Epidermal Growth Factor Receptor Mutations and Their Correlation with Gefitinib Therapy in Patients with Non-small Cell Lung Cancer: A Meta-Analysis Based on Updated Individual Patient Data from Six Medical Centers in Mainland China

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Background: Convincing data on epidermal growth factor receptor (EGFR) mutations in Chinese patients with non-small-cell lung cancer (NSCLC) remain limited. We investigated the relevance of demographic characteristics and EGFR mutations, correlations between the efficacy of gefitinib and EGFR mutations in NSCLC, and to identify individuals who would likely benefit from gefitinib.

Methods: We conducted a meta-analysis based on updated individual patient data from six medical centers in mainland China. Outcome measures included the EGFR mutation status, demographic characteristics, response, and survival.

Results: Among 506 patients with NSCLC who received EGFR mutation analysis, the EGFR mutation rate was 30.04%. Patients with adenocarcinoma had a higher mutation rate than those with non-adenocarcinoma (44.1% vs 9.2%; $p < 0.00001$). The EGFR mutation rate for smokers was 15.1%, lower than that for non-smokers (45.5%) ($p < 0.00001$). Male patients had a lower mutation rate than female patients (23.1% vs 42.9%; $p < 0.0001$). Multivariate analysis showed that "adenocarcinoma" and "non-smoker" were independent predictors of EGFR mutations. In a subgroup of 57 patients with complete treatment data, the response rate to gefitinib in the EGFR mutant group was 60.7%, significantly higher than that in the wild-type EGFR group (17.2%) (odds ratio, 5.78; 95% CI, 1.95–17.13; $p = 0.002$). "EGFR mutation", "adenocarcinoma," and "non-smoker" were independent predictors of response. Overall survival in the EGFR mutant group and the wild-type group did not differ significantly (hazard ratio, 0.60; 95% CI, 0.32–1.12; $p = 0.110$). "Adenocarcinoma status" was an independent prognostic factor for survival.

Conclusions: In mainland China, "adenocarcinoma" and "non-smoker" are independent predictors for EGFR mutations. Response to gefitinib favors patients with EGFR mutations. The clinical selected populations for gefitinib are non-smokers with adenocarcinoma.

Key Words: Protein kinase inhibitors, Receptor, Epidermal growth factor, Carcinoma, Non-small cell lung, Meta-analysis, Chinese.

(*J Thorac Oncol.* 2007;2: 430–439)

Lung cancer is the leading cause of cancer deaths in China and worldwide. It is estimated that, per 100,000 Chinese individuals, approximately 41.8 men and 19.3 women died from lung cancer in 2005.[1] Non-small-cell lung cancer (NSCLC) accounts for approximately 85%.[2] Despite treatment advances, chemotherapy is only marginally effective in most advanced cases.[3,4] For those patients refractory to or intolerant of the current chemotherapy, treatment options are limited. Hence, more effective therapy with fewer side effects is needed.

The epidermal-growth-factor receptor (EGFR) tyrosine-kinase (TK) forms a part of the signaling pathway that regulates tumor-cell proliferation, invasion, angiogenesis, metastasis, and apoptosis.[5] Because EGFR is often over-expressed in NSCLC and the level of EGFR expression correlates with poor prognosis, EGFR inhibitors have been developed as novel therapy for NSCLC.[6,7] Gefitinib, the first molecular targeted agent approved for the treatment of advanced NSCLC, is a highly effective EGFR TK inhibitor (TKI) that selectively blocks the signal transduction pathways implicated in cancer growth.[8,9]

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Disclosure: The authors indicated no potential conflicts of interest.

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ISSN: 1556-0864/07/0205-0430

In 2004, Lynch et al. and Paez et al. reported almost simultaneously that mutations of EGFR may predict the sensitivity of NSCLC to gefitinib,[10,11] which is regarded as a milestone for approaching individualized molecular targeted therapy for NSCLC. Subsequently, many publications have reported data consistent with this finding. Phase II trials with EGFR-TKI in patients with chemorefractory NSCLC have found response rates of 9% to 19% and median survival ranging from 7.6 to 8.4 months.[8,9,12] Furthermore, BR21, a phase III study of erlotinib, showed a significant survival benefit compared with placebo.[13] However, in a similarly designed study, ISEL, gefitinib did not show any survival gain over placebo. Subsets of patients who had never smoked and were of Asian origin seemed to benefit from gefitinib.[14] Whether gefitinib is less efficacious than erlotinib or whether the study design, the patients enrolled, the tumor molecular characteristics, and the dose might have contributed to the different outcome remain unclear.[15] One area of current research focuses on the identification of factors distinguishing those who are more likely to derive benefit from EGFR-TKIs therapy, this information could then aid in patient selection. Based on population, China is the largest country in the world, with a population of approximately 1.3 billion at the end of 2004. However, to date, data on EGFR mutations in mainland China are scarce. Comprehensive review of existing information regarding EGFR mutations is essential for personalized therapy for advanced NSCLC.

The gold standard for combining evidence from trials is individual patient data meta-analysis (IPD-MA), in which updated data from each relevant trial are centrally collected, processed, and analyzed.[16] In this report, we include all relevant trials from a comprehensive search to provide evidence on the relationship between EGFR mutations and gefitinib therapy for patients with NSCLC from mainland China.

MATERIALS AND METHODS

Selection Criteria

Both published and unpublished trials that match the criteria below were eligible. We included cohort studies on EGFR mutations in NSCLC. Individuals with histologically confirmed NSCLC were study participants. In refractory NSCLC with performance status (PS) of 0 to 2, tissue samples were taken and the EGFR mutation analyses were performed; 250 mg gefitinib was taken once daily uninterrupted until disease progression or intolerable toxicity. The EGFR mutation status, demographic characteristics of pathology, gender, age, smoking history and TNM stage, response, and survival were outcome measures. Any patients that were not from mainland China, patients with small cell lung cancer, and patients who lacked the IPD were excluded.

Search Strategy

Both published and unpublished studies were included. A systematic search was used to identify all relevant trials from January 2000 to June 2006. Computerized bibliographic searches with PubMed, EMBASE, Cochrance Library, Chinese biomedical literature database, and www.clinicaltrials.gov were supplemented with hand searches of conferences abstracts and specialty journals. Articles were identified by use of the related-articles function in PubMed. References of articles identified were also searched manually. All investigators who took part in the meta-analysis were asked to identify trials.[17] We eventually included six clinical trials that explored the role of EGFR mutations in NSCLC in mainland China. Four of these trials, conducted by Guangdong Provincial People's Hospital (GDPPH), Peking Union Medical College Hospital (PKUMCH), Sun Yat-sen University (SYSU), and Shanghai Pulmonary Hospital (SHPH) were reported at the 2005 ASCO annual meeting.[18–21] Fourteen published articles from 11 institutions were detected through electronic searches. Among these, two trials were excluded for lacking the IPD,[22,23] and seven were excluded because the data were generated outside mainland China (Hong Kong, Taiwan, Canada, Spain, and the United States). The remaining two trials[24–28] came from the same studies conducted by PKUMCH and SYSU presented at the 2005 ASCO annual meeting. Finally, 506 individuals from the above four trials and two other unpublished trials directed by Jilin University (JLU) and the Second Shanghai Medical College (SSHMC) through cooperation were included.

Data Collection

The Secretariat decided what data to collect. IPD were obtained directly from the responsible investigator in all eligible trials. Updated information on demographic characteristics, EGFR mutations, and efficacy of therapy were collected, sent to the central coordination center, and reviewed for consistency and completeness before analysis. All data were thoroughly checked and extracted by two reviewers independently; any queries were resolved by discussion to validate the accuracy of extraction.[29] The last follow-up date was February 14, 2006.

EGFR Mutation Analysis

The mutation analysis of the EGFR-TK domain was performed with frozen or paraffin-embedded tumor tissues. Tumor samples were obtained from thoracotomy in early-stage NSCLC, diagnostic procedures such as fiberbrochoscopy and transthoracic needle aspiration biopsy in advanced cases. Genomic DNA was extracted from specimens, and exons 18, 19, 20, and 21 were amplified with four pairs of primers. Uncloned PCR fragments were sequenced and analyzed in both sense and antisense directions. Both forward and reverse sequencing reactions were performed with the respective primers and the ABI (Applied Biosystems, Foster City, CA) company Big Dye Terminator v3.1 Cycle Sequencing Kit. Sequencing products were electrophoresed on an ABI3700 genetic analyzer. All sequence variations were confirmed by multiple independent PCR amplifications and repeated sequencing reactions.[10] EGFR mutations were analyzed using direct sequencing in all the six institutions included.

Assessment of Efficacy

Baseline evaluation included chest and upper abdomen computed tomography including adrenals, brain magnetic resonance imaging, and bone scan within 14 days before

entry. Patients were re-evaluated at the end of the first and third months of therapy, then every 3 months. Objective tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[30] Overall survival (OS) was assessed from the first dose of gefitinib to the date of death for any cause. Data for patients who were alive at the time of follow-up were censored. Efficacies were evaluated in the same procedure in the six institutions included.

Statistical Analysis

The relationship between EGFR mutation and demographic characteristics was analyzed with IPD-MA and logistic regression. The data were input to RevMan 4.2 (downloaded from www.cochrane.org) under the IPD category fix effect model, the pooled IPD Peto odds ratio (OR) and 95% confidence interval (CI) were calculated. Analyses were weighted by trial size.[16] In logistic regression, univariate analysis was first performed and combined with the indications of previous studies to identify the covariates for multivariate analyses. The binary logistic regression forward maximal likelihood ratio (LR) test was then performed to screen the variables. The relationship between response and various covariates were analyzed through IPD-MA and logistic regression. Pearson χ^2 and subgroup analyses were used to identify the subgroups that correlated best with response. In survival analysis, the log-rank expected number of events and variance were used to calculate the HR at the 95% CI for individual trials and pooled across all trials using the method of survival curve and hazard ratio plot (SCHARP) program.[31–33] Trials were grouped by mutation sites. Analyses were weighted by trial variance. We used χ^2 to test for gross statistical heterogeneity across all trials. The Kaplan-Meier method was used to estimate the distribution of OS in gefitinib-treated NSCLC stratified by mutation sites. The absolute effects of treatment on median survival were read from Kaplan-Meier curves. Multivariate Cox regression was used to determine the prognostic factors. The statistical analyses were performed using RevMan 4.2, SigmaPlot 10.0 with SigmaStat 3.5 integration, and STATA 8.0. All p values were two-sided, and $p < 0.05$ was considered significant.

RESULTS

Patient Characteristics

As illustrated in Table 1, 506 patients with NSCLC who were analyzed for EGFR mutations from six medical centers in Guangzhou, Beijing, Shanghai, and Changchun between 2002 and 2006 met the inclusion criteria. The overall EGFR mutation rate was 30.04% in activating mutations of exon 19 deletions and exon 21 L858R substitutions. Two point mutations in exons 18 G719C, a T790M mutation located in exon 20, and six other types of rare mutations in exon 18 and 21 were excluded from the analysis. Full data, including survival, response, and demography characteristics of EGFR mutations, were only available for 57 patients from GDPPH and PKUMCH. The efficacy data were not available from the other four centers.

Relationship Between EGFR Mutations and Patient Characteristics

In meta-analysis, we chose 0.01 to 100 as the logarithmic scale (Figure 1). For the comparison between adenocarcinoma and non-adenocarcinoma, JLU's study was excluded because all their cases were adenocarcinoma. All the other five centers reported a significant result except SYSU. Overall, patients with adenocarcinoma had a significantly higher EGFR mutation rate (44.1%) than those without adenocarcinoma (9.2%). The pooled IPD Peto OR and 95% CI was 5.41 (3.57–8.22) ($p < 0.00001$) (Figure 1*A*).

Men had a lower EGFR mutation rate (23.1%) than women (42.9%), with the Peto OR and 95% CI being 0.42 (0.28–0.63) ($p < 0.0001$). Differences in data from four of the six centers reached statistical significance. (Figure 1*B*).

The data from PKUMCH lacked information about smoking history, except for 30 patients who received gefitinib. The comparison between smokers and non-smokers from each center showed a tendency to favor the non-smokers, whereas only four reached significant difference. Smokers had a lower EGFR mutation rate (15.1%) than non-smokers (45.5%), with the Peto OR and 95% CI being 0.24 (016–0.36) ($p < 0.00001$). (Figure 1*C*).

Univariate analysis was first performed to select covariates for subsequent multivariate analysis. The dependent variable was EGFR mutation status (mutant and wild-type). The candidate covariate included institution (GDPPH, PKUMCH, SYSU, SHPH, JLU, and SHMC), age (years), TNM stage (I, II, III, and IV), adenocarcinoma status (adenocarcinoma and non-adenocarcinoma), histology (adenocarcinoma, squamous, large cell, and adenosquamous), smoking history (smoker and non-smoker), smoke index (pack-years), and gender (male and female). Institution and histology were categorical variables. Institution ($p = 0.074$, 0.153, 0.560, 0.096, 0.214, and 0.628, respectively), age ($p = 0.446$), and TNM ($p = 0.502$) were excluded because their value was $p > 0.05$ and there were no previous studies indications. Among the five variables screened by multivariate analysis, adenocarcinoma status (OR = 3.66; 95%CI, 1.89–7.07; $p < 0.00001$) and smoking history (OR = 0.38; 95%CI, 0.22–0.66; $p < 0.00001$) stayed in the model using binary logistic regression with forward maximal LR test.

Response to Gefitinib

The analyses were based on data for 57 patients with NSCLC from two institutions. The dependent variable was response (complete response [CR] + partial response [PR] and stable disease [SD] + progressive disease [PD]). The candidate variables included institution (GDPPH and PKUMCH) ($p = 0.088$), EGFR mutation status (mutant and wild-type) ($p = 0.001$), adenocarcinoma status (adenocarcinoma and non-adenocarcinoma) ($p = 0.01$), smoking history (smoker and non-smoker) ($p = 0.003$), and gender (male and female) ($p = 0.02$). All five variables were selected for the multivariate analysis based on previous study indications. Among them, adenocarcinoma status ($p = 0.998$), smoking history ($p = 0.039$), and EGFR mutation status ($p = 0.006$) continued in the model.

TABLE 1. Patient characteristics

	Institutions							
Characteristics	**GDPPH**	**PKUMCH**	**SYSU**	**SHPH**	**JLU**	**SHMC**	**Total**	**%**
n	142	76	52	81	54	101	506	100
Age (yr)								
Median	60	62.5	58	62	56.5	62.5	60	
Range	24–84	34–83	36–76	39–83	32–76	39–81	24–84	
Gender								
Male	98	41	39	52	27	72	329	65.0
Female	44	35	13	29	27	29	177	35.0
Smoking history								
Smoker	84	12[a]	33	41	18	63	251	55.6
Non-smoker	58	18[a]	19	40	36	38	209	44.4
Histology								
Adenocarcinoma	80	36	24	38	54	41	273	61.7
Squamous cell	37	25	20	31	0	33	146	28.8
Adenosquamous	5	0	4	12	0	14	35	6.9
Large cell	10	0	0	0	0	3	13	2.6
Bronchioalveolar[b]	10	15	4	0	0	10	39	7.7
EGFR mutation status[c]								
Mutant	42	31	10	21	21	27	152	30.04
Wild-type	100	45	42	60	33	74	354	69.96
TNM stage								
I	60	NA	NA	34	21	30	145	38.4
II	22	NA	NA	11	11	18	62	16.4
III	37	NA	NA	31	17	29	114	30.1
IV	23	NA	NA	5	5	24	57	15.1
Response to gefitinib[d]	27	30	NA	NA	NA	NA	57	100
Complete response	3	0	NA	NA	NA	NA	3	5.3
Partial response	10	9	NA	NA	NA	NA	19	33.3
Stable disease	8	12	NA	NA	NA	NA	20	35.1
Progressive disease	6	9	NA	NA	NA	NA	15	26.3
Survival status	27	30	NA	NA	NA	NA	57	100
Complete data	18	26	NA	NA	NA	NA	44	77.2
Censor data	9	4	NA	NA	NA	NA	13	22.8

Values are expressed as *n* of patients unless otherwise specified. EGFR, epidermal growth factor receptor; GDPPH, Guangdong Provincial People's Hospital; UMCH, Peking Union Medical College Hospital; SYSU, Sun Yat-sen University; SHPH, Shanghai Pulmonary Hospital; JLU, Jilin University; SHMC, Second Shanghai Medical College; NA, not available.

[a] The data from PKUMCH lacked information about smoking history, except for 30 patients who received gefitinib therapy.

[b] Patients with bronchioalveolar carcinoma were included in the adenocarcinoma group for analysis.

[c] Two point mutations in exons 18 G719C, a T790M mutation located in exon 20 and other six types of rare mutations in exon 18 and 21 were excluded from analysis.

[d] RECIST criteria.

In meta-analysis, both centers had a tendency to favor EGFR mutation group in response, and the IPD Peto OR and 95% CI was 5.78 (1.95–17.13) ($p = 0.002$). The response rate in the EGFR mutation group (60.7%, 17 of 28) was significantly higher than that of the EGFR wild-type group (17.2%, 5 of 29) (Figure 2*A*).

The overall response rate to gefitinib was 38.6 % (22 of 57); the EGFR mutation rate was 49.12% (28 of 57) in this subset. The response rate in subgroup of adenocarcinoma + non-smoker (60.0%) or adenocarcinoma + non-smoker + female (60.9%) was similar to that of the mutation group (60.7%); $p = 0.956$ and $p = 0.991$, respectively. The subgroup analyses showed that response rate favored the following six combinations with the overall effect Z value and p values as follows: A+NS+EM ($Z = 3.97$, $p < 0.0001$), A+NS ($Z = 3.52$, $p = 0.0004$), EM+A+NS+F ($Z = 3.14$, $p = 0.002$), A+NS+F ($Z = 2.94$, $p = 0.003$), NS+F ($Z = 2.77$, $p = 0.006$), and F+A ($Z = 2.65$, $p = 0.008$). The combined subgroup of A+NS+EM had the highest response rate of 76.5 % (13 of 17). (Figure 2*B*).

Survival

Analyses were based on IPD from 57 patients in two trials (GDPPH and PKUMCH) using SCHARP program and Kaplan-Meier method (Figure 3). The integration of data did not show significantly longer survival in the EGFR mutation

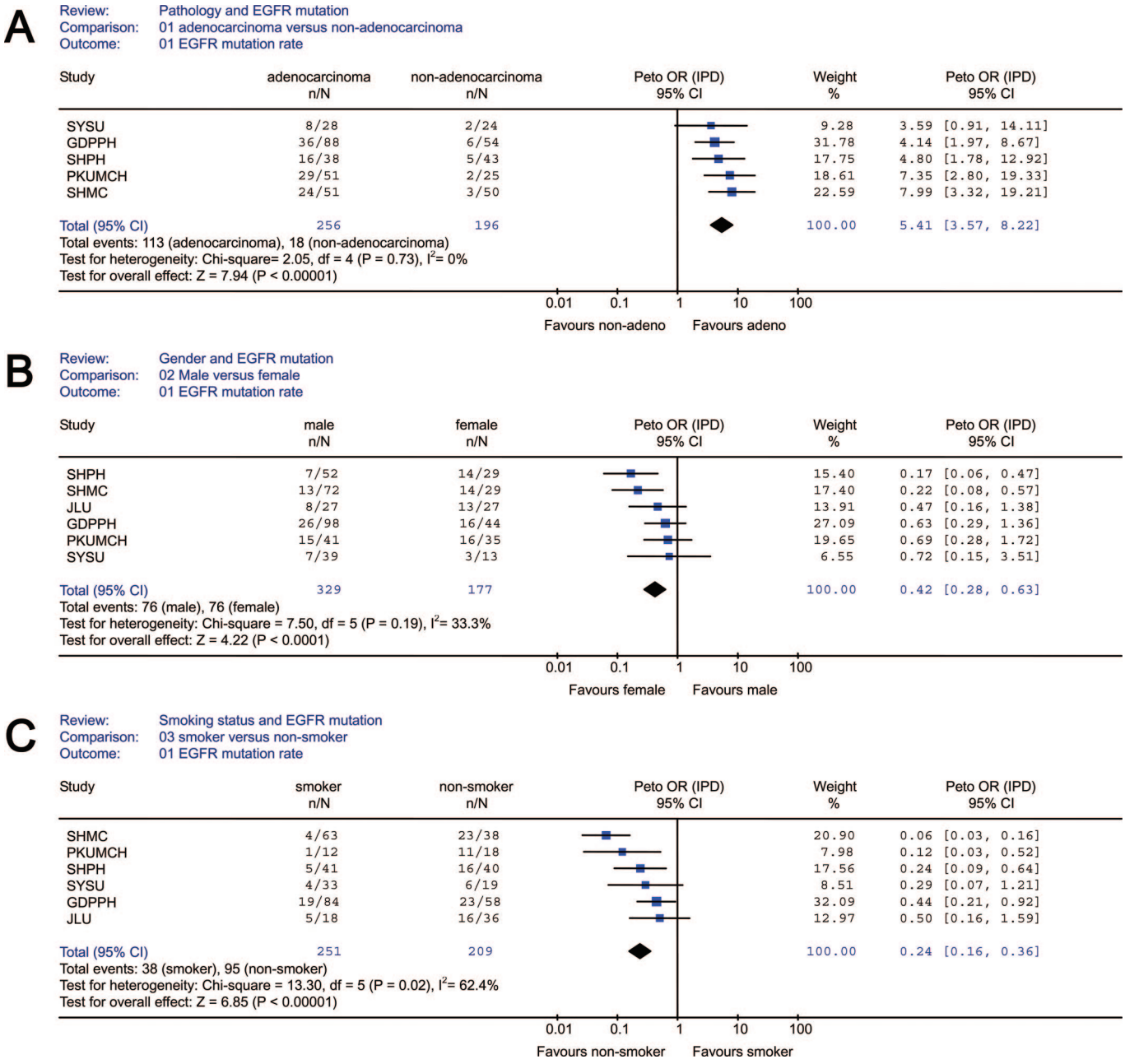

FIGURE 1. Relationship between EGFR mutations and the patient characteristics. **A**, Patients with adenocarcinoma had a significantly higher EGFR mutation rate (44.1%) than those without adenocarcinoma (9.2%). The pooled IPD Peto OR and 95% CI was 5.41 (3.57-8.22) ($p < 0.00001$). **B**, Men had a lower EGFR mutation rate (23.1%) than women (42.9%), with the Peto OR and 95% CI being 0.42 (0.28–0.63) ($p < 0.0001$). **C**, Smokers had a lower EGFR mutation rate (15.1%) than non-smokers (45.5%), with the Peto OR and 95% CI being 0.24 (016–0.36) ($p < 0.00001$).

group compared with the wild-type group (pooled HR for death, 0.60; 95% CI, 0.32–1.12; $p = 0.110$) with the absolute difference of median survival 257 days versus 115 days (Figure 3*A*); median survival was estimated to be 619 days versus 140 days for exon 19 deletions group versus the wild-type group (pooled HR, 0.59; 95% CI, 0.28–1.26; $p = 0.172$) (Figure 3*B*). The survival rates between the exon 21 L858R substitutions group and the wild-type group did not differ significantly (median survival 168 vs 182 days; pooled HR, 0.88; 95% CI, 0.45–1.74; $p = 0.723$) (Figure 3*C*). There was no evidence of gross statistical heterogeneity within trials.

In Cox regression, univariate analysis was performed first, followed by multivariate analysis. All the variables defined were used in multivariate analyses based on the indications of previously published studies regardless of their

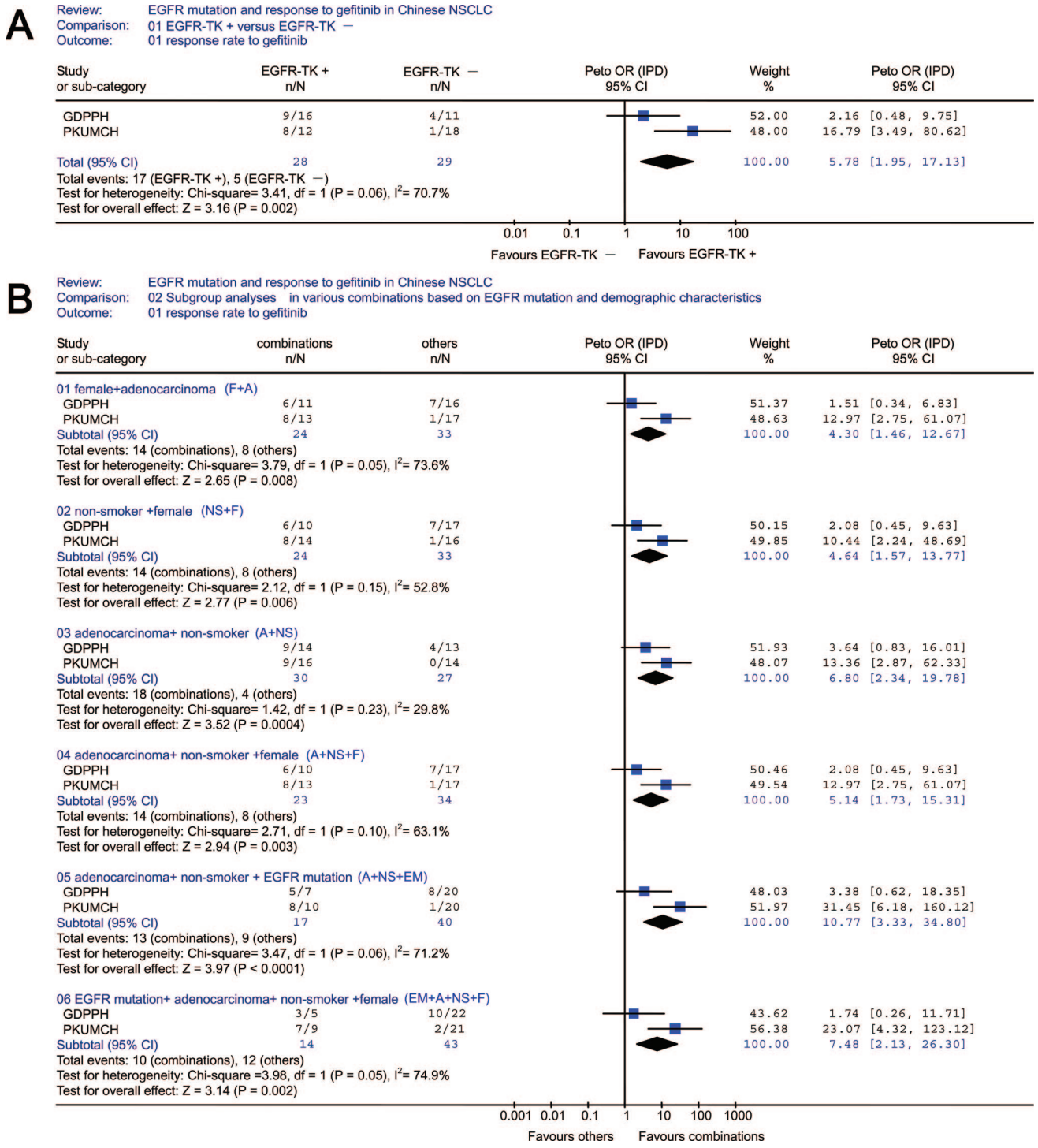

FIGURE 2. Relationship between EGFR mutations and response to gefitinib. **A**, The response rate in EGFR mutation group (60.7%, 17 of 28) was significantly higher than that of EGFR wild-type group (17.2%, 5 of 29). The IPD Peto OR and 95% CI was 5.78 (1.95–17.13) ($p = 0.002$). **B**, The overall response rate to gefitinib was 38.6 % (22 of 57); the EGFR mutation rate was 49.12 % (28 of 57) in this subset. The subgroup analyses showed that response rate favored all the following six combinations with the overall effect Z value and p values as follows: F+A ($Z = 2.65$, $p = 0.008$), NS+F ($Z = 2.77$, $p = 0.006$), A+NS ($Z = 3.52$, $p = 0.0004$), A+NS+F ($Z = 2.94$, $p = 0.003$), A+NS+EM ($Z = 3.97$, $p < 0.0001$), and EM+A+NS+F ($Z = 3.14$, $p = 0.002$).

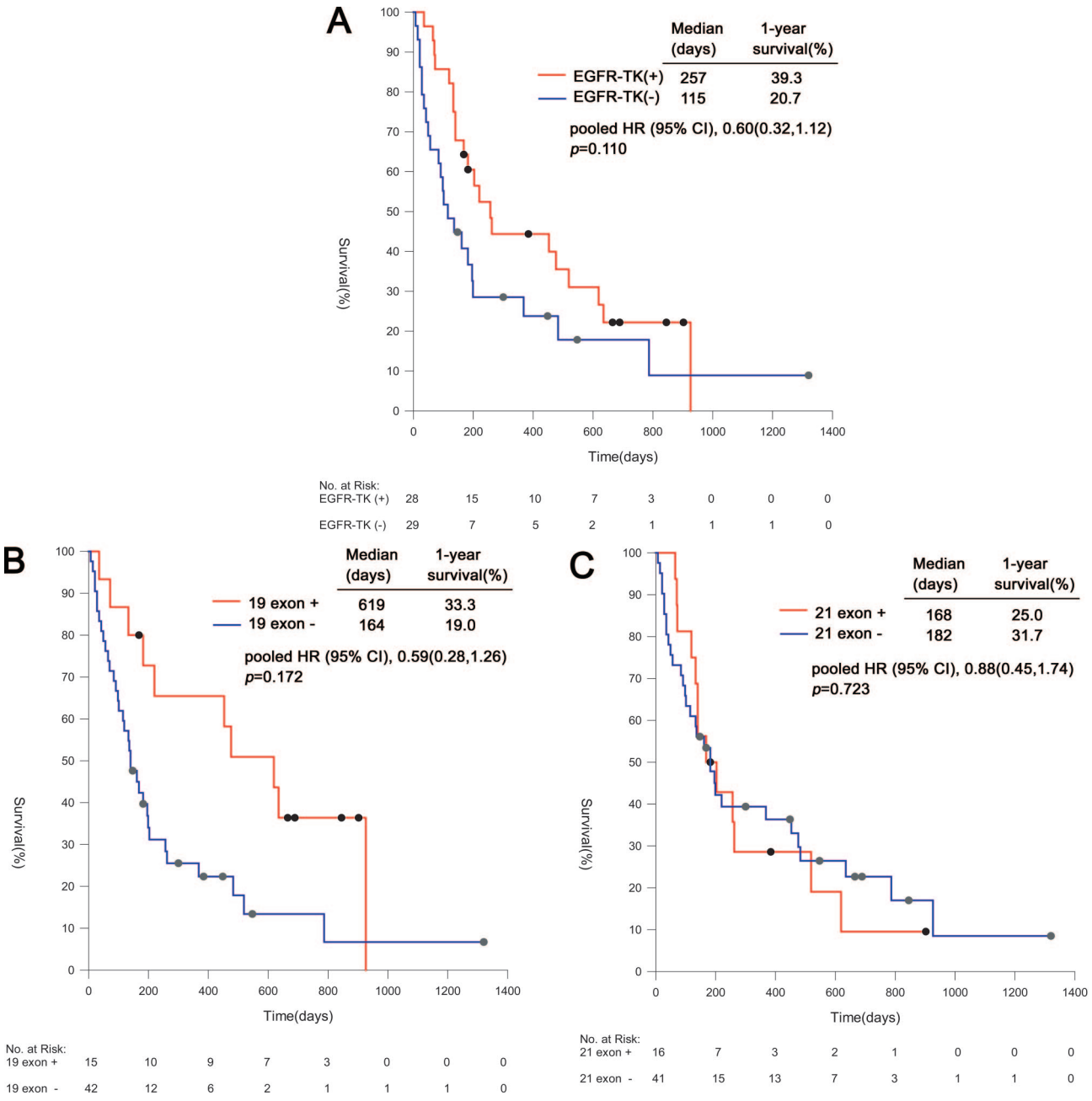

FIGURE 3. Kaplan-Meier plot of overall survival derived from IPD of GDPPH and PKUMCH. Data are grouped by exon mutation sites.

p values.[34–37] The candidate covariates included EGFR mutation status ($p = 0.076$), gender ($p = 0.042$), adenocarcinoma status ($p < 0.00001$), and smoking history ($p = 0.053$). Each variable was used in Cox regression for survival with forward LR test to identify prognostic factors. The only variable to stay was adenocarcinoma status (HR, 0.22; 95%CI, 0.10–0.45; $p < 0.00001$).

DISCUSSION

It is now apparent that only subsets of patients are responsive to EGFR-TKI. Gefitinib causes significant tumor shrinkage in only approximately 10% of Caucasian patients with NSCLC. Lynch et al. and Paez et al. similarly reported that mutations of the EGFR gene, which cluster near the ATP cleft of the TK domain, may predict sensitivity of NSCLC to gefitinib.[10,11] The mutations are also more common in patients who are Asian, female, non-smokers, and who have adenocarcinoma[38–42]—all characteristics linked to the known clinical predictors of gefitinib sensitivity.[34–37]

The present report is an IPD-MA elucidating the role of EGFR mutations in NSCLC in mainland China, which may be helpful in targeting patients for better responses to ge-

fitinib. The EGFR mutation rate in our study was 30.04%. Thus far, many studies have reported mutational analyses for the TK domain in thousands of patients with NSCLC. Chan et al. reported that the overall mutation rate in unselected cases of NSCLC was 16.7% but differed widely among various race: patients of Asian origin have a higher prevalence compared with Caucasians (30.6% vs 7.6%, $p < 0.0001$).[43] In this research, the EGFR mutation rate was higher in women, non-smokers, and patients with adenocarcinoma, but only adenocarcinoma and non-smoker were independent factors linked to EGFR mutations. Our findings are consistent with those of previous reports in different Caucasians and Asian ethnicities.[39–42,44,45] Otherwise, a selection bias of gefitinib-treated patients, which accounted for 11% of total cases, may have contributed to the higher frequency of EGFR-TKI mutations in our study. Furthermore, we observed that adenocarcinoma is a better predictor for mutations than non-smoker, as the OR for mutations was higher in adenocarcinoma. This may arise from the correlation between lung cancer and smoking, as well as the lifestyle pattern of Chinese. The relationship between smoking and adenocarcinoma is not as strong as its relationship to squamous carcinoma. Most adenocarcinomas may not be caused by smoking, but genetic instability contributes to the development of EGFR mutations. A variety of factors may lead to an underlying gene alteration, including exposure to other carcinogens such as radiation or second-hand smoke.[46] Moreover, in contrast to their Western counterparts, 92% to 96% of Chinese women have never smoked cigarettes in their lifetime. Among the women with lung cancer, 83% do not have smoking history.[47] Therefore, both female gender and nonsmoker status may be confounding factors for predicting EGFR mutations. Adenocarcinoma should be used as the prior clinical predictor for EGFR mutation. The secondary predictor may be smoking history. Pham et al. reported that the likelihood of EGFR mutations in exons 19 and 21 decreased as pack-years increased. Mutations were less common in patients who smoked for more than 15 pack-years or who stopped smoking less than 25 years ago. Thus, TKI therapy should not be limited to never-smokers, but expanded to former smokers with exposures of less than 15 pack-years or who are more than 25 years smoke-free.[48] Because institution is not a correlating factor, there may be no difference among several origins in China conferring EGFR mutations in NSCLC.

The correlation between the efficacies of TKI therapy and EGFR mutations in NSCLC is an area of interest. Because, in our analysis, only 57 patients received gefitinib therapy, efficacy data are limited and might lead to a selection bias. Nevertheless, research based on IPD is beneficial. A pooled IPD-MA could correct for some bias. Investigators could be contacted for additional information, which allowed for better compliance with regard to missing data and a more balanced interpretation of the results and subgroup analyses.[16] In this study, adenocarcinoma, non-smoker, and EGFR mutations were key factors that influenced response. The response rate in the EGFR mutation group was 60.7%. Mutation is a better predictor than gender, smoking, or pathology alone. When any two clinical factors combined, there was still no significant advantage compared with EGFR mutation alone. Exclusively, adenocarcinoma + non-smoker (60.0%) approached 60.7%. The highest response rate (76.5%) was seen for EGFR mutation + adenocarcinoma + non-smoker. The independent predictors for response in multivariate analysis, comparison of the response in various combinations, and the overall effect in the subgroup analyses provide evidence to choose non-smokers with adenocarcinoma as the selected population for TKI in mainland China. Conversely, we tentatively suggest that screening for mutations should only apply to patients within the male + smoker + non-adenocarcinoma category and patients with poor PS when first-line EGFR-TKI therapy is considered in clinical practice. According to our study, the response rate is lower than the EGFR mutation rate in the subgroup of gefitinib-treated patients. Although most patients developing PD possess wild-type EGFR and patients responsive to gefitinib are more likely to harbor mutations, some patients carrying mutations still have PD after TKI treatment. The presence of EGFR mutations only partially correlates with tumor response. Therefore, because not all responders carry mutations, there are probably alternative mechanisms conferring sensitivity to TKI therapy.

Although multiple retrospective studies reported that EGFR mutations are linked to better survival in gefitinib-treated patients with NSCLC,[36,39,49–51] retrospective molecular subgroup analyses of the prospective BR.21 trial failed to associate EGFR mutations with improved overall survival in erlotinib.[52] In our study, although the pooled analysis of HR for the 57 gefitinib-treated patients with NSCLC showed no significant difference between the EGFR mutation group and the wild-type group, the exon 19 mutation group had a tendency toward longer survival than the wild-type group. In contrast, the exon 21 wild-type group had a trend for longer survival compared with the mutation group. Two small-sample studies also reported that patients with exon 19 deletions had longer survival after EGFR-TKI therapy compared with those with L858R mutation. Prospective trials with greater numbers of patients are needed to further define the prognostic roles of different EGFR mutations with respect to EGFR-TKI.[53,54] The different distribution in the survival curve between mutation sites may explain why some patients with NSCLC with EGFR mutations gained favorable efficacy but others did not, suggesting differences in activating EGFR signaling by each mutation. The absence of statistical heterogeneity among the trials indicated that there may be no difference in survival after TKI therapy between GDPPH and PKUMCH. Among the four variables that may help in patient selection in the Cox regression, adenocarcinoma status may be considered an independent prognostic factor. In the ISEL study, median survival did not differ significantly between gefitinib and placebo in patients with adenocarcinoma in the overall participant population,[14] whereas subset analysis of patients of Asian origin and earlier experience from Korea both indicated that survival benefit was associated with adenocarcinoma and smoking history.[38,55] Considering the small sample sizes in our study, our conclusions are not definitive.

In mainland China, adenocarcinomas, non-smokers, and women with NSCLC have a higher EGFR mutation rate. Adenocarcinoma and non-smoker status, however, are independent predictors for the EGFR mutations. There may be little difference among several origins in mainland China conferring EGFR mutations. The response to TKI favors patients with EGFR mutations. The selected population for gefitinib may be non-smokers with adenocarcinoma. Although patients with a good response to TKI have longer survival, it is unclear why the EGFR mutations predict response but not survival. This may be the result of the limited sample in our study. Further efforts should be made to obtain data on survival from prospective translational trials in combination with the tissue sample analysis to predict clinical efficacy in EGFR-TKI therapy.

ACKNOWLEDGMENTS

This study was supported by grants from the Chinese State Key Program for basic research (2002BA711A08), the Foundation of Guangzhou Science and Technology Bureau(2001-Z-044-01), Guangdong Provincial Key Program for Medical Research (WSTJJ2003072644010256020340 1), and Guangdong Provincial Health Bureau (2004-199-25). This work was presented in part at the 2005 and 2006 American Society of Clinical Oncology annual meetings.

We thank the following investigators, groups, and secretariat for participating in this meta-analysis: all the staff and students in the Cancer Center of Guangdong Provincial People's Hospital (especially Jin-ji Yang, Yu-juan Huang, Ri-qiang Liao, and Yi-sheng Huang in the Department of Lung Cancer; Gang Chen, Pu Xiao, Xue-ning Yang, Ji-ming Tang, Xiao-song Ben, Liang Xie, and Hai-Yu Zhou in the Department of General Thoracic Surgery; Lin Yu and Hua Zhang in the editorial office of the Journal of Evidence Based Medicine; and Ai-ling Guo, Jian Su, Zhi-Hong Chen, Xu-Chao Zhang, Ying Huang, Hong-Yan Tang, Zhi Xie, Zhi-Lang Chen, Bin Gan, Yan Yang, and Fa-ye Jiang in the Research Center of Medical Sciences). All members of the group were involved in the protocol design, data extraction, and interpretation of the results and commented on early and final drafts of the paper. We would like to thank all patients who took part in the trials and contributed to this research. The meta-analysis would not have been possible without their help or without the collaborating institutions who kindly supplied their trial data.

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