Original Article

Correlation of *EGFR G873R* mutation with prognosis of docetaxel in non-small cell lung cancer

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Background: Clinical features of epidermal growth factor receptor (*EGFR*) mutations have been commonly recognized in variant cancers. The role of *EGFR* mutations in non-small cell lung cancer (NSCLC) has spurred research and drug development efforts. However, there are still mutations that have not been widely reported, and their influences on NSCLC have not been fully elucidated; *EGFR G873R* mutation is just one of them. The aim of this study was to investigate the correlation between *EGFR G873R* mutation and the prognosis of chemotherapy in NSCLC.

Methods: A total of 54 patients with NSCLC were enrolled in this study. Immunohistochemical staining was used to detect the expression of *EGFR*. A DNA extraction kit (GeneRead DNA FFPE Kit) was used to extract total DNA from resected cancer tissues. Genomic DNA targets were amplified by polymerase chain reaction (PCR), and then the amplicons were purified and sequenced. Statistical methods were performed to detect the relationship between *EGFR G873R* mutation and various clinicopathological features and the effect of *EGFR G873R* mutation on the prognosis of chemotherapy.

Results: *EGFR G873R* mutation did not show statistical significance, with *EGFR* high expression identified in 30 cases (P>0.05). Patients with *EGFR G873R* mutation had a significantly favorable prognosis of docetaxel (P=0.032), and for patients treated with docetaxel, *EGFR G873R* mutation was significantly correlated with better 5-year disease-free survival (DFS; P=0.026) and overall survival (OS; P=0.026). However, there was no statistical significance found between *EGFR G873R* mutation and the prognosis of vinorelbine (P>0.05), and for patients treated with vinorelbine, *EGFR G873R* mutation had no statistical significance with 5-year DFS (P>0.05) and OS (P>0.05).

Conclusions: *EGFR G873R* mutation was remarkably correlated with the prognosis of docetaxel in NSCLC, which indicates that *EGFR G873R* may be employed as a promising biomarker to identify individuals with better prognosis of docetaxel and as an antitumor target for NSCLC treatment.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor G873R mutation (*EGFR G873R* mutation); docetaxel; prognosis

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Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide, and non-small cell lung cancer (NSCLC) is the most common malignancy (1), accounting for more than 80% of lung cancer cases (2-4). Chemotherapy plays an important role in the management of NSCLC patients, particularly those at advanced stages, and docetaxel is one of the most important first- or second-line chemotherapeutic agents for NSCLC patients (5-7). However, the response to chemotherapy is variable, and biomarkers that predict its sensitivity are urgently required.

Mutations of epidermal growth factor receptor (*EGFR*), which occur more frequently in NSCLC of women, non-smokers, and those with adenocarcinoma cell type (8-10), have been shown to have favorable clinical efficacy in advanced NSCLC. Mutations including deletions in *exon 19*, *L858R*, and *T790M*, and insertions in *exon 20*, have been well reported in literature and widely recognized in the clinical setting (11). However, there are still other *EGFR* mutations, such as *EGFR G873R* mutation, which was initially identified in 10% of samples by implementing the multiplex polymerase chain reaction (PCR)-based Ion AmpliSeq Cancer Hotspot Panel (12). To the best of our knowledge, *EGFR G873R* mutation has not been widely reported, and its clinical influences on NSCLC have not been elucidated.

In the present study, we investigated the correlation between *EGFR G873R* mutation and prognosis of chemotherapy in NSCLC to increase understanding of the entire *EGFR* mutation spectrum. We employed immunohistochemical method to examine *EGFR* expression in clinical NSCLC patients, and analyzed relationships between *EGFR G873R* mutation and clinicopathological factors and patients' prognoses. Moreover, we assessed independent prognostic factors that may affect patients' 5-year disease-free survival (DFS) and overall survival (OS). We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-1505).

Methods

Ethics statement

This study was approved by the Ethics Committee of the Second Hospital of Shandong University and informed consent was taken from all the patients. Tissue specimen acquisition was carried out in accordance with institutional guidelines. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Patients

This multicenter study was performed on 54 patients who were diagnosed with NSCLC and treated with pulmonary lobectomy plus regional lymph node dissection between February 2010 and June 2012 at the Department of Thoracic Surgery in 3 hospitals (2 university hospitals and 1 provincial hospital). Samples were obtained from these patients immediately after resection.

The patients did not receive preoperative radiotherapy or chemotherapy, did not have had distant metastases or basic diseases that may affect survival, and accepted only mono-chemotherapy after the surgery. Complete data on patients' follow up and clinicopathological features were obtained. Clinicopathological characteristics and demographic data of all patients are summarized in *Table 1*.

For all patients, histological type and differentiation of cancer cells were evaluated and determined based on the classification system of the World Health Organization (modified in 2015), and postsurgical staging was determined according to the eighth edition of TNM classification system of the National Comprehensive Cancer Network (NCCN).

Follow up

After surgery, patients were required to undergo re-examination routinely every 3–6 months in the first 5 years and then annually thereafter. Necessary examinations, such as chest X-ray, computed tomography, and transabdominal ultrasound, were performed during the follow-up evaluation. Magnetic resonance imaging and other specific procedures were performed if necessary. Recurrence and metastasis were identified by imaging evidence or pathological examinations, and recorded in detail at the first time they were detected.

Immunohistochemistry

All specimens were collected during the surgery and were formalin fixed and paraffin embedded (FFPE). The tissues were then cut to 4 μm's thick, deparaffinized by using xylene, and rehydrated through an ethanol series to water. High-temperature antigen retrieval was carried

Table 1 Clinicopathological characteristics of patients

Characteristics	Number of patients	Percentage
Sex		
Male	37	68.5
Female	17	31.5
Age (years)		
<60	30	55.6
≥60	24	44.4
Histological type		
Adeno-	27	50.0
Squamous-	27	50.0
Differentiation		
Good, moderate	36	66.7
Poor	18	33.3
TNM stage		
IIB	22	40.7
IIIA	32	59.3
Chemotherapy regimen		
Docetaxel	34	63.0
Vinorelbine	20	37.0
EGFR G873R mutation		
Yes	17	31.5
No	37	68.5
Prognosis		
Good	27	50.0
Poor	27	50.0

EGFR, epidermal growth factor receptor.

out in citrate buffer for 30 min in a microwave oven, then 3% hydrogen peroxide was used to block the endogenous peroxidase enzyme activity in methanol for 30 min at room temperature. The slides were then washed with phosphate-buffered saline (PBS) 3 times and incubated with primary rabbit anti-*EGFR* polyclonal antibody (Abcam, Cambridge, MA, USA) overnight at 4 ℃ in a high-humidity fridge. The following day, sections were washed with PBS 3 times and then incubated for 30 min at 37 ℃ with biotinylated secondary antibodies and streptavidin-peroxidase complex. Finally, a 3,3'-diaminobenzidine solution was added, and the slides were counterstained with hematoxylin and mounted with neutral balsam.

Immunohistochemical analysis

Staining intensity and percentage of positively stained tumor cells were invited to score the stained slides, and a semi-quantitative method that combines them was used. Staining intensity was rated from 0 to 3, and graded as 0 (negative staining), 1 (weak staining), 2 (moderate staining), and 3 (strong staining). The percentage of positively stained cells was classified as 0 (0–5%), 1 (6–25%), 2 (26–50%), 3 (51–75%), and 4 (≥76%). The sum of these two scores was the final grade, classified as: (–), 0–1; (+), 2–3; (++), 4–5; and (+++), 6–7. *EGFR* was defined as high expression if the final score was >4.

DNA purification and quantification

All FFPE specimens were cut to 10 μm's thick, then a DNA extraction kit (GeneReadDNA FFPE Kit; Qiagen) was used for DNA extraction according to the manufacturer's instructions. Qubit dsDNA HS Assay Kit (Life Technologies, Carlsbad, CA, USA) and a Qubit 3.0 Fluorometer were used to quantify DNA, followed by the recommended protocol.

Library preparation

The template that contained 10 ng of DNA was used to generate an amplicon library for sequencing. Ion AmpliSeq Library Kits 2.0 and Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies) were used to prepare the libraries. Genomic DNA targets were amplified by PCR, and primer sequences were then partially digested. DNA ligase was used to ligate adapters to amplicons. Agencourt AMPure XP Reagent (Beckman Coulter) was used to purify the unamplified library; quantitative PCR (qPCR) with the Ion Library Quantitation Kit was used to dilute the concentration of each Ion AmpliSeq library to 100 pM. And each diluted library (100 pM) was amplified through emulsion PCR by OneTouch Instrument (Life Technologies) according to the manufacturer's instructions.

DNA sequencing and data processing

The Ion OneTouch Template Kit and the Ion OneTouch System (Life Technologies) were used to perform emulsion PCR and enrichment steps according to the manufacturer's

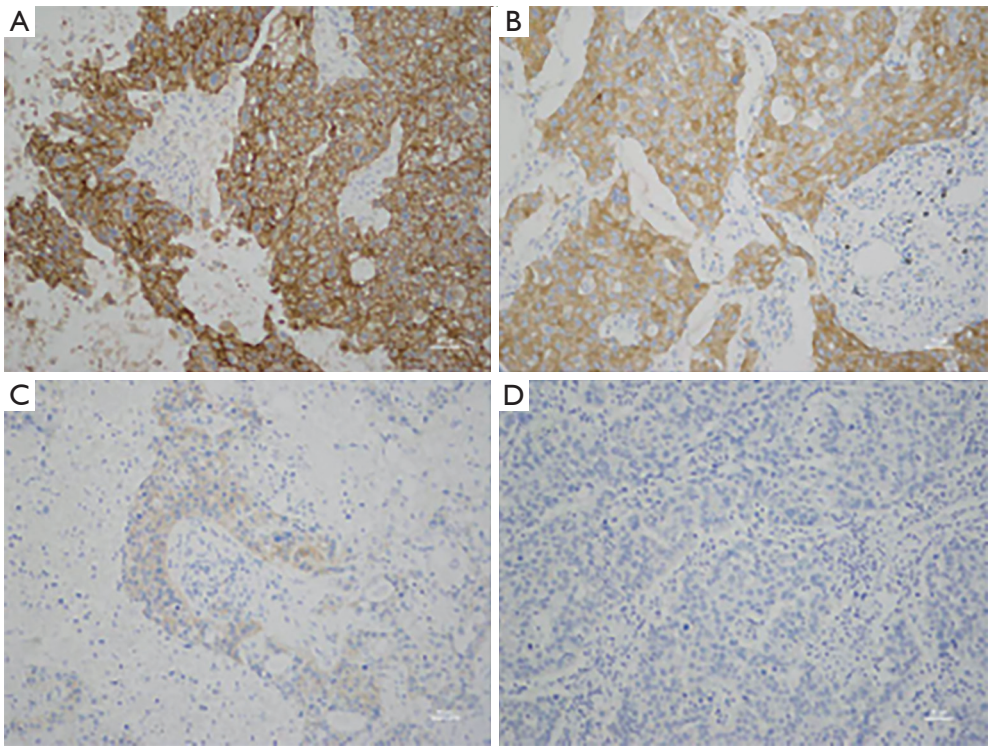

Figure 1 Expression pattern of *EGFR* in NSCLC tissues (A-D) as detected by immunohistochemical staining, which was graded as (+++), (++), (+), and (–) respectively (magnification ×200). *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

instructions. The 318 Chips (Life Technologies), Ion Xpress Barcode Adapters 1-16 Kit (Life Technologies), and Ion PGM System (Life Technologies) were then used to carry out the sequencing of amplicon libraries. After the sequencing was completed, the Torrent Mapping Alignment Program was used to map the readings of the reference genome (hg19). Sequencing success was determined by meeting a cut-off of 300,000 AQ20 readings on the 318V2 Chip. Torrent Variant Caller (3.6.6; Life Technologies) was then used to identify the variants. Minimum requirement of sequencing coverage is 500× to verify the credibility of variants.

Statistical methods

All statistical analyses were performed by using SPSS 24.0 (IBM, Armonk, NY, USA) for Windows; χ^2-test and Fisher's exact test were used to test the correlation between *EGFR G873R* mutation and *EGFR* expression, and associations between *EGFR G873R* mutation and clinicopathological factors. Kaplan-Meier method was used to analyze DFS and OS. Log-rank test was used to identify differences between patient subgroups, and factors that may independently affect patients' outcomes were tested with a multivariate Cox regression model. P<0.05 was considered statistically significant.

Results

EGFR G873R mutation and EGFR expression

EGFR expression of all 54 specimens was detected by immunohistochemical staining. Based on the score method described earlier, 30 (55.6%) of the 54 tumor specimens had high *EGFR* expression (*Figure 1A*,*1B*), while the other 24 (44.4%) had low *EGFR* expression (*Figure 1C*,*1D*). The χ^2-test was then used to detect the correlation between *EGFR* expression and *EGFR G873R* mutation. *EGFR* expression did not show statistical significance with *EGFR G873R* mutation (P>0.05) (*Table 2*).

EGFR G873R mutation and baseline characteristics

Relationships between *EGFR G873R* mutation and

Table 2 Correlation of *EGFR* expression of NSCLC patients with *EGFR G873R* mutation

EGFR expression	*EGFR G873R* mutation		P value
	No	Yes	
High	23	7	0.149
Low	14	10	

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Table 3 Correlation of clinicopathological characteristics of NSCLC patients with *EGFR G873R* mutation

Characteristics	EGFR G873R mutation		P value
	No	Yes	
Sex			0.394
Male	24	13	
Female	13	4	
Age (years)			0.149
<60	23	7	
≥60	14	10	
Histological type			0.379
Adeno-	17	10	
Squamous-	20	7	
Differentiation			0.679
Good, moderate	24	12	
Poor	13	5	
TNM stage			0.965
IIB	15	7	
IIIA	22	10	
Prognosis of vinorelbine			0.417
Good	6	1	
Poor	9	4	
Prognosis of docetaxel			0.032
Good	10	10	
Poor	12	2	

NSCLC, non-small cell lung cancer; *EGFR*, epidermal growth factor receptor.

clinicopathological factors were detected by χ^2-test; our data showed that *EGFR G873R* mutation was significantly correlated with the prognosis of docetaxel (P=0.032) (*Table 3*). However, no other clinicopathological variables that have statistical significance with *EGFR G873R* mutation were found, including the prognosis of vinorelbine (P>0.05) (*Table 3*).

EGFR G873R mutation and prognosis

During the follow-up period, 27 (50%) of the 54 patients had tumor relapse, and all 27 of these patients died due to cancer-related causes within 5 years after operation.

Kaplan-Meier analysis showed that, in patients treated with docetaxel, *EGFR G873R* mutation was significantly correlated with better 5-year DFS (P=0.026) and OS (P=0.026) (*Figure 2A,2B*). In patients with *EGFR G873R* mutation, the prognostic difference between docetaxel (P=0.001) and vinorelbine (P=0.001) was statistically significant (*Figure 2C,2D*). However, there was no statistical significance between *EGFR G873R* mutation (P>0.05) and the prognosis of vinorelbine (P>0.05) (*Figure 2E,2F*), and between patients without *EGFR G873R* mutation (P>0.05) and the prognostic difference between docetaxel and vinorelbine (P>0.05) (*Figure 2G,2H*).

Univariate analysis demonstrated that *EGFR G873R* mutation in patients treated with docetaxel significantly predicted increased 5-year DFS (P=0.032) and OS (P=0.032) (*Tables 4,5*). For patients treated with vinorelbine, *EGFR G873R* mutation had no statistical significance with DFS (P>0.05) and OS (P>0.05) (*Tables 6,7*).

Moreover, the results of the multivariate Cox regression analysis showed that *EGFR G873R* mutation retained its significance as an independent prognostic factor for favorable 5-year DFS (P=0.020) and OS (P=0.022) in patients treated with docetaxel (*Tables 4,5*).

Discussion

Though has been concentrated for decades, NSCLC is still one of the most common cause of cancer-related mortality worldwide. Given that more than 60% of NSCLC express *EGFR*, *EGFR* has become an important therapeutic target

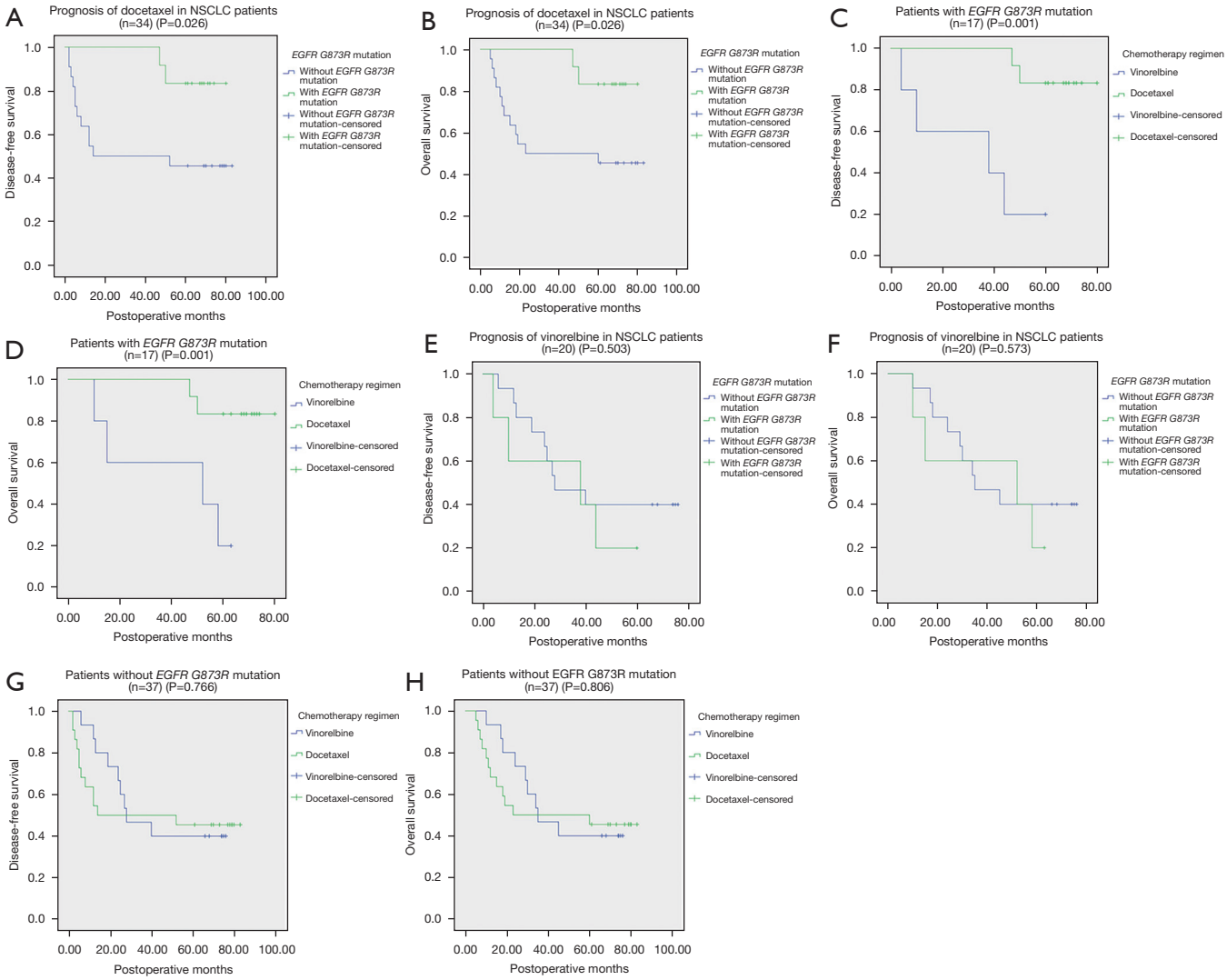

Figure 2 Kaplan-Meier survival curves of NSCLC patients. (A) DFS curves stratified by docetaxel; (B) OS curves stratified by docetaxel; (C) DFS curves stratified by *EGFR G873R* mutation; (D) OS curves stratified by *EGFR G873R* mutation; (E) DFS curves stratified by vinorelbine; (F) OS curves stratified by vinorelbine;(G) DFS curves stratified by *EGFR G873R* mutation; (H) OS curves stratified by *EGFR G873R* mutation. NSCLC, non-small cell lung cancer; DFS, disease-free survival; OS, overall survival; *EGFR*, epidermal growth factor receptor.

for the treatment of NSCLC (13). *EGFR* mutations have been widely studied, and have found to be associated with the better prognosis of lung cancer. *EGFR exon 19* deletion, for example, has been found to be associated with favorable DFS and OS in patients receiving first-line gefitinib treatment. Patients with *EGFR exon 19* deletion who receive long-term *EGFR* tyrosine kinase inhibitor (TKI) therapy have been shown to have a high prevalence of *EGFR T790M* mutation, which leads to a significantly longer median total duration (14,15). Other mutations, such as *EGFR exon 20* insertion, have been reported to perform an unexpected prognosis in advanced NSCLC patients treated with luminespib (16). However, effect of drug therapies in NSCLC is still unsatisfied; therefore, evaluating novel biomarkers for NSCLC is important.

We reviewed PubMed and COSMIC (Catalogue Of Somatic Mutations In Cancer) to determine whether *EGFR G873R* mutation has been widely identified by others. We

Table 4 Univariate and multivariate analyses of DFS (docetaxel)

Variables	DFS univariate analysis	DFS multivariate analysis		
	P value	95% confidence interval	Exp (B)	P value
Sex (male *vs.* female)	0.142	0.164–2.065	0.582	0.402
Age, years (<60 *vs.* ≥60)	0.905	0.544–5.903	1.792	0.338
Histological type (adeno *vs.* squamous)	0.052	0.077–1.553	0.345	0.166
Differentiation (good and moderate *vs.* poor)	0.704	0.246–2.766	0.825	0.755
TNM stage (IIB *vs.* IIIA)	0.112	0.983–24.558	4.914	0.052
EGFR G873R mutation (yes *vs.* no)	0.032	0.032–0.748	0.156	0.020

DFS, disease-free survival; *EGFR*, epidermal growth factor receptor.

Table 5 Univariate and multivariate analyses of OS (docetaxel)

Variables	OS univariate analysis	OS multivariate analysis		
	P value	95% confidence interval	Exp (B)	P value
Sex (male *vs.* female)	0.142	0.128–1.576	0.450	0.212
Age, years (<60 *vs.* ≥60)	0.905	0.446–4.252	1.377	0.578
Histological type (adeno *vs.* squamous)	0.052	0.104–1.844	0.438	0.260
Differentiation (good and moderate *vs.* poor)	0.704	0.291–3.175	0.961	0.947
TNM stage (IIB *vs.* IIIA)	0.112	0.971–24.473	4.876	0.054
EGFR G873R mutation (yes *vs.* no)	0.032	0.035–0.767	0.164	0.022

OS, overall survival; EGFR, epidermal growth factor receptor.

Table 6 Univariate and multivariate analyses of DFS (vinorelbine)

Variables	DFS univariate analysis	DFS multivariate analysis		
	P value	95% confidence interval	Exp (B)	P value
Sex (male *vs.* female)	0.195	0.135–7.188	0.983	0.987
Age, years (<60 *vs.* ≥60)	0.895	0.191–6.157	1.085	0.927
Histological type (adeno *vs.* squamous)	0.142	0.551–117.587	8.046	0.128
Differentiation (good and moderate *vs.* poor)	0.171	0.189–7.718	1.208	0.842
TNM stage (IIB *vs.* IIIA)	0.094	0.374–12.517	2.165	0.388
EGFR G873R mutation (yes *vs.* no)	0.444	0.754–71.203	7.328	0.086

DFS, disease-free survival; *EGFR*, epidermal growth factor receptor.

found only one reference to mutation at *EGFR G873R*, which just reported an identification of *EGFR G873R* mutation and some other uncommon mutations in *EGFR*, *KRAS*, and *BRAF* in lung and colorectal adenocarcinomas (12). To the best of our knowledge, this is the first study to analyze the relationship between *EGFR G873R* mutation and the prognosis of chemotherapy in NSCLC.

In the present study, we discovered the *EGFR G873R* mutation in NSCLC tissues and found that the mutation was significantly correlated with the prognosis of docetaxel, whereas other clinicopathological factors, such as sex, age, histological type, differentiation, TNM

Table 7 Univariate and multivariate analyses of OS (vinorelbine)

Variables	OS univariate analysis	OS multivariate analysis		
	P value	95% confidence interval	Exp (B)	P value
Sex (male *vs.* female)	0.195	0.117–6.189	0.850	0.872
Age, years (<60 *vs.* ≥60)	0.895	0.188–5.449	1.012	0.989
Histological type (adeno *vs.* squamous)	0.142	0.593–91.379	7.360	0.120
Differentiation (good and moderate *vs.* poor)	0.171	0.185–7.788	1.201	0.848
TNM stage (IIB *vs.* IIIA)	0.094	0.434–13.421	2.412	0.315
EGFR G873R mutation (yes *vs.* no)	0.444	0.729–66.636	6.969	0.092

OS, overall survival; EGFR, epidermal growth factor receptor.

stage, and prognosis of vinorelbine, were not found to have statistical significance with *EGFR G873R* mutation. Our survival analysis demonstrated that *EGFR G873R* mutation significantly predicted increased 5-year DFS and OS in patients treated with docetaxel, and results of multivariate Cox regression analysis confirmed that *EGFR G873R* mutation was an independent prognostic factor for favorable 5-year DFS and OS in patients treated with docetaxel. In contrast, for patients treated with vinorelbine, *EGFR G873R* mutation did not predict better 5-year DFS and OS, and was not an independent prognostic factor for favorable 5-year DFS and OS.

However, our study still has some limitations. The study was retrospective in design, and as for the underlying mechanism of *EGFR G873R* mutation, we only excluded the correlation between *EGFR G873R* mutation and *EGFR* expression by using immunohistochemical staining, which means the mechanism is still largely unknown and requires further investigation.

In conclusion, our study demonstrated a potential role between *EGFR G873R* mutation and the prognosis of docetaxel in NSCLC. Further findings of *EGFR G873R* mutation may help in the development of new therapeutic strategies against the progression of NSCLC.

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Footnote

Reporting Checklist: The authors have completed the REAMRK reporting checklist. Available at https://dx.doi.org/10.21037/jtd-21-1505

Data Sharing Statement: Available at https://dx.doi.org/10.21037/jtd-21-1505

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jtd-21-1505). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Second Hospital of Shandong University and informed consent was taken from all the patients.

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