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ORIGINAL RESEARCH

RETRACTED ARTICLE: Efficacy and Safety of Gefitinib Plus Pemetrexed/Platinum in Advanced EGFR-Mutated Lung Adenocarcinoma Patients: A Real-World Observational Study

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Background: Recent clinical trials illustrated that gefitinib plus pemetrexed/platinum regimen improves survival in advanced lung adenocarcinoma patients with EGFR mutation, while data on its efficacy and safety in a real clinical setting are limited. Thus, this real-world observational study aimed to explore this issue.

Methods: Fifty-one advanced lung adenocarcinoma patients with EGFR mutation who received gefitinib plus pemetrexed/platinum (GPP) were enrolled as GPP group, meanwhile 30 patients who only received gefitinib were retrospectively recruited as control group. Progression-free survival (PFS), overall survival (OS), and adverse events were assessed.

Results: PFS was prolonged in GPP group compared to control group (P=0.013) (median PFS: 23.0 vs 14.0 months, 1-year PFS rate: 78.4% vs 60.0%, 3-year PFS rate: 19.6% vs 5.3%). Furthermore, OS was longer in GPP group compared to control group (P=0.023) (median PFS: 42.0 vs 28.0 months, 1-year PFS rate: 94.1% vs 86.7%, 3-year PFS rate: 39% vs 17%). After adjustment by multivariate Cox proportional hazard regression, GPP group vs control group was independent predictive factor of prolonged PFS (P=0.004, hazard ratio (HR)=0.450) and OS (P=0.031, HR=0.462). Moreover, the most common adverse events among patients in GPP group included myelosuppression (66.7%), digestive toxicity (62.7%), renal toxicity (31.4%), and hepatotoxicity (23.5%), and most of them were grade 1–2.

Conclusion: Gefitinib plus pemetrexed/platinum exhibits favorable efficacy with low occurrence of severe adverse events in advanced lung adenocarcinoma patients with EGFR mutation, suggesting it could be a potential option for these patients.

Keywords: advanced lung adenocarcinoma, efficacy, gefitinib, pemetrexed/platinum, safety

Introduction

Lung adenocarcinoma is the most prevalent pathological type of lung cancer, which mostly originates from bronchial mucosal epithelium, and only a small proportion originates from large bronchial mucinous gland.[1,2] Over the decades, the onset age of lung adenocarcinoma has been relatively young compared to other types of lung cancer.[1] Moreover, lung adenocarcinoma is often diagnosed at advanced stage accompanied by tumor metastasis; thereby, systemic chemotherapy and molecular targeted therapy are widely adopted in lung adenocarcinoma patients.[3,4]

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Epithelial growth factor receptor (EGFR) mutation is recognized as a crucial driver of lung adenocarcinoma.[5] Currently, EGFR tyrosine kinase inhibitors (TKIs) are the first-line treatment for advanced lung adenocarcinoma with EGFR mutation.[6] Gefitinib, a classic representative of EGFR-TKI, could effectively induce tumor apoptosis and inhibit tumor angiogenesis.[7,8] However, gefitinib monotherapy often faces the problem of drug resistance and early progression, consequently affecting the prognosis of advanced lung adenocarcinoma patients with EGFR mutation.[9]

Apart from gefitinib, pemetrexed plus platinum chemotherapy has also illustrated favorable efficacy and tolerable toxicity in EGFR-mutated non-small-cell lung cancer.[10] Notably, two recent clinical trials have found that gefitinib plus pemetrexed/platinum chemotherapy can further improve the survival benefit in advanced lung adenocarcinoma patients with EGFR mutation.[6,7] However, the data about gefitinib plus pemetrexed/platinum regimen vs gefitinib alone in advanced lung adenocarcinoma patients with EGFR mutation under real-clinical settings are limited, not to mention in Chinese patients.

Therefore, the purpose of this study was to observe the efficacy, safety and prognostic factors of gefitinib plus pemetrexed/platinum regimen in advanced lung adenocarcinoma patients with EGFR mutation under a real-world setting.

Materials and Methods

Patients

A total of 51 advanced lung adenocarcinoma patients with EGFR mutation treated with gefitinib plus pemetrexed/platinum in our hospital between June 2015 and April 2020 were consecutively enrolled in this study. The inclusion criteria were: 1) pathologically confirmed lung adenocarcinoma; 2) advanced stage, which was defined as TNM stage IIIB to IVB; 3) age ≥ 18 years; 4) confirmed EGFR mutation. The exclusion criteria were: 1) allergy to the study drugs; 2) unsuitable for chemotherapy due to concomitant liver or kidney diseases; 3) complicated with other pulmonary diseases; 4) presented with systemic infections; 5) had mental illness and was unable to communicate well; 6) had other primary malignancies; 7) pregnancy. The eligible 51 patients were termed as GPP (gefitinib plus pemetrexed/platinum) group. This study was implemented with approval from the Institutional Review Board of The Second Affiliated Hospital of Anhui Medical University, and written informed consent was acquired from patients. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Council for Harmonisation.

Treatment

The regimen of gefitinib plus pemetrexed/platinum was administered to patients in the GPP group as follows: gefitinib 250 mg orally once a day, combined with pemetrexed 500 mg/m^2 intravenously over 10 min on day 1 and platinum dosed at area under the curve of 5 (calculated by the Calvert formula) intravenously over 30 min on day 1, repeated every 3 weeks (a treatment cycle), and lasted for at least 4 cycles. On the day before chemotherapy, all patients underwent liver and kidney function, blood routine, urine routine, electrocardiogram and other examinations to evaluate their physical conditions. During chemotherapy, appropriate protective and supportive treatments were also administered to patients, including antiallergy, antiemetic, and acid suppression to protect the stomach. Routine re-examinations covering liver and kidney function, blood routine and urine were performed in the patients weekly. The necessary biochemical markers were monitored before each cycle of chemotherapy.

Outcome Assessment

Radiographic examinations were conducted to monitor disease progression and the visceral metastasis status of patients every 2 months in the first year, then every 3 months during the subsequent follow-up period. Progression-free survival (PFS) and overall survival (OS) were documented to evaluate the efficacy of the treatment regimen on survival of patients, with a final follow-up date of December 31, 2020. Meanwhile, the adverse events during treatment were recorded and graded 1 to 4 according to the World Health Organization (WHO) classification criteria.

Control Cohort

This study also retrospectively collected data of 30 advanced lung adenocarcinoma patients with EGFR mutation who only received gefitinib (250 mg orally once a day) treatment. The screening criteria for these 30 patients were consistent with GPP group, and they served as control group in the analysis. The clinical data and follow-up data of these 30 patients were collected from medical records, and the PFS and OS were calculated

as well. Since the data of these 30 patients were retrospectively collected from their medical records, there were no detailed records about adverse events. As a result, the adverse event data of control group were not analyzed in the study.

Statistical Analysis

Characteristics of patients were described using mean with standard deviation (SD), median with 95% confidence interval, frequency and percentage. Comparison between two groups was determined by independent sample *t*-test, Chi-squared test or Wilcoxon rank sum test. PFS and OS were displayed using Kaplan-Meier curves and analyzed by Log rank test, meanwhile, the cumulative 1-year and 3-year survival rates were estimated by Kaplan-Meier method. Prognostic factors were analyzed by univariate and multivariate Cox proportional hazard regression model analyses with forward stepwise method (conditional (Likelihood Ratio)). In Cox proportional hazard regression model analyses, higher ECOG PS score meant that the ECOG PS score was included as an ordinal categorical variable (encoded as 0, 1, and 2), and higher TNM stage meant that the TNM stage was included in the Cox regression analysis as an ordinal categorical variable (encoded as stage III =0, stage IVA=1, and stage IVB=2). SPSS 22.0 software (IBM Corp., Armonk, New York, USA) was applied for statistical analysis, and GraphPad Prism 7.02 software (GraphPad Software Inc., San Diego, California, USA) was used for figure making. A *P* value less than 0.05 indicated statistical significance.

Results

Study Flow

In the current study, 71 advanced lung adenocarcinoma patients with EGFR mutation were invited, 13 patients refused to participate in the study, consequently, 58 patients were screened for eligibility. Among them, 7 patients were excluded (3 patients were unsuitable for chemotherapy due to concomitant liver or kidney diseases, 1 patient had allergy to the study drugs, 1 patient was complicated with other pulmonary disease, 1 patient presented with systemic infections and 1 patient had other primary malignancies); afterwards, 51 patients were analyzed in the GPP group.

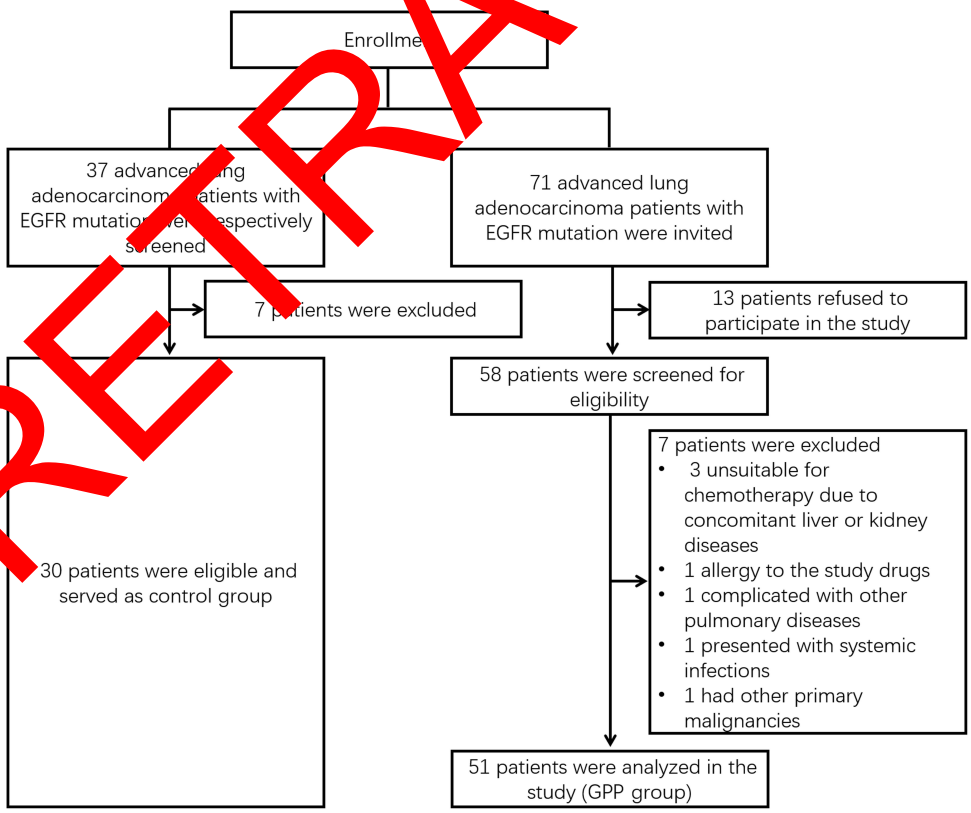


Figure 1 Study flow.
Abbreviations: EGFR, epithelial growth factor receptor; GPP, gefitinib plus pemetrexed/platinum.

In addition, in order to better clarify the efficacy of GPP, another cohort of 30 advanced lung adenocarcinoma patients with EGFR mutation who only received gefitinib were retrospectively enrolled as control group (Figure 1).

Clinical Characteristics

There were 51 patients in GPP group and 30 patients in control group in the present study. In GPP group, the mean age was 56.6±10.0 years; meanwhile, there were 29 (56.9%) males and 22 (43.1%) females. In the control group, the mean age was 58.3±8.0 years; besides, there were 22 (73.3%) males and 8 (26.7%) females. Furthermore, no difference was found in age, gender, history of smoking, family history of cancer, ECOG PS score, T stage, N stage, M stage, site of tumor metastasis or site of EGFR mutation between the two groups (all $P>0.05$) (Table 1).

Cumulative PFS and OS

In GPP group, 1-year PFS rate and 3-year PFS rate was 78.4% and 19.6%, respectively; meanwhile, median PFS (95% confidence interval (CI)) was 23.0 (17.6–28.4) months. In control group, 1-year PFS rate and 3-year PFS rate was 60.0% and 5.3%, respectively; besides, median PFS (95% CI) was 14.0 (11.3–16.7) months. Moreover, PFS was prolonged in GPP group compared to control group ($P=0.013$), (Figure 2A).

In GPP group, 1-year OS rate and 3-year OS rate was 94.1% and 56.9%, respectively; besides, median OS (95% CI) was 42.0 (33.3–50.7) months. In control group, 1-year OS rate and 3-year OS rate was 86.7% and 32.7%, respectively; meanwhile, median OS (95% CI) was 28.0 (20.0–36.0) months. Additionally, OS was also longer in GPP group compared to control group ($P=0.023$), (Figure 2B).

Furthermore, patients in GPP group received either another TKI plus chemotherapy or another TKI plus bevacizumab and chemotherapy after disease progression, while no difference in OS was found between them ($P=0.249$) (Supplementary Figure 1).

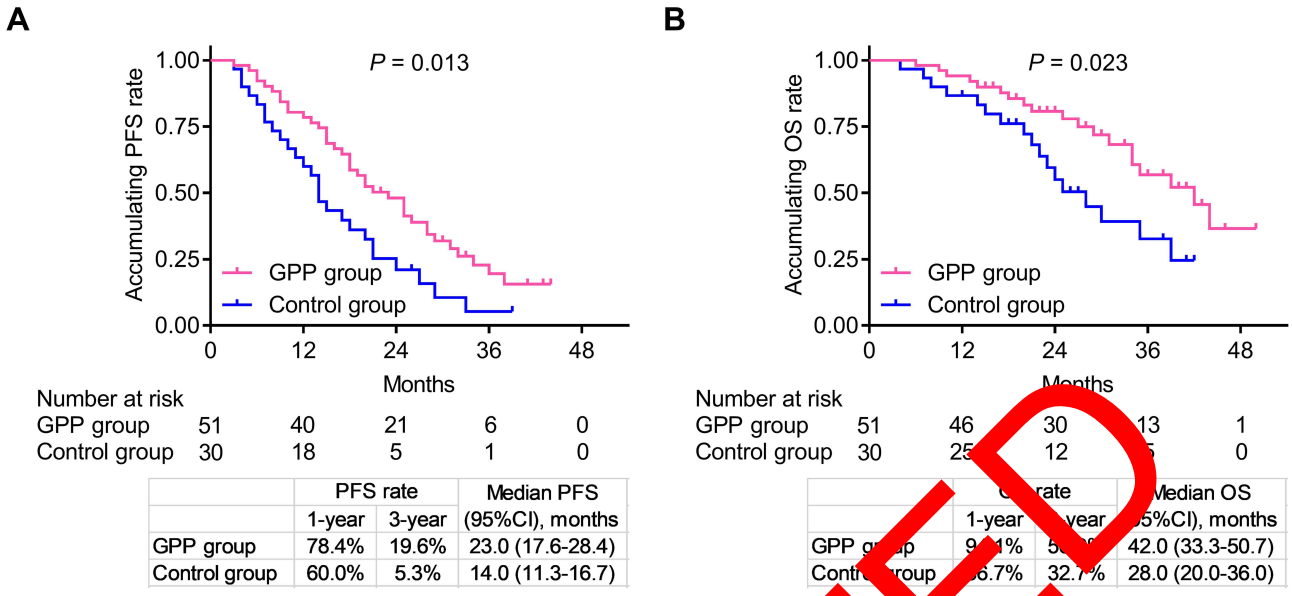
Univariate and Multivariate Cox Regression Model Analysis for PFS

Univariate Cox regression analysis illustrated that GPP group vs control group ($P=0.016$, hazard ratio (HR) (95% CI): 0.537 (0.324–0.891)) was correlated with better

Table 1 Clinical Characteristics of Patients with EGFR-Mutated Advanced Lung Adenocarcinoma

Items	GPP Group (N = 51)	Control Group (N = 30)	*P* value
Age (years), mean ±SD	56.6±10.0	58.3±8.0	0.449
Gender, No. (%)			0.138
Male	29 (56.9)	22 (73.3)	
Female	22 (43.1)	8 (26.7)	
History of smoking, No. (%)	21 (41.2)		0.177
Family history of cancer, No. (%)	7 (13.7)	5 (16.7)	0.971
ECOG PS score, No. (%)			0.739
0	5 (9.8)	2 (6.7)	
1	41 (80.4)	25 (83.3)	
2	5 (9.8)	3 (10.0)	
T stage, No. (%)			0.499
T1	3 (10.0)	4 (7.8)	
T2	10 (33.3)	11 (21.6)	
T3	5 (16.7)	15 (29.4)	
T4	12 (40.0)	21 (41.2)	
N stage, No. (%)			0.955
N0	6 (20.0)	8 (15.7)	
N1	4 (13.3)	8 (15.7)	
N2	11 (36.7)	21 (41.2)	
N3	9 (30.0)	14 (27.5)	
M stage, No. (%)			0.485
M0	4 (13.3)	5 (9.8)	
M1	6 (20.0)	14 (27.5)	
M2	9 (30.0)	6 (11.8)	
M3	11 (36.7)	26 (51.0)	
Site of tumor metastasis, No. (%)			
Bone	20 (39.2)	10 (33.3)	0.597
Brain	9 (17.6)	7 (23.3)	0.535
Liver	7 (13.7)	3 (10.0)	0.887
Others	37 (72.5)	18 (60.0)	0.243
Site of EGFR mutation, No. (%)			0.742
Exon 19 deletion	28 (54.9)	14 (46.7)	
L858R	21 (41.2)	15 (50.0)	
Others	2 (3.9)	1 (3.3)	

Abbreviations: EGFR, epithelial growth factor receptor; GPP, gefitinib plus pemetrexed/platinum; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; PS, performance status.



	PFS rate		Median PFS
	1-year	3-year	(95%CI), months
GPP group	78.4%	19.6%	23.0 (17.6-28.4)
Control group	60.0%	5.3%	14.0 (11.3-16.7)

	rate		Median OS
	1-year	year	5%CI), months
GPP group	9 1%	5 %	42.0 (33.3-50.7)
Contr roup	6.7%	32.7%	28.0 (20.0-36.0)

Figure 2 Cumulative PFS and OS. Comparison of cumulative PFS rate (**A**) and OS rate (**B**) between G group and co l grou
Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; EGFR pi ial growth fact eptor; GPP, gefitinib plus pemetrexed/platinum.

PFS, while higher ECOG PS score (*P*=0.019, HR (95% CI): 1.907 (1.113–3.266)), higher T stage (*P*=0.031, HR (95% CI): 1.332 (1.026–1.729)), higher M stage (*P*= HR (95% CI): 1.480 (1.156–1.894)) and brain meta asis (yes vs no) (*P*<0.001, HR (95% CI): 3.905 (948–7.4 were all correlated with poor PFS. Furth more, multiva iant Cox regression analysis showed at GP up vs control group (*P*=0.004, HR (9 % CI .450 (0.260–0.779)) was independently related wi satisfying PFS, while higher ECOG S sco (*P*=0.014, HR (95% CI): 1.942 (1.145–3.29)), higher T ge (*P*=0.011, HR (95% CI): 1.434 (1 84–1.89)) and brain metastasis (yes vs no) (*P*<0.001, H (95% CI): 3.539 (1.835–6.829)) were all indepen ly co elated with unfavorable PFS (Figure 2

Univariate and Multivariate Cox Regression Model Analysis for OS

Univariate Cox regression analysis illustrated that GPP group vs control group (*P*=0.027, HR (95% CI): 0.469 (0.240–0.917)) was correlated with longer OS, while higher ECOG PS score (*P*=0.015, HR (95% CI): 2.540 (1.198–5.386)), higher T stage (*P*=0.017, HR (95% CI): 1.583 (1.087–2.305)), higher M stage (*P*= 0.001, HR (95% CI): 1.800 (1.260–2.570)) and brain metastasis (yes vs no) (*P*<0.001, HR (95% CI): 5.679 (2.363–3.648)) were all correlated with worse OS. In addition, multivariant Cox regression analysis showed that GPP group control group (*P*=0.031, HR (95% CI): 0.462 (.229–0.932)) was independently correlated with favorable OS, while higher M stage (*P*=0.009, HR (95% CI): 1.683 (1.138–2.490)) and brain metastasis (yes vs no) (*P*=0.037, HR (95% CI): 2.732 (1.063–7.018)) were both independently associated with unfavorable OS (Figure 4).

Adverse Events

The main adverse events were myelosuppression (34 (66.7%)), digestive toxicity (32 (62.7%)), renal toxicity (16 (31.4%)) and hepatotoxicity (12 (23.5%)). Among them, the majority were grade 1 and grade 2; furthermore, grade 3 adverse events were myelosuppression (9 (17.6%)) and digestive toxicity (11 (21.6%)); meanwhile, grade 4 adverse events only included myelosuppression (4 (7.8%)), (Table 2).

Discussion

In our real-world analysis, we found that 1) PFS and OS were prolonged in GPP group compared to control group; 2) GPP group vs control group was an independent predictive factor of better prognosis, while higher ECOG PS score, higher T stage, higher M stage brain metastasis (yes vs no) were independent predictive factors of poor prognosis; 3) the most common adverse events among patients

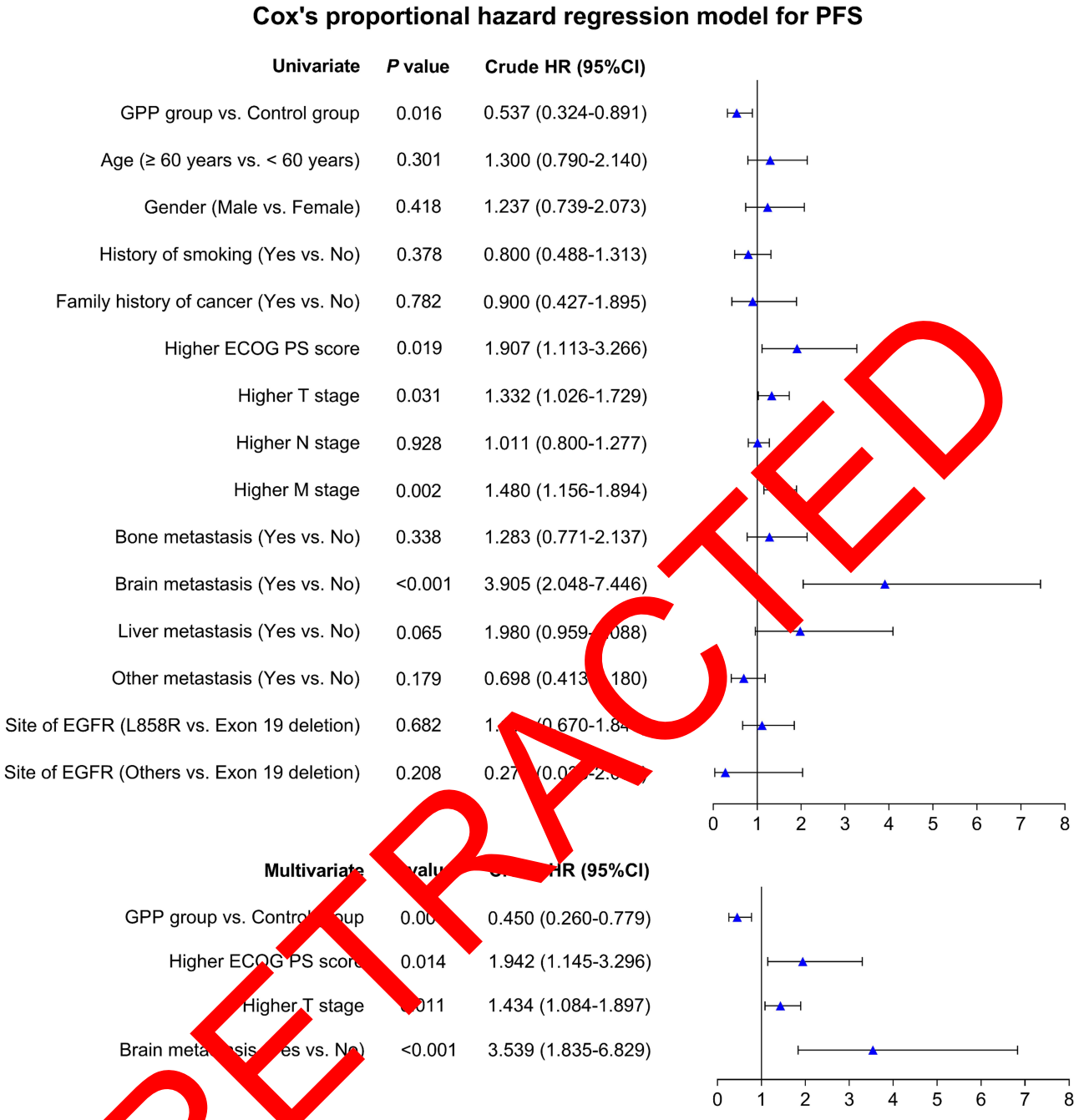
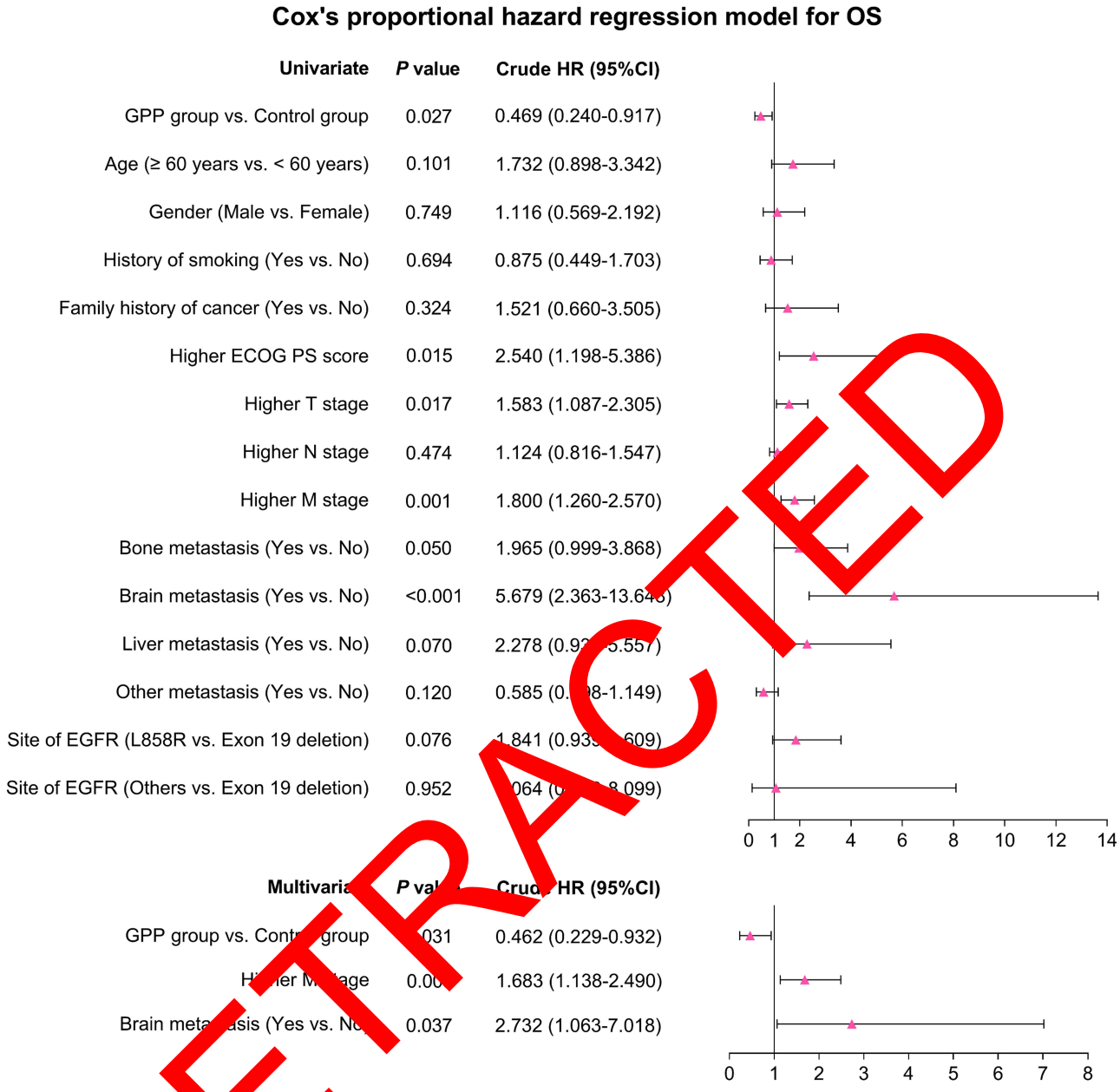


Figure 3 Relate ctors f iate and multiple Cox proportional hazard regression were conducted to explore risk factors for PFS with *P* value and crude HR (95% CI).

Abbreviations: ECO astern Cooperative Oncology Group; PS, performance status; EGFR, epithelial growth factor receptor; TNM, tumor node metastasis; HR, hazard ratio; CI, confidence inte PFS, progression-free survival; GPP, gefitinib plus pemetrexed/platinum.

in GPP group were myelosuppression, digestive toxicity, renal toxicity and hepatotoxicity; meanwhile, the majority of them were tolerable and manageable.

As to the efficacy of gefitinib vs gefitinib plus pemetrexed/platinum in advanced lung adenocarcinoma patients with EGFR mutation, a previous study illustrated that PFS and OS were prolonged in the gefitinib plus pemetrexed/platinum group compared to gefitinib alone group.[6,11,12] In the present real-world observational study, PFS and OS were also prolonged in GPP group compared to control group in advanced lung adenocarcinoma patients with EGFR mutation, which was consistent with previous studies.[6,11,12] The possible explanation might be that patients might develop drug resistance to EGFR-TKIs;



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besides, GPP
gimen might decrease resistance, consequently enhancing survival.[6] Hence, the survival of patients treated with GPP regimen was longer than those treated with gefitinib alone. Furthermore, the median PFS of the current study was relatively longer, but not OS, compared to previous gefitinib plus pemetrexed/platinum combination treatment trials,[6,11] which could be explained by: 1) the treatment cycle was different between the present study and previous trials, which might have led to different prognosis; 2) the real-world setting might have caused difference in survival data compared to previous trials; 3) the relatively small sample size of the study would enlarge the error value. In addition, these data underlined the potential of gefitinib plus pemetrexed/platinum as an effective therapeutic option in advanced lung adenocarcinoma patients with EGFR mutation.

Regarding prognostic factors in advanced lung adenocarcinoma patients with EGFR mutation after gefitinib

Table 2 Adverse Events in GPP Group

Adverse Events	Total	Grade 1	Grade 2	Grade 3	Grade 4
Myelosuppression, No. (%)	34 (66.7)	7 (13.7)	14 (27.5)	9 (17.6)	4 (7.8)
Digestive toxicity, No. (%)	32 (62.7)	8 (15.7)	13 (25.5)	11 (21.6)	0 (0.0)
Renal toxicity, No. (%)	16 (31.4)	15 (29.4)	1 (2.0)	0 (0.0)	0 (0.0)
Hepatotoxicity, No. (%)	12 (23.5)	8 (15.7)	4 (7.8)	0 (0.0)	0 (0.0)
Neurotoxicity, No. (%)	3 (5.9)	3 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Baldness, No. (%)	2 (4.0)	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)
Cardiotoxicity, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

monotherapy, a single-center study presented that smoking status and maintenance regimens were independently correlated with PFS.[13] However, the information of the prognostic factors of gefitinib plus chemotherapy regimen in treating these patients is limited. Therefore, in order to explore prognostic factors in EGFR-mutant advanced lung adenocarcinoma after gefitinib plus pemetrexed/platinum therapy, we conducted Cox proportional hazard regression model for PFS and OS. Interestingly, we discovered that GPP group vs control group was independently associated with better PFS and OS, while higher ECOG PS score, higher T stage and brain metastasis were independently associated with poor PFS; and higher M stage as well as brain metastasis were independently correlated with unfavorable OS.

In terms of safety of gefitinib monotherapy in advanced lung adenocarcinoma patients with EGFR mutation, it has been illustrated that the most common adverse events are skin rash, diarrhea, general malaise, nausea, vomiting and infection, among which, the grade 3–4 adverse events included skin rash, diarrhea, and general malaise.[14] As for safety of pemetrexed/platinum treatment, a previous clinical trial showed that leukopenia, neutropenia, anemia, fatigue and thrombocytopenia were common adverse events; meanwhile, the grade ≥3 toxicities included neutropenia, thrombocytopenia and anemia.[5] Regarding the safety of gefitinib plus pemetrexed/platinum combinational therapy, a study presented that neutropenia, anemia and thrombocytopenia were the main therapy-related adverse events;[6] another trial also showed that neutropenia, fatigue and liver dysfunction often occur.[7] In our study, we found that the main adverse events among patients in GPP group were myelosuppression, digestive toxicity, renal toxicity, hepatotoxicity and neurotoxicity, which were relatively tolerable and manageable. In addition, our findings were similar to previous studies.[6,7,14,15]

There are several limitations in our study. 1) death events were a little low due to relatively short follow-up duration; hence, the OS data might need long-term follow-up period for validation; 2) the sample size of the present study was not big enough; therefore, larger sample size of enrolled patients is suggested in the future; 3) we did not assess quality of life in patients after gefitinib plus pemetrexed/platinum treatment, which should be further explored in the future study.

In conclusion, gefitinib plus pemetrexed/platinum exhibits favorable efficacy with low occurrence of severe adverse events in advanced lung adenocarcinoma patients with EGFR mutation, suggesting it is a potential option for these patients.

Disclosure

The authors have no conflicts of interest to declare.

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