, accounting for the largest proportion. Among the *EGFR*-mutant subgroup, 44 (5.1%) patients showed early recur-

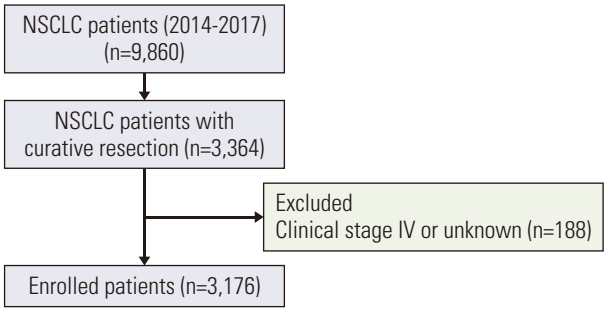

Fig. 1. Study flow diagram. NSCLC, non–small cell lung cancer.

Table 1. Baseline characteristics of *EGFR*-mutant patients (n=867)

Characteristic	No. of patients (%)
Age (yr)	62.54±9.97
≤ 65	511 (58.9)
> 65	356 (41.1)
Sex	
Male	338 (39.0)
Female	529 (61.0)
Smoking status	
Never	592 (68.3)
Ever	272 (31.4)
Unknown	3 (0.3)
ECOG	
0-1	754 (87.0)
≥ 2	19 (2.2)
Unknown	94 (10.8)
PFT	
FVC (L)	3.23±0.83
FEV_1 (L)	2.46±0.65
DL_{CO} (%)	93.97±19.69
Pathologic T category	
T1	494 (57.0)
T2	331 (38.2)
T3	36 (4.2)
T4	4 (0.5)
Unknown	2 (0.2)
Pathologic N category	
N0	669 (77.2)
N1	87 (10.0)
N2	102 (11.8)
N3	3 (0.3)
Unknown	6 (0.7)
Surgery type	
Wedge resection	61 (7.0)
Segmentectomy	77 (8.9)
Lobectomy	712 (82.1)
Pneumonectomy	17 (2.0)
Pathologic TNM stage	
I	652 (75.2)
II	97 (11.2)
III	102 (11.8)
IV	8 (0.9)
Unknown	8 (0.9)
Histologic type	
Squamous	35 (4.0)
Adenocarcinoma	818 (94.3)
Large cell carcinoma	0
NSCLC, NOS	1 (0.1)
Adenosquamous	8 (0.9)
Carcinoid	0
Others	5 (0.6)
Pleural invasion	
None (PL0)	637 (73.5)
Visceral pleural invasion (PL1)	167 (19.3)
Invasion to the surface of the visceral pleura (PL2)	45 (5.2)
Extend to the parietal pleura (PL3)	14 (1.6)
Pleural invasion, NOS	0
Unknown	4 (0.5)
Mediastinal LN resection	
No	43 (5.0)
Sampling	51 (5.9)
Dissection	768 (88.6)
Unknown	5 (0.6)
ALK	
Positive	26 (3.0)
Negative	700 (80.7)
Unknown	141 (16.3)
Recurrence	
No recurrence	702 (81.0)
Late recurrence	121 (14.0)
Early recurrence (≤ 1 yr)	44 (5.1)
Death	
No	749 (86.4)
Yes	118 (13.6)
Observation time (mo)	36.56±10.97
Recurrence-free survival time (mo)	33.02±13.52
Recurrence-free survival rate (%)	
1-Year	94.9
2-Year	85.8
3-Year	81.7

Values are presented as mean±SD or number (%). ALK, anaplastic lymphoma kinase; ALK positive, ALK immunohistochemistry or fluorescence *in situ* hybridization positive; DLco, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FEV_1, forced expiratory volume exhaled in the first second; FVC, forced vital capacity; LN, lymph node; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; PFT, pulmonary function test; SD, standard deviation.

rence and 121 (14.0%) patients showed late recurrence. The median RFS was 33.02 months.

3. Comparison between early, late, and no recurrence groups among *EGFR*-mutant patients

There was no significant difference in age, sex, ECOG performance status, or pulmonary function among the early recurrence group (ERG), late recurrence group (LRG), or no recurrence group (NRG) (Table 2). In the ERG, the proportion

Table 2. Clinical characteristics of ERG, LRG, and NRG among *EGFR*-mutant patients

Characteristic	ERG (n=44)	LRG (n=121)	NRG (n=702)	p-value
Age (yr)	63.20±10.22	61.94±11.18	62.61±9.74	0.778
≤ 65	24 (54.5)	73 (60.3)	414 (59.0)	
> 65	20 (45.5)	48 (39.7)	288 (41.0)	
Sex				
Male	20 (45.5)	50 (41.3)	268 (38.2)	0.266
Female	24 (54.5)	71 (58.7)	434 (61.8)	
Smoking status				
Never	21 (47.7)	78 (64.5)	493 (70.2)	0.015
Ever	23 (52.3)	42 (34.7)	207 (29.5)	
Unknown	0	1 (0.8)	2 (0.3)	
ECOG				
0-1	37 (84.1)	107 (88.4)	611 (87.0)	0.555
≥ 2	4 (9.1)	1 (0.8)	14 (2.0)	
Unknown	3 (6.8)	13 (10.7)	77 (11.0)	
PFT				
FVC (L)	3.22±0.84	3.22±0.80	3.24±0.83	0.968
FEV_1 (L)	2.38±0.63	2.45±0.59	2.46±0.66	0.690
DL_{CO} (%)	91.23±24.77	93.06±19.50	94.21±19.36	0.524
Pathologic T category				
T1	14 (31.8)	47 (38.8)	433 (61.7)	< 0.001
T2	23 (52.3)	66 (54.5)	242 (34.5)	
T3	6 (13.6)	8 (6.6)	22 (3.1)	
T4	1 (2.3)	0	3 (0.4)	
Unknown	0	0	2 (0.3)	
Pathologic N category				
N0	23 (52.3)	68 (56.2)	578 (82.3)	< 0.001
N1	8 (18.2)	24 (19.8)	55 (7.8)	
N2	12 (27.3)	28 (23.1)	62 (8.8)	
N3	0	1 (0.8)	2 (0.3)	
Unknown	1 (2.3)	0	5 (0.7)	
Surgery type				
Wedge resection	3 (6.8)	7 (5.8)	51 (7.3)	0.304
Segmentectomy	2 (4.5)	11 (9.1)	64 (9.1)	
Lobectomy	38 (86.4)	98 (81.0)	576 (82.1)	
Pneumonectomy	1 (2.3)	5 (4.1)	11 (1.6)	
Pathologic TNM stage				
I	15 (34.1)	60 (49.6)	577 (82.2)	< 0.001
II	13 (29.5)	24 (19.8)	60 (8.5)	
III	13 (29.5)	35 (28.9)	54 (7.7)	
IV	2 (4.5)	1 (0.8)	5 (0.7)	
Unknown	1 (2.3)	1 (0.8)	6 (0.9)	
Histologic type				
Squamous	4 (9.1)	5 (4.1)	26 (3.7)	0.986
Adenocarcinoma	40 (90.9)	111 (91.7)	667 (95.0)	
Large cell carcinoma	0	0	0	
NSCLC, NOS	0	0	1 (0.1)	
Adenosquamous	0	4 (3.3)	4 (0.6)	
Carcinoid	0	0	0	
Others	0	1 (0.8)	4 (0.6)	

(Continued to the next page)

Table 2. Continued

Characteristic	ERG (n=44)	LRG (n=121)	NRG (n=702)	p-value
Pleural invasion				
None (PL0)	24 (54.5)	63 (52.1)	550 (78.3)	< 0.001
Visceral pleural invasion (PL1)	13 (29.5)	45 (37.2)	109 (15.5)	
Invasion to the surface of the visceral pleura (PL2)	5 (11.4)	11 (9.1)	29 (4.1)	
Extend to the parietal pleura (PL3)	2 (4.5)	1 (0.8)	11 (1.6)	
Pleural invasion, NOS	0	0	0	
Unknown	0	1 (0.8)	3 (0.4)	
Mediastinal LN resection				
No	3 (6.8)	5 (4.1)	35 (5.0)	0.624
Sampling	2 (4.5)	7 (5.8)	42 (6.0)	
Dissection	39 (88.6)	107 (88.4)	622 (88.6)	
Unknown	0	2 (1.7)	3 (0.4)	
ALK				
Positive	3 (6.8)	5 (4.1)	18 (2.6)	0.549
Negative	37 (84.1)	94 (77.7)	569 (81.1)	
Unknown	4 (9.1)	22 (18.2)	115 (16.4)	
Chemotherapy				
Adjuvant	31 (70.5)	82 (67.8)	155 (22.1)	< 0.001
Neoadjuvant	5 (11.4)	5 (4.1)	14 (2.0)	
None	8 (18.2)	34 (28.1)	533 (75.9)	
RT				
Adjuvant	21 (47.7)	41 (33.9)	48 (6.8)	< 0.001
Neoadjuvant	3 (6.8)	4 (3.3)	7 (1.0)	
None	20 (45.5)	76 (62.8)	647 (92.2)	
Observation time (mo)	32.69±11.10	37.21±7.89	36.69±11.38	0.05
Recurrence-free survival time (mo)	10.56±7.37	24.48±9.04	35.90±12.49	

Values are presented as mean±SD or number (%). The significance level of p-value was set after Bonferroni correction. ALK, anaplastic lymphoma kinase; ALK positive, ALK immunohistochemistry or fluorescence *in situ* hybridizationpositive; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ERG, early recurrence group; FEV_1, forced expiratory volume exhaled in the first second; FVC, forced vital capacity; LN, lymph node; LRG, late recurrence group; NOS, not otherwise specified; NRG, no recurrence group; NSCLC, non–small cell lung cancer; PFT, pulmonary function test; RT, radiotherapy; SD, standard deviation.

of patients with smoking history was higher than in the LRG and NRG (p=0.015). Also, the proportion of patients with higher T, N, and TNM stage cancer was higher in the ERG than the other groups (p < 0.001). Regarding pleural invasion, 15.9% of patients in the ERG were PL2 or PL3, which is significantly higher than the invasion seen in the LRG or NRG. The proportion of patients with perioperative chemotherapy and radiotherapy (RT) was higher in the ERG compared to the LRG and NRG.

4. Clinicopathologic risk factors associated with postoperative recurrence in NSCLC patients after curative surgery

S3 Table shows univariate and multivariate analyses of clinicopathologic risk factors for postoperative recurrence. In multivariate analysis, sex, body mass index (BMI), smoking, diffusing capacity of the lungs for carbon monoxide (DLco), pathologic N and TNM stages, and pleural invasion significantly associated with RFS.

Female sex (female vs. male: hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.57 to 0.88; p=0.001), patients with higher BMI (HR, 0.97; 95% CI, 0.94 to 1.00; p=0.027), and higher DLco (HR, 0.99; 95% CI, 0.99 to 1.0; p=0.001) had lower risk of recurrence. Ever smokers (ever vs. never-smokers: HR, 1.47; 95% CI, 1.20 to 1.80; p < 0.001), patients with higher N (pN1 vs. pN0: HR, 2.15; 95% CI, 1.63 to 2.83; p < 0.001; pN2 vs. pN0: HR, 2.07; 95% CI, 1.57 to 2.73; p < 0.001) and TNM stages (stage II vs. stage I: HR, 2.11; 95% CI, 1.68 to 2.64; p < 0.001; stage III vs. stage I: HR, 2.83; 95% CI, 2.24 to 3.57; p < 0.001), and patients with pleural invasion (visceral pleural invasion [VPI] vs. no pleural invasion: HR, 1.54; 95% CI, 1.19 to 2.01; p=0.001) had higher risk of recurrence.

Table 3. Univariate and multivariate analyses of risk factors associated with recurrence (n=867) in *EGFR*-mutated NSCLC patients after curative surgery

Parameter	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Female vs. male (Ref)	0.75 (0.51-1.10)	0.136	0.73 (0.53-1.00)	0.053
Age (yr)				
> 65 vs. ≤ 65 (Ref)	1.46 (1.05-2.03)	0.023	1.41 (1.02-1.94)	0.037
BMI	0.96 (0.91-1.00)	0.074		
Smoking				
Ever vs. never (Ref)	1.00 (0.67-1.48)	0.994	-	-
ECOG				
≥ 2 vs. 0-1 (Ref)	0.67 (0.16-2.74)	0.573		
DL_{CO} (per)	0.99 (0.99-1.00)	0.106	0.99 (0.99-1.00)	0.080
pT				
T3-4 vs. T1-2	1.42 (0.70-2.90)	0.332	-	-
pN				
N1 vs. N0 (Ref)	2.08 (1.15-3.75)	0.015	2.00 (1.12-3.56)	0.019
N2 vs. N0 (Ref)	2.68 (1.37-5.25)	0.004	2.53 (1.31-4.91)	0.006
pStage				
Stage II vs. stage I (Ref)	1.92 (1.07-3.45)	0.028	1.93 (1.10-3.39)	0.021
Stage III vs. stage I (Ref)	1.34 (0.65-2.75)	0.431	1.38 (0.71-2.71)	0.345
Pleural invasion				
Visceral pleural invasion vs. no pleural invasion (Ref)	1.97 (1.37-2.83)	0.000	1.89 (1.33-2.70)	< 0.001
Surgery type				
Lobectomy vs. limited resection (Ref)	0.64 (0.30-1.33)	0.228	0.66 (0.32-1.37)	0.264
Pneumonectomy vs. limited resection (Ref)	0.45 (0.25-0.79)	0.006	0.45 (0.26-0.79)	0.006

BMI, body mass index; CI, confidence interval; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non–small cell lung cancer.

5. Clinicopathologic risk factors associated with mortality in NSCLC patients after curative surgery

S4 Table shows univariate and multivariate analyses of clinicopathologic risk factors for mortality. In multivariate analysis, sex, age, BMI, DLco (%), *EGFR* mutation, pathologic TNM stage, and pleural invasion were significantly associated with OS.

Female sex, patients with higher BMI, patients with higher DLco, and patients with *EGFR* mutation had a lower risk of mortality. Patients with older age, higher pathologic stage, and VPI had a higher risk of mortality.

6. Clinicopathologic risk factors associated with postoperative recurrence in *EGFR*-mutant NSCLC patients after curative surgery

Table 3 shows univariate and multivariate analyses of clinicopathologic risk factors for recurrence. In multivariate analysis, age, pathologic N and TNM stages, pleural invasion, and surgery type were significantly associated with RFS. The HR of recurrence in patients with pathologic N2 category was 2.53 compared to patients with pathologic N0 (p=0.019). Also, the HR of recurrence in patients with pathologic stage II was 1.93 compared to patients with pathologic stage I (p=0.021). Patients with VPI had a 1.89-fold higher risk of recurrence compared to patients without pleural invasion (p < 0.001). Also, the HR of recurrence in patients with pneumonectomy was 0.45 compared to patients with wedge resection (p=0.006).

7. Clinicopathologic risk factors associated with mortality in *EGFR*-mutant NSCLC patients after curative surgery

Table 4 shows univariate and multivariate analyses of clinicopathologic risk factors for mortality. In multivariate analysis, sex, age, BMI, ECOG performance status, DLco, pathologic TNM stage, and pleural invasion were significantly associated with OS.

Female sex or patients with higher BMI or DLco had a lower risk of mortality in *EGFR*-mutant NSCLC patients after curative surgery. Patients with older age, higher ECOG performance status, higher pathologic stage, and PL3 had a

Table 4. Univariate and multivariate analyses of risk factors associated with overall survival (n=867) in *EGFR*-mutated NSCLC patients after curative surgery

Parameter	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Female vs. male (Ref)	0.48 (0.30-0.76)	0.002	0.48 (0.32-0.71)	< 0.001
Age (yr)				
> 65 vs. ≤ 65 (Ref)	2.02 (1.35-3.00)	0.001	1.99 (1.35-2.94)	0.001
BMI	0.94 (0.89-0.99)	0.014	0.93 (0.89-0.99)	0.012
Smoking				
Ever vs. never (Ref)	1.04 (0.65-1.65)	0.877	-	-
ECOG				
≥ 2 vs. 0-1 (Ref)	2.88 (1.14-7.30)	0.026	2.86 (1.14-7.19)	0.026
DL_{CO} (per)	0.99 (0.98-1.00)	0.002	0.98 (0.98-0.99)	0.002
pT				
T3-4 vs. T1-2	0.68 (0.32-1.45)	0.318	-	-
pN				
N1 vs. N0 (Ref)	1.04 (0.51-2.15)	0.911	-	-
N2 vs. N0 (Ref)	1.29 (0.55-3.00)	0.561	-	-
pStage				
Stage II vs. stage I (Ref)	2.77 (1.64-4.69)	0.000	2.61 (1.58-4.31)	< 0.001
Stage III vs. stage I (Ref)	5.27 (3.10-8.97)	0.000	4.69 (2.85-7.71)	< 0.001
Pleural invasion				
Visceral pleural invasion vs. no pleural invasion (Ref)	3.84 (1.27-11.61)	0.017	3.34 (1.33-8.40)	0.010
Surgery type				
Lobectomy vs. limited resection (Ref)	0.71 (0.26-1.91)	0.496	-	-
Pneumonectomy vs. limited resection (Ref)	0.73 (0.33-1.64)	0.448	-	-

BMI, body mass index; CI, confidence interval; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non–small cell lung cancer.

higher risk of mortality.

8. RFS of patients with *EGFR* mutation according to pleural invasion

The duration of RFS was significantly shorter for patients with parietal pleural invasion than in patients with VPI and patients without pleural invasion ($p < 0.001$, log-rank test) (S5 Fig.). The mean time to recurrence after curative surgery was 36.77 months for patients with parietal pleural invasion, 45.02 months for patients with VPI, and 53.42 months for patients without pleural invasion. At 24 months, 85.7% of patients with parietal pleural invasion were recurrence-free compared to 91.5% in patients with VPI and 96.2% in patients without pleural invasion.

9. RFS of patients with *EGFR* mutation according to pathologic N category

The RFS was significantly shorter according to pathologic N category ($p < 0.001$, log-rank test) (S6 Fig.). The mean time of RFS was 22.28 months for pathologic N3, 39.41 months for pathologic N2, 40.08 months for pathologic N1, and 53.75 months for pathologic N0. At 24 months, 88.2% of patients with pathologic N2 category were recurrence-free compared to 90.8% in patients with pathologic N1 category and 96.6% in patients with pathologic N0 category.

10. RFS of patients with *EGFR* mutation according to pathologic stage

The duration of RFS was significantly shorter according to pathologic stage ($p < 0.001$, log-rank test) (S7 Fig.). The mean time of RFS was 40.41 months for stage III, 42.90 months for stage II, and 53.80 months for stage I. At 24 months, 97.7% of the patients with pathologic stage I were recurrence-free compared to 86.6% in patients with pathologic stage II and 87.3% in patients with pathologic stage III.

11. Comparison between early, late, and no recurrence groups among *EGFR*-mutant stage IA patients

Subgroup analysis was done among 390 patients with *EGFR*-mutant stage IA (AJCC 7th edition) without neo-

adjuvant treatment. There was no significant difference in age, BMI, sex, smoking status, ECOG performance status, or pulmonary function, surgery type, histologic type, presence of mediastinal lymph node (LN) resection or anaplastic lymphoma kinase (ALK) among the ERG, LRG, or NRG (S8 Table). The proportion of patients with adjuvant chemotherapy and RT was higher in the ERG compared to the LRG and NRG.

12. Clinicopathologic risk factors associated with postoperative recurrence in *EGFR*-mutant stage IA NSCLC patients after curative surgery

S9 Table shows univariate and multivariate analyses of clinicopathologic risk factors for recurrence in *EGFR*-mutant stage IA NSCLC patients after curative surgery. In multivariate analysis, sex and surgery type were significantly associated with recurrence. The HR of recurrence in female patients was 0.46 compared to male patients (95% CI, 0.22 to 0.97; p=0.043). The HR of recurrence in patients who took lobectomy was 0.35 compared to patients who took wedge resection (95% CI, 0.14 to 0.90; p=0.029).

13. Comparison between early, late, and no recurrence groups among *EGFR*-mutant stage IB patients

Subgroup analysis was done among 203 patients with *EGFR*-mutant stage IB (AJCC 7th edition) without neoadjuvant treatment. There was no significant difference in age, BMI, sex, smoking status, ECOG performance status, or pulmonary function, surgery type, histologic type, presence of mediastinal LN resection or ALK among the ERG, LRG, or NRG (S10 Table). As pleural invasion, there were higher proportion of patients with pleural invasion in the ERG and LRG compared to NRG. The proportion of patients with adjuvant chemotherapy and RT was higher in the ERG compared to the LRG and NRG.

14. Clinicopathologic risk factors associated with postoperative recurrence in *EGFR*-mutant stage IB NSCLC patients after curative surgery

S11 Table shows univariate and multivariate analyses of clinicopathologic risk factors for recurrence in *EGFR*-mutant stage IB NSCLC patients after curative surgery. In multivariate analysis, pleural invasion was significantly associated with recurrence. Increased DLco showed a trend toward decreased risk for recurrence, but statistical significance was not present (p=0.078). The HR of recurrence in patients with VPI was 2.75 compared to patients without pleural invasion (95% CI, 1.31 to 5.75; p=0.007).

15. Clinicopathologic risk factors associated with early recurrence in *EGFR*-mutant stage NSCLC patients after curative surgery

S12 Table shows univariate and multivariate logistic regression analyses of risk factors for early recurrence in *EGFR*-mutant NSCLC patients after curative surgery. In multivariate analysis, ever-smokers showed 2.24 fold higher risk of early postoperative recurrence compared to never-smokers (95% CI, 1.18 to 4.23; p=0.013). Patients with pathologic T3 category were 5.11 times higher risk of early recurrence after curative resection, compared to patients with pathologic T1 category (95% CI, 1.75 to 14.93; p=0.003). Also, patients with pathologic N2 category were 3.11 times higher risk of early recurrence after curative resection, compared to patients with pathologic N0 category (95% CI, 1,44 to 6.68; p=0.004).

Discussion

The present study evaluated a nationwide lung cancer database to assess patients who are at risk of postoperative relapse, specifically for *EGFR*-mutant populations. We showed that, among various clinical parameters, patients with older age, higher N and pathologic stages, and those with presence of VPI are more likely to experience postoperative relapse and are in need of adjuvant EGFR TKI treatment. In regard to OS in *EGFR*-mutant NSCLC patients after curative surgery, male sex, older age, low BMI, high ECOG performance status, low DLco, high pathologic stage, and pleural invasion were significant prognostic markers.

There are some notable studies regarding the assessment of risk factors associated with postoperative relapse specifically for *EGFR*-mutant NSCLC patients who underwent resection. In a retrospective analysis of 531 patients, N category along with lympho-vascular invasion and cytokeratin 5/6 positivity were independent predictors of locoregional recurrence [12]. In another retrospective study, smoking history, vessel invasion, and lymph node metastasis were associated with RFS in *EGFR*-mutant patients [13]. In addition, Yu et al. [14] indicated that smoking history, large tumor size, elevated lymph node ratio, and platelet to lymphocyte ratio in stage pIIIA-N2 NSCLC patients after complete resection are associated with early recurrence. In the present study, among curatively resected *EGFR*-mutant NSCLC patients, the 1-year RFS was 94.9%, the 2-year RFS was 85.8%, and the 3-year RFS was 81.7%. At 24 months, 85.7% of patients with parietal pleural invasion were recurrence-free compared to 91.5% in patients with VPI and 96.2% in patients without pleural invasion. VPI is an important prognostic factor regardless of tumor size or N category [15]. In a previous study, exfoliated tumor cells were found to drain through the

pleural lymphatics, which supports the association between VPI and extensive N2 involvement [16]. The visceral pleura is rich in lymphatics and can easily involve the hilar lymph nodes. As a consequence, VPI is associated with locoregional recurrence and distant metastasis [17].

EGFR TKI treatment has provided better clinical outcomes in *EGFR*-mutant NSCLC patients [18,19]. Osimertinib treatment has shown longer progression-free survival compared to earlier-generation EGFR TKIs [18]. According to a recent study, a significant OS benefit was shown in *EGFR*-mutant NSCLC patients with adjuvant osimertinib treatment after complete resection [5]. Therefore, an updated version of the NCCN guidelines suggests adjuvant osimertinib treatment in *EGFR*-mutant patients in stage IIB-IIIA and stage IB-IIA with high-risk factors.

However, in clinical practice, we have encountered medical insurance problems. In many countries including Korea, the nationwide medical reimbursement system does not cover the cost of adjuvant osimertinib treatment in *EGFR*-mutant NSCLC patients, and the recommended 3 years of prescription often entail significant financial burden for the patients. A previous study showed that certain features associated with postoperative relapse do not translate directly to need for adjuvant EGFR TKI treatment. Patients enrolled in the ADAURA study were stage IB to IIIA (classified according to the AJCC 7th edition) *EGFR*-mutant (Ex19del or L858R) NSCLC [20]. Specifically for the *EGFR*-mutant subgroup, certain enrollment criteria between ADAURA and present study do not match. In our study, there were 4.0% squamous lung cancer patients included in the *EGFR*-mutant subgroup, and it is likely that *EGFR* mutations other than Ex19del and L858R could have been included. However, it was interesting to see that enrollment criteria of the ADURA study mostly overlapped with factors associated with postoperative relapse in our study, suggesting a possibility that patients with stage N1-2 or pleural invasion could have benefited from adjuvant EGFR TKI treatment. Clearly, more studies to better predict postoperative relapse are necessary to enable selection of patients for adjuvant EGFR TKI treatment.

When *EGFR*-mutant patients were stratified according to timing of postoperative relapse (early, late, or no recurrence), several features were distinguished. TNM stage, pleural invasion level, and smoking history showed significant difference between the groups. Early recurrence patients show a higher proportion of PL2 and PL3 compared to late recurrence patients. Furthermore, VPI was an independent factor associated with RFS. However, according to logistic regression analysis for early recurrence in *EGFR*-mutant NSCLC patients in the present study, only pathologic T, N stage and smoking history were significantly associated with early postoperative recurrence. While these risk factors need to be validated in larger population study, patients with regarding risk factors should undergo close surveillance for early postoperative recurrence.

In a previous retrospective analysis of NSCLC patients who underwent complete resection, association between VPI and *EGFR* mutation was shown, with a higher frequency of *EGFR* mutation patients among the subgroup [21]. In our study, risk of postoperative relapse was stratified by level of VPI. Considering that the presence of sole pleural invasion (PL1) is staged as T2, we should concurrently approach T stage and presence of VPI [22], and it is likely that clinicians should consider the presence and level of pleural invasion as an important factor when initiating and maintaining adjuvant EGFR TKI treatment.

In our analysis of stage IA lung cancer patients without pleural invasion, we observed that epidemiological factors, such as sex and age, might correlate with recurrence risk. ERG group showed significantly higher proportion of old-age patients, and male sex was associated with higher risk of recurrence in the multivariate analysis. In a retrospective study of NSCLC patients who underwent surgery for stage I and II cancer, females demonstrated significantly higher 5-year OS rates (76.2%) compared to males (57.3%), with gender identified as a favorable prognostic factor in multivariate analysis [23]. Among *EGFR*-mutant stage IA NSCLC patients, patients with lobectomy had lower risk of recurrence, compared to patients with wedge resection. This finding is consistent with the previous study, which compared locoregional RFS between wedge resection versus lobectomy for early-stage NSCLC. In the study, overall locoregional RFS was worse in wedge resection patients vs. lobectomy patients, 82.0% vs 93.4% [24]. In addition, one meta-analysis of comparison between wedge resection and lobectomy for early-stage NSCLC showed that patients with lobectomy had higher OS than patients with wedge resection [25]. So, even in early-stage NSCLC, lobectomy should be actively considered in patients without contraindication such as low lung function or poor general condition.

In our study, a subgroup analysis of *EGFR*-mutant stage IB (AJCC 7th edition) patients revealed that the hazard ratio for recurrence in patients with VPI was 2.75 times higher compared to those without pleural invasion. Despite differences in TNM editions, this finding aligns with a recent article by Choi et al. [3], which also identified VPI as a high-risk factor for postoperative recurrence in the stage IB patients. Another notable finding is that the ERG had a higher percentage of adjuvant chemotherapy and RT compared to late-recurrence or no-recurrence groups. It is more reasonable to consider that patients with more risk factors underwent postoperative treatment at the time of adjuvant therapy, rather than attrib-

uting recurrence risk to the adjuvant treatment itself. Therefore, we believe that efficacy of adjuvant treatment is difficult to be analyzed due to the limitations of the retrospective design. Future studies are needed to evaluate the efficacy of adjuvant treatment in patients with *EGFR* mutations.

Among the factors associated with postoperative outcomes in the EGFR subgroup of our study, DLco was independently associated with postoperative survival but not with RFS. DLco, along with other pulmonary function parameters, has long been shown to affect postoperative course of patients who undergo lung resection [26], and our results reconfirm this finding [27]. Low DLco values are associated with several lung conditions including emphysema or pulmonary fibrosis [28]. Patients with relatively low DLco values may have underlying emphysema or other chronic lung diseases that could impact their survival. Additionally, a study found that a low preoperative DLco is predictive of postoperative cardiopulmonary complications, mortality, and poor long-term survival in surgical patients [29]. Clinicians should pay more attention to patients with poor lung function when managing lung cancer patients who undergo lobectomy.

In the present study, duration of OS was significantly shorter for *EGFR*-wild type patients than *EGFR*-mutant patients. However, the RFS showed no significant difference between *EGFR*-wild type and mutant patients. Further studies should be done about treatment after recurrence.

There are notable limitations of this study. First, a large proportion of overall study patients did not undergo *EGFR* mutation testing. The database includes patients diagnosed with lung cancer from years 2014 to 2017, during the early phase of which mutation testing was not routinely performed. Despite this limitation, a large number of *EGFR*-mutant patients added to the importance of the present study. Second, no detailed results on *EGFR* mutation subtype or next-generation sequencing results were available for our study, which deterred us from confirming the association between mutation subtype and postoperative outcomes. Third, TNM staging was based on the AJCC 7th edition TNM staging, and it is likely that some T2 patients would have been classified as T3 according to the 8th edition [30]. Lastly, in our study, there was no statistically significant difference in recurrence risk between stage I and stage III *EGFR*-mutant patients. Although other clinical outcomes appeared relatively more favorable for stage I patients compared to stage III patients, we believe this discrepancy may be due to the smaller sample size of stage III patients. A larger sample size in future studies could potentially address this discrepancy.

Among the population that underwent complete resection for early NSCLC with *EGFR* mutation, patients with advanced stage, pleural invasion, or limited resection are more likely to show postoperative relapse.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The study protocol was reviewed and approved by the Institutional Review Board at the National Cancer Center (NCC2018-0193), which waived the requirement for informed consent due to the retrospective nature of the study.

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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