

EGFR mutations as a prognostic and predictive marker in non-small-cell lung cancer

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Abstract: Non-small-cell lung cancer (NSCLC) has entered the age of individual treatment, and increasing point mutations of specific oncogenes and rearrangement of some chromosomes are biomarkers used to predict the therapeutic effect of targeted therapy. At present, there is a consensus among clinicians that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown favorable efficacy in NSCLC patients with *EGFR* mutation, and some relevant research has suggested that the presence of *EGFR* mutations is a favorable prognostic marker. However, the association of *EGFR* mutation status with the responsiveness to conventional chemotherapy agents and survival in NSCLC patients is still unclear. This review provides an overview of and assesses the role of *EGFR* as a prognostic marker for postoperative patients and as a predictive marker for response to cytotoxic chemotherapy. In addition, we review the comparison of response to chemotherapy between *EGFR* mutations in exon 19 and in exon 21 and the predictive role of p.T790M mutation.

Keywords: epidermal growth factor receptor, prediction, prognosis

Introduction

At present, lung cancer is the leading cause of carcinoma-related death in industrialized countries,¹ and 75%–80% of primary lung cancers are non-small-cell lung cancer (NSCLC).² Although surgical operation is the most effective therapy for NSCLC, many cases with advanced stage are unresectable,^{3–5} and, for these patients, the preferred treatment is chemotherapy. Even though NSCLC patients have a chance to receive complete resection, they also face the risk of recurrence.⁶ Therefore, whether certain biomarkers could exist as predictive factors of the chemotherapy and be used for decisions about treatment options is extremely important in clinical decision-making.

Epidermal growth factor receptor (*EGFR*) is a member of the ErbB receptor tyrosine kinase (TK) family and has an essential action in the development and progression of NSCLC.^{7–9} It has been reported that the signaling pathways of *EGFR* could influence angiogenesis, activation and regulation of cellular proliferation, and the epithelial–mesenchymal transition (Figure 1).^{10–13} The gene with the most frequent mutations in NSCLC is *EGFR*. The most common *EGFR* mutations reported are deletions in exon 19 and the p.L858R point mutation in exon 21 (85%–90%).^{14,15} It has been reported that *EGFR* mutations usually occur in a subset of NSCLC patients with the following features: nonsmoker, female, East Asian, adenocarcinoma with bronchioloalveolar carcinoma, and well- or moderately differentiated tumor cells.^{16–18} During the past decade, some research demonstrated that EGFR TK inhibitor (EGFR-TKI) sensitivity was influenced by the presence of *EGFR* mutations and increased *EGFR* copy numbers.^{19–25} Some Phase III trials also revealed that, compared with those treated with erlotinib or gefitinib, the *EGFR*-mutated NSCLC

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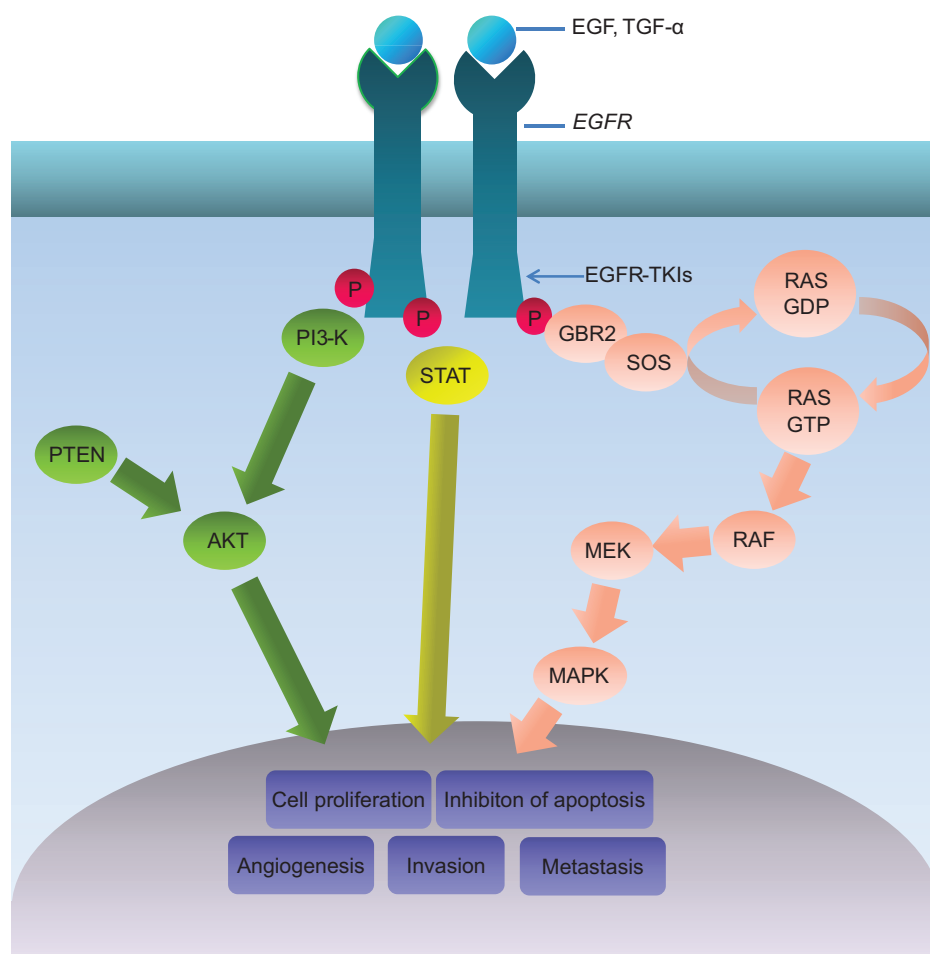


Figure 1 EGFR signaling pathway.

Abbreviation: EGFR, epidermal growth factor receptor; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; P, phosphorylate.

patients who were treated with normal chemotherapy had poorer clinical outcomes.^{26,27} Currently, relevant research results suggest that the mutant status of *EGFR* can likely be a predicting factor for the response to cytotoxic chemotherapy and prognosis of advanced NSCLC patients; however, this issue remains debatable.

In this review, we aim to summarize the role of *EGFR* as a prognostic marker for postoperative patients and as a predictive marker for response to cytotoxic chemotherapy. In addition, we review the comparison of response to chemotherapy between *EGFR* mutations in exon 19 and in exon 21 and the predictive role of p.T790M mutation.

Materials and methods

Search strategy

PubMed was searched using the following keywords: “non-small-cell lung cancer”, “*EGFR*”, “erlotinib”, “gefitinib”, “afatinib”, “chemotherapy”, “p.T790M”, “mutation”, “predictive”, and “prognostic”. The online proceedings of the

American Society of Clinical Oncology annual meeting and the World Conferences on Lung Cancer were searched for publications from 2004 to 2014 using the same keywords. In addition, the reference lists of relevant articles were searched. Search results were limited to articles in English.

Trial identification criteria

Clinical randomized trials, prospective cohort studies, and retrospective studies were included. Studies that evaluated the relationship between *EGFR* mutations and the outcomes of NSCLC patients were included. In addition, the included studies had to satisfy the following criteria: patients had a pathological diagnosis of NSCLC; patients had a clear *EGFR* mutation status; and at least one outcome regarding response rate (RR) or survival time was reported.

Data extraction

Data recorded from each single study included authors' names, publication year, study design, objectives, sample

size, *EGFR* mutation rate, and effects on patient outcomes (RR, survival, recurrence). Two reviewers independently conducted a data extraction from the original reports. Disagreements were resolved by consensus or by arbitration of a third reviewer.

Outcome definition

Based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines,²⁸ complete response and partial response (PR) were defined as the RR, and complete response, PR, and stable disease were defined as the disease control rate (DCR). Disease-free survival (DFS) was defined as the time from the date of surgery to proven recurrence or death. Progression-free survival (PFS) was defined as the time from the date of starting the therapy to disease progression or death. Overall survival (OS) was defined as the time from the date of surgery or starting the therapy to death or last follow-up. Post-recurrence survival was defined as the time from the date of recurrence to death or last follow-up. Time to treatment failure (TTF) was defined as the time from the date of starting the treatment to disease progression or death. Two-sided *P*-values <0.05 were considered statistically significant.

EGFR mutations as a prognostic marker for postoperative patients with NSCLC

Recently, the predictive factors of postoperative prognosis in NSCLC patients have received much attention. Although outcomes after curative resection are improving, long-term survival time is still poor, resulting from a high rate of relapse.^{29–31} Several studies have shown that the 5-year OS rates remained at 24%–58% after complete resection in stage IA–IIIA NSCLC patients.^{32–34} Therefore, clarifying the role of *EGFR* mutation status in predicting the outcome of NSCLC patients with resection is essential clinical work.

The prognostic value of *EGFR* mutations in resected NSCLC remains debatable (Table 1). Several studies have indicated that the presence of *EGFR* mutations meant longer survival times for patients with NSCLC who received surgical treatment. In a study by Lee et al³⁵ 117 patients with surgically resected pulmonary adenocarcinoma were reviewed, including 53 patients with *EGFR* mutations and 64 patients with wild-type *EGFR*. The results revealed that *EGFR* mutations were significantly associated with longer DFS (34.4 versus 20.1 months, *P*=0.003), but *EGFR* mutations had no correlation with OS (*P*=0.39). In multivariate analysis of DFS, wild-type *EGFR* was associated with a higher risk of recurrence after curative resection (hazard ratio [HR] 1.42, 95% confidence interval [CI]: 1.10–2.41,

P=0.04). Although there was not a statistically significant difference, isolated brain metastasis as the first recurrence was found more frequently in patients with *EGFR* mutations (24% versus 9%, *P*=0.15).

In a recent study performed by Jeon et al³⁶ 138 patients who underwent surgical resection with adenocarcinoma and had postoperative recurrence were included in the research. *EGFR* mutation was an independent prognostic factor for post-recurrence survival (HR 0.552, *P*=0.013) and survival time (HR 0.552, 95% CI: 0.345–0.882, *P*=0.013) in multivariable analysis.

Similarly, Sasaki et al³⁷ analyzed the information of 95 NSCLC patients who underwent surgical resection. Compared with those with wild-type *EGFR*, they found that the patients with *EGFR* mutations had a longer survival time (*P*=0.0143). However, a multivariate analysis did not prove that *EGFR* mutation was the significant factor (*P*=0.1824). Kosaka et al³⁸ analyzed 397 Japanese patients who were treated with curative pulmonary resection with lung adenocarcinoma. Although the results of multivariate analysis showed *EGFR* mutations were not independent factors related to the prognosis (*P*=0.3225), the authors found that the *EGFR* mutation patients had a longer survival time than those with wild-type *EGFR*.

A study by D'Angelo et al³⁹ enrolled the largest cohort ever reported (n=1,118) in an investigation of whether *EGFR* mutations could be used to predict the prognosis of postoperative patients with NSCLC. *EGFR* mutation was detected in 222 (19.9%) patients. The results showed that patients with *EGFR* mutations had a lower risk of death (HR 0.51, *P*<0.001) and a longer OS (HR 0.51, 95% CI: 0.34–0.76, *P*<0.001) than those with *EGFR* wild-type. They also found that a survival time of more than 10 years (n=286) only occurred in patients with *EGFR* mutation in lung cancer.

However, several studies revealed that *EGFR* mutation status had no prognostic value in patients who underwent surgical resection with adenocarcinomas. A total of 131 patients with completely resected lung adenocarcinoma whose pathologic stage was IA–IIIA were included in a study by Liu et al⁴⁰ in which no significant correlation was observed between median DFS (36.6 versus 25.7 months, *P*=0.533), OS (*P*=0.564), the recurrence rate, and *EGFR* mutation status. The results of multivariate analysis revealed that the lymph node (N) status (*P*=0.037) and distant metastasis (*P*<0.001) were significant predictive factors for OS.

Kobayashi et al⁴¹ performed a retrospective study to evaluate the factors related to poor outcomes of stage IA lung adenocarcinoma patients with surgical resection; 127 patients

Table 1 Select studies related to the association of EGFR mutations with prognosis in patients with resected NSCLC

Author/trial (year)	Number	EGFR mutation status, n		DFS/PFS (months)		OS (months)	
		Mutation	Wild-type	Mutation	Wild-type	Mutation	Wild-type
Kosaka et al (2004) ⁴²	224	110 (49.1%)	114 (50.9%)	NR	NR	P=0.9933	
Sasaki et al (2006) ³⁷	95	35 (36.8%)	60 (63.2%)	NR	NR	P=0.1824	
Lim et al (2007) ⁴³	27	15 (55.6%)	12 (44.4%)	DFS 18.13	16.87	P=0.45	
Kobayashi et al (2008) ⁴¹	127	64 (50.4%)	63 (49.6%)	DFS	P=0.83	HR 1.60 (0.49–5.23) P=0.44	
Lee et al (2009) ³⁵	117	53 (45.2%)	64 (54.8%)	DFS 34.4	20.1	NR	
Nose et al (2009) ⁴⁴	393	147 (37.4%)	246 (62.6%)	DFS	HR 1.42 (1.10–2.41) P=0.04	NR	
Kosaka et al (2009) ³⁸	397	196 (49.4%)	201 (50.6%)	DFS	P=0.367	P=0.3225	
D'Angelo et al (2012) ³⁹	1,118	222 (19.9%)	896 (80.1%)	DFS	NR	HR 0.51 (0.34–0.76) P< 0.001	
Liu et al (2013) ⁴⁰	131	58 (44.3%)	73 (55.7%)	DFS 36.6	25.7	HR 0.946 (0.500–1.791) P=0.865	
Jeon et al (2014) ³⁶	138	73 (52.9%)	65 (47.1%)	PRS	P=0.533	HR 0.552 (0.345–0.882) P=0.013	

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival; PRS, post-recurrence survival; DFS, disease-free survival; NR, not reported; HR, hazard ratio.

were included in the study. The results indicated that there was no correlation between *EGFR* mutations and recurrence (HR 1.42, 95% CI: 0.38–5.29, $P=0.60$) or survival (HR 1.60, 95% CI: 0.49–5.32, $P=0.44$) in patients with lung adenocarcinoma 20 mm or less. These results were consistent with those of a study by Kosaka et al⁴² who revealed that *EGFR* mutations did not influence the prognosis of patients with adenocarcinoma who underwent surgical resection ($P=0.9933$).

A total of 27 patients with resected lung adenocarcinomas were enrolled in a study performed by Lim et al.⁴³ *EGFR* mutations were detected in 15 patients (55.6%). The results showed there was no significant difference in DFS (16.87 versus 18.13 months, $P=0.83$) and OS ($P=0.45$) between *EGFR* mutation patients and those with wild-type *EGFR*. Similarly, among 393 Japanese patients who underwent a complete resection of adenocarcinoma in a study by Nose et al⁴⁴ there was no significant DFS difference between *EGFR* mutation patients and patients with wild-type *EGFR* ($P=0.367$).

At present, *EGFR* and *KRAS* mutations are known for having biologic relevance. Marks et al⁴⁵ analyzed the clinical outcomes data of 296 patients with stage I–III lung adenocarcinoma who underwent resection and compared outcomes between patients with *EGFR* mutation and *KRAS* mutation. The results revealed that patients with *EGFR* mutation had a higher 3-year OS than patients with *KRAS* mutant tumors (90% versus 66%) and suggested the NSCLC patients with *EGFR* mutation might have a more favorable prognosis.

Based on the previous studies,^{35–45} the prognostic role of *EGFR* mutations was not clear in patients with resected NSCLC. Although several studies did not report a significant difference in survival time between patients with and without *EGFR* mutations who underwent a resection of NSCLC,^{40–44} we believe that the presence of *EGFR* mutations is related to improved prognosis because of the better clinicopathologic characteristics. However, we cannot obtain a certain conclusion on this issue because of different postoperative treatments and the small population of patients in previous research. Therefore, further prospective studies are needed to investigate the prognostic value of *EGFR* mutations after surgical resection.

EGFR mutations as a predictive marker for response to cytotoxic chemotherapy in NSCLC

First-line treatment

Platinum-based doublet chemotherapy is the standard first-line therapy for advanced-stage NSCLC.^{46–48} Currently, although chemotherapy regimens are continuously updated,

the curative effect of chemotherapy for NSCLC has reached a plateau.^{49,50} There is an urgent need to develop individualized treatments for NSCLC patients. Some research has indicated that *EGFR* mutations may be used as a predictive marker for the response to conventional cytotoxic chemotherapies (Table 2).^{51–69} Although the results of these studies differed, they may suggest that there is a certain correlation between *EGFR* mutations and the response to cytotoxic agents.

The IRESSA Pan-Asia Study (IPASS)^{51,52} was a randomized Phase III study that included 1,217 patients with advanced lung adenocarcinoma from 87 clinical research centers of nine Asian countries. The purpose of the study was to compare the efficiency of gefitinib and carboplatin/paclitaxel. The researchers found that the RR was higher in *EGFR* mutation patients compared with wild-type *EGFR* cases (47.3% versus 23.5%). The research revealed that *EGFR* mutations may be a favorable predictive factor for the response to cytotoxic chemotherapy in NSCLC patients. However, the results of another Phase III trial indicated that patients with *EGFR* mutations had a similar RR to *EGFR* wild-type patients after receiving chemotherapy.⁵³ In the first-line randomized Phase III Iressa NSCLC Trial Assessing Combination Treatment (INTACT) trials, Bell et al⁵⁴ found that *EGFR* mutation-positive patients treated only with chemotherapy had a better OS (19.4 versus 9.2 months) than those with wild-type mutations, but there was no significant difference in RR between the two groups (40.0% versus 39.0%).

Similar results were found in other studies. The study by Eberhard et al⁵⁵ indicated that the presence of *EGFR* mutations was associated with higher RR (38% versus 23%, $P=0.01$) and longer time to progression despite a therapeutic regimen (8.0 versus 5.0 months, $P<0.001$). The study by Hotta et al⁵⁶ demonstrated that *EGFR* mutations were significantly correlated with a better PFS (HR 0.422, $P=0.0422$) and OS (HR 0.263, $P=0.0074$) in 54 Japanese patients with advanced NSCLC receiving first-line cytotoxic regimens, whereas they observed that the objective response was not affected by the presence of *EGFR* mutations ($P=0.6842$). However, the correlation of *EGFR* mutation with PFS was not found in the patients who received chemotherapy after the failure of the first-line gefitinib ($P=0.0764$).

Kalikaki et al⁵⁷ evaluated the clinical outcome of 162 patients with advanced NSCLC who received first-line chemotherapy and divided patients with *EGFR* mutations into two groups, which included those who had classical activating mutations (Del19, p.L858R, p.G719D, and p.E746V) and those who carried other mutations of unknown effect. The data indicated that patients with

Table 2 Select studies related to the association of EGFR mutations with the response to cytotoxic chemotherapy in non-small-cell lung cancer

Author/ trial (year)	Number	EGFR mutation status, n		RR	PFS (months)			OS (months)		
		Mutation	Wild-type		Mutation	Wild-type	Mutation	Wild-type	Mutation	Wild-type
Eberhard et al (2005) ⁵⁵	228	29 (12.7%)	199 (87.3%)	38.0%	P=0.01	23.0%	5.0	TTP 8.0	NR	NR
Lee et al (2006) ⁶⁰	90	17 (18.9%)	73 (81.1%)	42.9%	P=0.553	34.4%	6.67	TTP 7.97	NR	NR
Hotta et al (2007) ⁵⁶	54	14 (25.9%)	40 (74.1%)	21.4%	P=0.6842	15.0%		P=0.96 0.422 (0.179–0.991)	0.263 (0.099–0.699)	0.263 (0.099–0.699)
INTEREST (2010) ^{66,67}	142	19 (13.4%)	123 (86.6%)	21.1%	P=0.6842	9.8%		NR	16.6	6.0
Kalikaki et al (2010) ⁵⁷	162	Classical 31 Other 9	Wild-type 122 (75.3%)		WT vs classical HR 4.85 (1.13–20.83)			TTP 4.4		P=0.59 WT vs Classical HR 2.25 (0.81–6.24)
Wu et al (2010) ³	145	55 (37.9%)	90 (62.1%)	34.5%	P=0.034	33.3%	3.0	P=0.69	23.0	16.0
IPASS (2011) ^{5,152}	214	129 (60.3%)	85 (39.7%)	47.3%	P=0.881	23.5%	5.5	P=0.2148	21.9	12.7
Park et al (2012) ⁵⁹	217	137 (63.1%)	80 (36.9%)	33.6%		35.0%	4.4		NR	NR
Dong et al (2013) ⁵⁸	229	120 (52.4%)	109 (47.6%)	35.0%		34.9%	8.3	P=0.840	NR	NR
								P=0.008		

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: EGFR, epidermal growth factor receptor; HR, hazard ratio; INTEREST, Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere; IPASS, IRESSA Pan-Asia Study; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression; vs, versus; WT, wild-type.

classical *EGFR* mutations had a higher effectiveness of first-line chemotherapy than those with wild-type *EGFR* mutations patients (55.6% versus 21.8%, $P=0.023$), while, among patients treated with platinum-based regimens as the first-line treatment, OS was significantly longer in patients with classical *EGFR* mutations than in those without mutations (35.9 versus 15.3 months, $P=0.043$). In multivariate analysis, the presence of *EGFR* mutations was an independent factor associated with response to first-line chemotherapy (HR 4.85; 95% CI: 1.13–20.83; $P=0.034$).

Wu et al³ retrospectively analyzed 145 cases of stages IIIB and IV NSCLC patients who received first-line chemotherapy. The results indicated that no statistical difference in RR to the first-line chemotherapy between *EGFR* mutation carriers and wild-type *EGFR* patients was observed (34.5% versus 33.3%, $P=0.881$). The mutated *EGFR* patients had a longer median survival time and higher 1- and 2-year survival rates than those with wild-type *EGFR* (23 versus 16 months, 86.38% versus 62.64%, and 38.78% versus 27.16%, respectively, $P=0.0273$). Among stage IV patients, those with *EGFR* mutations had a longer PFS than wild-type *EGFR* patients (5 versus 3 months, $P=0.040$). Multivariate analysis demonstrated that the efficiency of the first-line chemotherapy and *EGFR* mutation status were independent prognostic factors (HR 0.461, $P=0.0042$ and HR 0.598, $P=0.0335$, respectively) for advanced NSCLC patients. The results of the study³ suggested that *EGFR* mutations had a relationship with survival time rather than with the response to first-line chemotherapy in patients with advanced NSCLC.

There are some related studies which indicate that certain therapies could demonstrate higher efficiency in NSCLC patients with *EGFR* mutation. Dong et al⁵⁸ reviewed 229 patients with advanced NSCLC who received platinum-based doublet chemotherapy as the first-line treatment. Although the RRs were not influenced by *EGFR* mutation status, there was significant difference in the PFS between patients with wild-type *EGFR* and *EGFR* mutations (8.3 versus 9.1 months, $P=0.008$). In 120 patients with *EGFR* mutation, DCR was higher in patients treated with docetaxel when compared with patients treated with gemcitabine (88.6% versus 67.5%, $P=0.031$), and docetaxel- or vinorelbine-based treatment showed a longer PFS compared to gemcitabine (9.4, 9.6, and 8.3 months, respectively, $P=0.033$ and $P=0.028$). Multivariate analysis indicated that the presence of an *EGFR* mutation was an independent predictive factor for PFS to first-line chemotherapy (95% CI: 1.086–1.840, $P=0.01$).

Park et al⁵⁹ included 217 patients with advanced NSCLC who had received platinum doublet chemotherapy as a

first-line regimen, with gemcitabine-based and taxane-based therapies administered in 131 (60.4%) and 86 (39.6%) cases, respectively. They found that taxane-based therapies had a higher DCR (71.8% versus 88.5%, $P=0.022$) and longer PFS (5.7 versus 4.1 months, $P=0.002$) compared with gemcitabine-based treatment in patients with *EGFR* mutations, particularly in those with deletions in exon 19 (5.3 versus 3.7 months, $P=0.012$). The results suggested that an optimal cytotoxic chemotherapy regimen could be selected based on the *EGFR* mutation status in patients with NSCLC.

However, the results of some research showed that there was no relationship between *EGFR* mutations and the response to cytotoxic chemotherapy. Lee et al⁶⁰ investigated 90 patients, of whom 75 received platinum and 45 received paclitaxel as first-line chemotherapy agents. RR to first-line chemotherapy for patients with *EGFR* mutations was 42.9%, which was similar to that for wild-type *EGFR* patients (34.4%, $P=0.55$). Similarly, Takano et al⁶¹ reported that the RRs to first-line cytotoxic chemotherapy were not significantly different between *EGFR* mutation patients and *EGFR* wild-type cases (31.0% versus 28.0%, respectively, $P=0.50$).

In contrast, a chemosensitivity test performed by Yoshimasu et al⁶² demonstrated that the sensitivity to docetaxel was lower in lung cancers with *EGFR* mutations compared with in tumors with wild-type *EGFR*.

Second-line treatment

At present, international recommendations for second-line drugs in NSCLC patients are docetaxel, pemetrexed, and EGFR-TKIs. However, patients with *EGFR* mutations receiving EGFR-TKIs after progression on chemotherapy demonstrated a lower RR compared with those on first-line therapy.^{63–65} The Phase III Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) trial^{66,67} compared the response to gefitinib and docetaxel as a second-line therapy in advanced NSCLC. The results showed that the RR to docetaxel was higher in patients with *EGFR* mutation-positive tumors compared with those with wild-type *EGFR* (21.1% versus 9.8%). Moreover, among patients who were treated with docetaxel, those with *EGFR* mutations had a longer OS than wild-type patients, although there was no significant difference (16.6 versus 6.0 months, $P=0.59$).

Wu et al⁶⁸ analyzed 95 patients with stage IIIB or IV NSCLC after treatment with gefitinib as the first-line therapy who received a second-line treatment with a platinum-based or taxane-containing regimen. The results showed that the

gemcitabine-plus-platinum regimen achieved better OS than erlotinib in patients with *EGFR* mutations (27.1 versus 10 months, $P=0.035$) but not in patients with wild-type *EGFR* (10.1 versus 12.7 months, $P=0.785$).

In the BR.21 trial,^{63,69} researchers compared erlotinib with a placebo in advanced NSCLC patients. Among the placebo subgroup, the data showed that patients with classical mutations had a longer median survival time than patients with *EGFR* wild-type or novel *EGFR* mutations (9.1, 3.5, and 3.5 months, respectively). However, there was no significant survival difference between *EGFR* classical or novel mutation patients and patients with wild-type *EGFR* (HR 0.65, 0.67, and 0.73, respectively).

As we can see from the results of the abovementioned studies, it has not been established whether *EGFR* mutations could predict the outcomes in NSCLC patients treated with cytotoxic chemotherapy. Regarding the results that showed that NSCLC patients with *EGFR* mutations achieved better therapeutic effect and longer survival time, one possible reason is that *EGFR* mutation patients have a favorable natural process, regardless of the efficacy of chemotherapy itself. Although a better outcome was found in mutation-positive NSCLC patients, this was not always obvious. Moreover, a majority of the previous related studies involved retrospective analysis and had a relatively small sample size, which could lead to some biases. Therefore, it is necessary to conduct further prospective studies to determine the predictive role of *EGFR* mutations for cytotoxic chemotherapy and the detailed prediction mechanism.

Comparison of the response to chemotherapy or EGFR-TKIs between EGFR mutations in exon 19 and mutations in exon 21 in NSCLC

In different types of *EGFR* mutations, in-frame deletions in exon 19 and amino acid replacements in exon 21 (leucine to arginine at condon 858, p.L858R) were the most common mutations, and accounted for about 85% of all *EGFR* mutations in patients with NSCLC.^{70–72} The predictive and prognostic value in patients with *EGFR* exon 19 mutation or with *EGFR* exon 21 mutation remains unclear (Table 3). In research performed by Cappuzzo et al⁷³ *EGFR* mutation was detected in 24 patients, which included deletion in exon 19 in 15 cases and point mutation in exon 21 in seven cases. The authors found a 46.6% RR to chemotherapy in patients with *EGFR* deletions in exon 19 compared with 0% RR

in patients with other *EGFR* mutations ($P=0.02$), which suggested that patients with *EGFR* exon 19 mutation might be more sensitive to EGFR-TKIs than patients with other *EGFR* mutations.

Jackman et al⁷⁴ compared the clinical data and outcomes of patients whose tumors had an *EGFR* exon 19 mutation to those with *EGFR* exon 21 mutation in 36 NSCLC patients who were treated with gefitinib or erlotinib. The results indicated that patients with deletions in exon 19 (delp.729–761) had a significantly improved time to progression (24 versus 10 months, $P=0.04$) and OS (38 versus 17 months, $P=0.0384$) than patients with a p.L858R mutation. Although there were no significant differences in multivariate analysis, patients with exon 19 mutation showed a higher RR than those with exon 21 mutation (73% versus 50%, $P=0.25$).

Riely et al⁷⁵ noted that patients with *EGFR* exon 19 mutation had a longer median PFS (12 versus 5 months, $P=0.01$) and OS (34 versus 8 months, $P=0.01$) compared with those with *EGFR* exon 21 mutation after receiving EGFR-TKI treatment. Similar results were shown in a study by Rosell et al.⁷⁶ A pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials⁷⁷ indicated that the patients with deletions in exon 19 receiving first-line afatinib had a longer OS than those treated with standard chemotherapy (HR 0.59; 95% CI: 0.45–0.77, $P<0.001$); however, in patients with p.L858R mutation, HR =1.25 (95% CI: 0.92–1.71, $P=0.160$). The results suggested that the patients with a particular *EGFR* mutation (eg, deletion in exon 19) could acquire more obvious benefit from the first-line afatinib therapy.

In a study by Liu et al⁴⁰ which enrolled 131 patients with completely resected lung adenocarcinoma, the results showed that, compared with the patients with exon 21 mutation, those with exon 19 mutation (delp.746–750) had longer DFS (46.2 versus 21.9 months, $P=0.056$) and 1-, 2-, and 3-year OS (100%, 96.7%, and 93.3%, respectively, versus 91.3%, 82.6%, and 60.9%, respectively, $P=0.01$). However, several randomized Phase III studies reported no significant difference in PFS with EGFR-TKIs between the patients with deletions in exon 19 and those with exon 21 p.L858R mutation.^{52,78,79}

Conversely, Shigematsu et al⁸⁰ analyzed early-stage NSCLC patients who underwent resections and never received EGFR-TKIs. After comparing the outcomes of 31 cases with *EGFR* p.L858R and 31 cases with *EGFR* deletions in exon 19 (delp.729–761), they reported that patients with p.L858R attained a longer survival time ($P=0.05$).

However, the study by Lee et al³⁵ found that patients with exon 19 mutation recurred more frequently compared

Table 3 Select studies related to the association of EGFR mutations in exon 19 and exon 21 with the response to treatment in NSCLC

Author/trial (year)	Number		RR		PFS (months)		OS (months)	
	Exon 19	Exon 21	Exon 19	Exon 21	Exon 19	Exon 21	Exon 19	Exon 21
Shigematsu et al (2005) ⁸⁰	62	52	NR	NR	NR	NR	NR	NR
Riely et al (2006) ⁷⁵	43	27	NR	NR	12	5	34	P=0.05
Jackman et al (2006) ⁷⁴	22	10	73.0%	25%	24	10	38	P=0.01
Cappuzzo et al (2007) ⁷³	15	7	46.6%	0%				P=0.0384
Rosell et al (2009) ⁷⁶	135	82						NR
WJTOG3405 (2010, 2012) ^{78,79}	50	36			9	9.6		NR
Cisplatin and docetaxel	37	49			6	6.7		NR
IPASS (2011) ^{51,52}	140	111	NR	NR				NR
Liu et al (2013) ⁴⁰	30	23	NR	NR	DFS	21.9		P=0.01

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; RR, response rate; PFS, progression-free survival; OS, overall survival; DFS, disease-free survival; NR, not reported; HR, hazard ratio; IPASS, IRESSA Pan-Asia Study; WJTOG3405, West Japan Thoracic Oncology Group 3405; EGFR-TKIs, EGFR tyrosine kinase inhibitors.

presence of p.T790M mutation before receiving EGFR-TKIs and prognosis of patients. The results suggested that the abundance rather than the presence of p.T790M mutation caused the benefits of EGFR-TKI treatment in NSCLC.

Kuiper et al⁹³ analyzed the clinical data of 66 patients with *EGFR* mutations, and the results showed that patients with p.T790M mutation at post-TKI biopsy attained a longer PFS (14.2 versus 11.1 months, $P=0.034$) and longer OS (45.9 versus 29.8 months, $P=0.213$) than those without p.T790M mutation on EGFR-TKI therapy.

Similar results were reported in a study by Li et al.⁹⁴ p.T790M mutation was detected in 29 patients after the failure of EGFR-TKIs, and the authors found that the time from the date of starting EGFR-TKI treatment to disease progression or death (PFS1) was not influenced by p.T790M mutation (13.0 versus 10.5 months, $P=0.894$). However, among 41 patients treated with EGFR-TKIs beyond progression, the results showed that patients with p.T790M mutation had a longer time from the date of the first disease progression to the second disease progression (PFS2) (6.3 versus 2.6 months, $P=0.002$) and OS (39.8 versus 23.2 months, $P=0.044$) than those with p.T790M wild-type. The data indicated that patients with p.T790M mutation after acquired resistance to EGFR-TKIs had better therapeutic effect to the continuous EGFR-TKI therapy. This conclusion requires further investigation.

In contrast, Sun et al⁹⁵ analyzed 70 NSCLC patients who had acquired resistance to EGFR-TKIs and of whom 36 (51%) had *EGFR* p.T790M mutation at post-TKI biopsy. No significant difference was found in post-progression survival (14.7 versus 14.1 months, $P=0.26$) and OS (43.5 versus 36.8 months, $P=0.23$) between patients with and without p.T790M mutation. Thirty-four patients were treated with subsequent afatinib after progression on EGFR-TKIs, and the patients with p.T790M mutation had a higher RR than those without p.T790M mutation (5% versus 38%, $P=0.01$). However, the median PFS for afatinib was 3.2 months in the p.T790M mutation group and 4.6 months in the p.T790M wild-type group ($P=0.33$).

A meta-analysis⁹⁶ was performed to identify the role of *EGFR* p.T790M mutation in the prognosis of patients receiving EGFR-TKI therapy. The incidence of patients who had pretreatment p.T790M mutation ranged from 34.88% to 80.00%. The authors found that patients with p.T790M mutation had a shorter PFS on EGFR-TKI treatment compared with p.T790M wild-type patients.

The studies above evaluated whether there was a prognostic value to the p.T790M mutation in NSCLC patients with *EGFR* mutations, but this remains unclear. Rather than

finding a negative prognostic effect of p.T790M mutation with EGFR-TKI treatment, some research has indicated that the p.T790M mutation might have a positive prognostic value after progression on EGFR-TKIs. In a fundamental study, the existence of p.T790M mutation was correlated with a slow speed of tumor growth,⁸⁶ which may be the reason why patients with *EGFR* p.T790M mutation were usually found to have a longer survival time in clinical research. Knowledge of p.T790M mutation is essential for determining the optimal treatment for these patients and we expect that the p.T790M mutation will become the first acquired molecular marker with prognostic significance.

Some studies have demonstrated that there were activities against p.T790M mutation tumors *in vitro* and *in vivo*,^{97,98} and some clinical trials are ongoing.^{99,100} The results of CO-1686 indicated that three-quarters of patients with p.T790M mutation who progressed following EGFR-TKIs treatment could have PR in a Phase I trial.¹⁰¹ Preliminary data from a Phase I study in NSCLC patients with acquired resistance to EGFR-TKIs also showed that about one-half of the patients receiving AZD9291 treatment could achieve responses.^{100,102} Moreover, a Phase II trial suggested that the combination of cetuximab and afatinib had modest clinical activity in NSCLC patients with p.T790M mutation.¹⁰³ However, there is still no standard therapy for patients with p.T790M mutation.

First-line therapy in NSCLC patients with *EGFR* mutations

Six randomized Phase III trials indicated that NSCLC patients with *EGFR* mutations receiving EGFR-TKIs as the first-line therapy could achieve higher RR and longer PFS than those receiving chemotherapy; however, no significant difference was found in OS between the two groups (Table 5).^{51,51,78,79,105–108,110,111} However, a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials reported an improvement in OS in *EGFR* mutant patients receiving EGFR-TKIs in 2014.⁷⁷

Among the subgroup of NSCLC patients with *EGFR* mutation, the results of IPASS^{51,52} indicated that the gefitinib arm had a higher RR (71.2% versus 47.3%, $P<0.001$) and a longer PFS (9.5 versus 6.3 months, $P<0.001$) compared to the carboplatin/paclitaxel group, while no significant difference was found in OS between these two groups (21.6 versus 21.9 months, $P=0.990$).

WJTOG (West Japan Thoracic Oncology Group) 3405^{78,79} was a Phase III study that analyzed the outcomes of 177 Japanese patients harboring *EGFR* mutations with advanced NSCLC. The researchers found that the patients who received gefitinib showed a significantly higher RR (62.1% versus 32.2%,

Table 5 Select studies related to first-line therapy in NSCLC patients with EGFR mutations

Author/trial (year)	Number	RR		PFS (months)		OS (months)	
		TKI	Chemotherapy	TKI	Chemotherapy	TKI	Chemotherapy
IPASS (2008, 2011) ^{51,52}	261	71.2%	47.3%	9.5	6.3	21.6	21.9
			$P<0.001$		HR 0.48 (0.34–0.64) $P<0.001$		HR 1.00 (0.76–1.33) $P=0.990$
WJTOG 3405 (2010, 2012) ^{78,79}	177	62.1%	32.2%	9.2	6.3	35.5	38.8
			$P<0.001$		HR 0.489 (0.336–0.710) $P<0.001$		HR 1.185 $P=0.443$
OPTIMAL (2011) ¹⁰⁴	154	83.0%	36.0%	13.7	4.6	22.6	28.8
			$P<0.001$		HR 0.16 (0.10–0.26) $P<0.001$		HR 1.065 $P=0.685$
First-SIGNAL (2012)	42	84.6%	37.5%	8.0	6.3	27.2	25.6
			$P=0.002$		HR 0.544 (0.269–1.100) $P=0.086$		HR 1.043 (0.498–2.182) $P=0.984$
EURTAC (2012) ¹⁰⁵	173	58.0%	15.0%	9.7	5.2	19.3	19.5
			$P<0.001$		HR 0.37 (0.25–0.54)		HR 1.04 $P=0.87$
NEJ002 (2013) ¹⁰⁶	228	73.7%	30.7%	10.8	5.4	27.7	26.6
			$P<0.001$		HR 0.322 (0.236–0.438) $P<0.001$		HR 0.887 (0.634–1.241) $P=0.483$
LUX-Lung 3 (2013) ¹⁰⁸	345	56.0%	23.0%	11.1	6.9		
			$P=0.001$		HR 0.58 (0.43–0.78) $P=0.001$		HR 1.12 (0.73–1.73) $P=0.60$
LUX-Lung 6 (2014) ¹⁰⁹	364	66.9%	23.0%	11.0	5.6	22.1	22.2
			$P<0.0001$		HR 0.28 (0.20–0.39) $P<0.0001$		HR 0.95 (0.68–1.33) $P=0.76$

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; IPASS, IRESSA Pan-Asia Study; WJTOG, West Japan Thoracic Oncology Group; First-SIGNAL, First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung; EURTAC, European Tarceva versus Chemotherapy; RR, response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; TKI, tyrosine kinase inhibitors.

$P < 0.001$) and longer PFS (9.2 versus 6.3 months, $P < 0.001$) than those receiving cisplatin plus docetaxel.

The randomized Phase III First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung (First-SIGNAL) trial enrolled 313 Korean never-smokers with advanced lung adenocarcinoma. Ninety-six patients were evaluated for *EGFR* mutation status and *EGFR* mutation was detected in 42 patients. Of the patients who had *EGFR* mutation-positive tumors, the gefitinib group had a higher objective response rate (ORR) (84.6% versus 37.5%, $P = 0.002$) and a longer PFS (8.0 versus 6.3 months, $P = 0.086$); however, the results failed to show a significant difference in OS. Similar results were shown in OPTIMAL study,¹⁰⁴ European Tarceva versus Chemotherapy (EURTAC) study,¹⁰⁵ and NEJ002 study.¹⁰⁶

In 2013, a meta-analysis¹⁰⁷ was performed to evaluate the favored therapy for first-line treatment in NSCLC patients with *EGFR* mutations. The results demonstrated that patients receiving EGFR-TKI therapy showed a higher RR (66.60% versus 30.62%, HR 5.68, 95% CI: 3.17–10.18, $P < 0.001$) and an improved PFS (9.5 versus 5.9 months, HR 0.37, 95% CI: 0.27–0.52, $P < 0.001$) compared with those receiving chemotherapy treatment. There was no significant difference in OS (30.5 versus 23.6 months, HR 0.94, 95% CI: 0.77–1.15, $P = 0.57$).

Recently, in two randomized Phase III trials,^{108,109} patients with *EGFR* mutations treated with second-generation EGFR-TKIs such as afatinib had better outcomes than those receiving chemotherapy (Table 5). The results of the LUX-Lung 3 study¹⁰⁸ demonstrated that significantly improved RR and PFS were found with afatinib compared to chemotherapy in *EGFR* mutation patients (56% versus 23%, $P = 0.001$ and 11.1 versus 6.9 months, $P = 0.001$, respectively). Similar results were found in the LUX-Lung 6 trial.¹⁰⁹ At the American Society of Clinical Oncology 2014 meeting, a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials⁷⁷ provided new efficacy and safety data to support treatment with afatinib. The analysis included 631 advanced NSCLC patients with common *EGFR* mutations (deletions in exon 19 or p.L858R substitutions) and demonstrated that the patients attained longer OS when treated with first-line afatinib compared to standard chemotherapy (27.3 versus 24.3 months, HR 0.81, 95% CI: 0.66–0.99, $P = 0.037$). This is the first time an actual survival benefit not seen in previous trials with gefitinib or erlotinib was shown.

The pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials⁷⁷ suggested that patients with *EGFR* mutations receiving EGFR-TKIs had a greater improvement in OS

than those treated with chemotherapy, which provided the latest evidence toward determining whether EGFR-TKIs should be used as first- or second-line treatment. The results may influence the therapeutic regimen of the *EGFR* mutant patients in clinical practice. Afatinib is an irreversible inhibitor against p.T790M mutation and all *EGFR* family members. Although several related studies have been carried out,^{110–113} whether different EGFR-TKIs have different effects in *EGFR*-mutant patients is still unclear.

Conclusion

At present, *EGFR* mutation is the strongest predictive biomarker for the efficiency of EGFR-TKIs.^{114,115} Through analyzing relevant research of the past 20 years, we found that the prognostic and predictive value of *EGFR* mutation status in NSCLC remains uncertain, and it is difficult to understand the detailed mechanism by which cytotoxic agents influence *EGFR*-mutant and wild-type tumors differently. One study reported the differences in carcinogenic molecular genetic pathways between *EGFR* mutation tumors and tumors with wild-type *EGFR*.¹¹⁶ The results showed that mutant *EGFR* selectively activated Akt and signal transducer and activator of transcription (STAT) signaling is related to cell survival; however, mutant *EGFR* could not act on extracellular signal-regulated kinase signaling, the function of which is to induce proliferation. Wild-type *EGFR* was proved to promote cellular proliferation and cell survival. Future molecular studies are needed to support this mechanism.

Although the majority of the selected research was performed retrospectively, and the studies achieved various conclusions, the results provide new information which can play an essential role in choosing the best treatment option for patients with NSCLC according to the *EGFR* mutation status. We believe that the presence of *EGFR* mutations has an intrinsic relationship with the outcomes in patients with NSCLC. With improvements in technology for detecting gene mutations, some novel mutations in *EGFR* have been reported to be sensitive to TKIs, such as p.V765A, p.T783A, p.V774A, p.S784P, and p.V769A.^{117–121} The role of *EGFR* should be evaluated in more detail in prospectively designed research so that we can have a deeper understanding of the association of *EGFR* mutation with the curative effect and survival benefit of chemotherapy in the future.

Disclosure

The authors report no conflicts of interest in this work.

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