

Positive expression of p53, c-erbB2 and MRP proteins is correlated with survival rates of NSCLC patients

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Abstract. The incidence of lung cancer is one of the leading causes of mortality. This study aimed to investigate the prognostic and predictive importance of p53, c-erbB2 and multidrug resistance proteins (MRP) expression and its correlation with clinicopathological characteristics of patients with non-small cell lung cancer (NSCLC). Expression of p53, c-erbB2 and MRP proteins in 152 tumor samples from resected primary NSCLCs was detected by immunohistochemical staining. The correlation of proteins, survival and clinicopathological characteristics was investigated in 152 patients undergoing potentially curative surgery. The positive rates of p53, c-erbB2 and MRP expression were 53.9 (82/152), 44.1 (67/152) and 43.4% (66/152), respectively. Overall survival rates of patients were markedly correlated with the overexpression of p53, c-erbB2 and MRP proteins. One, 2- and 3-year survival rates of patients exhibiting a positive expression of these proteins were 72.6, 54.8 and 32.2%, respectively. These rates were lower compared with those of patients with a negative expression of these proteins (92.1, 78.5 and 63.4%) ($P=0.02$, 0.01 or 0.00 , respectively). Results of Cox's regression analysis showed that c-erbB2 expression and cell differentiation were independent prognostic factors in patients with NSCLC. These findings suggest that the positive expression of p53, c-erbB2 and MRP proteins is correlated with the survival rates of NSCLC patients. Detection of positive p53, c-erbB2 and MRP expression may be a useful predictive indicator of prognosis. Positive c-erbB2 expression is an independent prognostic factor, with a potential to be used as a predictive indicator of chemotherapy efficacy in NSCLC patients.

Introduction

Lung cancer is one of the leading causes of mortality, with a curing rate of only ~13% (1). Non-small cell lung cancers (NSCLC) account for 80% of lung cancers. Approximately 75-80% of NSCLC patients, when diagnosed, are already in the late stage of the cancer. Surgery is the main treatment for NSCLC patients in clinical stage I-IIIa. Following surgery, administration of adjuvant chemotherapy (combination of two platinum drugs) may lead to significant survival benefits (2), even though 30-60% of patients receiving adjuvant chemotherapy experience tumor recurrence or distant metastasis (3). Multidrug resistance (MDR) constitutes a challenge with regard to effective chemotherapeutic interventions. The occurrence of MDR, regardless of whether it is congenital or acquired, is a serious challenge for effective administration of NSCLC treatments.

p53 tumor suppressor gene is a multifunctional protein that is involved in the regulation of cell cycles, apoptosis, gene transcription, stress response and DNA repair. Previous studies focused on the correlation between p53 protein expression and cisplatin-based chemotherapy for late-stage NSCLC patients. In their study, Tsao *et al* (4) observed that among 253 NSCLC cases, positive p53 protein expression was more likely to be found in male and squamous cell carcinoma patients. However, Bai *et al* (5) observed that a high expression of p53 protein is correlated with tumor invasion status in hilar, pericardium, blood vessels and thrombosis.

Multidrug resistance proteins (MRP), including MRP1 and MRP2, are key members of the ATP-binding transporter superfamily (ABC proteins). These proteins are involved in the transmembrane transportation of prokaryotic and eukaryotic cells. By regulating the pH in cytoplasm and organelles, MRP proteins may decrease the amount of drugs at the functioning sites and reduce the intracellular concentration of drugs, leading to drug resistance. MRP expression may be associated with drug resistance and prognosis of lung cancers (6). However, the correlation between MRP expression and lung cancer types, differentiations and clinical stages remains to be clarified.

Overexpression of c-erbB2 protein expression may be detected in a variety of malignancies, including NSCLC. c-erbB2 protein is a marker of endogenous MDR, which can be used as an independent predictor (7). c-erbB2 protein

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overexpression is associated with mutations in chromosome 17q21 locus (8). Turken *et al* (9) demonstrated that 35% of NSCLC cases were associated with a high c-erbB2 protein expression. A high c-erbB2 protein expression is frequently detected in lung adenocarcinoma tissues in stage IIIb-IV ($P=0.04$). NSCLC patients with a positive c-erbB2 protein expression are prone to recurrence and metastasis following treatment. Therefore, a high c-erbB2 protein expression is an indicator of tumor progression (8,9), but a high c-erbB2 protein expression is not associated with the sensitivity of chemotherapy (9).

In this study, immunohistochemical methods were used to investigate expression levels of three drug resistance-associated proteins (p53, c-erbB2 and MRP) in NSCLC tissues. The correlation between expression levels of p53, c-erbB2 and MRP and the clinicopathological characteristics of NSCLC, as well as the prognostic significance of these protein expressions, was investigated.

Materials and methods

Patients. In total, 152 NSCLC samples were confirmed by surgery and pathological detection. Inclusion criteria were: i) pathologically proven NSCLC cells; ii) primary lung cancer cases; iii) no adjuvant radiotherapy or chemotherapy received prior to surgery; iv) no distant metastasis found prior to surgery and v) no serious heart and lung diseases or other combined diseases diagnosed (Table I).

Immunohistochemistry (IHC). Tissue samples were fixed with formaldehyde solution, embedded in paraffin, followed by regular (4 μ m) slicing. IHC was performed by the S-P method, as per the manufacturer's instructions, using p53, c-erbB2 and MRP mouse anti-human monoclonal antibodies and the S-P immunohistochemistry kit (Kit-9710; Maixin Biotechnology, Fujian, China). Samples were treated under the same conditions, including staining and 3,3'-diaminobenzidine (DAB) coloring. Lung sections with known protein expression were used as positive controls under the same conditions. Phosphate-buffered saline (PBS) was used as the blank control for primary antibodies. Normal mouse serum was used as the negative control for primary antibodies. For each immunohistochemical staining sample, 10 high-power views (magnification, x200) were randomly selected for microscopic observation.

Criteria for p53 protein staining were (10): cells without nucleus-stained particles were considered negative, while cells with nucleus-stained particles were considered positive. For the tissue samples: i) if <30% of the cells were positive, the tissues were considered to be weak positive; ii) if 30-70% of the cells were positive, the tissues were considered to be moderately positive and iii) if >70% of the cells were positive, the tissues were considered to be strongly positive. MRP and c-erbB2 protein staining was analyzed based on the Hercep score (7,11), as recommended by the Food and Drug Administration (FDA). Staining scores were described as: 0-1, negative; 1-2, weakly positive and 2-3, strongly positive.

Statistical analysis. Data were analyzed using the SPSS 16.0 software. Survival rate analyses were performed using the

Kaplan-Meier method. Sample rates were compared using the χ^2 test. Single-factor analyses were carried out using the log-rank test. Multivariate analyses were performed using Cox's regression analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Expression of p53, c-erbB2 and MRP proteins in NSCLC cells. In this study, correlations between the survival rates of 152 NSCLC patients and positive expression of p53, c-erbB2 and MRP proteins in NSCLC tissues were investigated. Positive expression of p53, c-erbB2 and MRP was detected by IHC (Fig. 1). IHC staining results indicated that of the 152 NSCLC cases, the positive expression of p53, c-erbB2 and MRP proteins was 53.9 (82/152), 44.1 (67/152) and 43.4% (66/152), respectively. Spearman's rank correlation coefficient revealed a correlation in the expression of the three proteins in NSCLC tissues. The r-values between p53 and MRP, and those between p53 and c-erbB-2 were 0.248 ($P=0.019$) and 0.335 ($P=0.002$), respectively. The r-values between MRP and c-erbB-2 were 0.321 ($P=0.005$).

Correlations between p53, c-erbB2, MRP expression and clinicopathological characteristics of NSCLC. p53 protein expression in NSCLC tissues was markedly correlated with patient gender, cancer cell differentiation, clinical stages of NSCLC and lymph node metastasis ($P<0.05$ and $P<0.01$) (Table I). A positive expression rate of MRP was markedly higher in lung adenocarcinomas (67.6%) compared with lung squamous cell carcinoma (33.0%) ($P<0.05$). However, c-erbB2 expression was not correlated with the clinicopathological characteristics of NSCLC ($P>0.05$).

Correlations between expression of p53, c-erbB2 and MRP proteins and the survival rates of NSCLC patients. The combination of positive p53, c-erbB2 and MRP expression indicated poor prognosis (Table II). One, 2- and 3-year survival rates of patients with a positive expression of these three proteins were markedly lower compared with those of patients with a negative expression of the three proteins ($P=0.02$, 0.01 and 0.00, respectively).

Patients with a positive expression of two of the three proteins had lower 1-, 2- and 3-year survival rates compared with those of patients with a positive expression of one or a negative expression of two proteins ($P=0.02$ and $P=0.01$, respectively).

Correlations between expression of p53, c-erbB2 and MRP proteins and the cumulative survival rates of NSCLC patients receiving surgery. Correlations between expression of p53, c-erbB2 and MRP proteins and the cumulative survival rates of NSCLC patients receiving surgery were also investigated. The cumulative 1-, 2- and 3-year survival rates of patients with a positive expression of p53, c-erbB2, and MRP proteins were markedly lower compared with those of patients with a negative expression of the three proteins ($P<0.05$) (Table III). Patients with a negative expression of the three proteins had the highest survival rates. Patients with a positive expression of one or two proteins had mediate survival rates, while patients

Table I. Correlation between expression of p53, MRP and c-erbB2 proteins and clinicopathological characteristics of NSCLC patients.

Clinicopathological characteristics	No.	p53		MRP		c-erbB2	
		Positive (%)	χ^2	Positive (%)	χ^2	Positive (%)	χ^2
Gender							
Male	127	73 (57.5)	54 (42.5)	55(43.3)			
Female	25	9 (36.0)	3.879 ^a	12 (48.0)	0.255	12 (48.0)	0.214
Age (years)							
≤59	69	32 (46.4)	30(43.5)	35 (50.7)			
>59	83	50 (60.2)	2.915	36 (43.4)	0.000	32 (38.6)	1.237
Pathological types							
Squamous cell carcinoma	97	35 (36.1)	32 (33.0)	46 (47.4)			
Adenocarcinoma	37	15 (40.5)	25 (67.6)	13 (35.1)			
Others	18	5 (27.8)	1.520	9 (50.0)	7.545 ^a	8 (44.4)	0.978
Differentiation							
High and medium	99	43 (43.4)	38 (38.4)	51 (51.5)			
Low	53	39 (73.6)	12.63 ^b	28 (52.8)	2.932	16 (30.2)	2.548
TNM staging							
I-II	99	46 (46.5)	49 (49.5)	50 (50.5)			
III	53	36 (67.9)	6.399 ^a	17 (32.1)	3.125	17 (32.1)	3.087
Lymph node metastasis							
Yes	78	51 (65.4)	32 (41.0)	29 (37.2)			
No	74	31 (41.9)	8.436 ^b	34 (45.9)	0.374	38 (51.4)	1.963
Vascular tumor thrombus							
Yes	17	7 (41.2)	5 (29.4)	6 (35.3)			
No	135	75 (55.6)	1.257	61 (45.2)	1.529	61 (45.2)	1.102
Margin							
Negative	148	79 (53.4)	65 (43.9)	66 (44.6)			
Positive	4	3 (75.0)	0.733	1 (25.0)	0.567	1 (25.0)	0.379

^aP<0.05, ^bP<0.01. NSCLC, non-small cell lung cancer; MRP, multidrug resistance proteins.

with a positive expression of all three proteins had the lowest survival rates. Survival rates in the subgroups were statistically significant (Fig. 2, P<0.05).

Correlations between expression of p53, c-erbB2 and MRP proteins and the cumulative survival rates of NSCLC patients receiving surgery and chemotherapy. In patients who received surgery plus chemotherapy following surgery, and had a positive expression of MRP and c-erbB2 protein, the cumulative 1-, 2- and 3-year survival rates were markedly lower compared with those of patients with a negative expression of these proteins (Table III, P<0.05). However, the survival rate differences of patients with a positive or negative p53 expression were not statistically significant (Table III, P=0.82). Cumulative survival rates of patients with a negative expression of MRP and c-erbB2 were higher compared with those of patients with a positive expression of the two proteins. Additionally, patients with a positive expression of either MRP or c-erbB2 had cumulative survival rates between them. The results of the comparisons were statistically significant (Fig. 3, P=0.01).

Cox multi-element analyses. Age, gender, pathological types, cancer cell differentiation and other clinical or pathological characteristics, as well as expression patterns of p53, c-erbB2 and MRP proteins were analyzed in NSCLC patients, using the multi-element Cox model. Cancer cell differentiation and c-erbB2 expression were identified as two independent predictors of the prognosis of NSCLC patients suitable for surgery (95% CI, P=0.000 and 0.029).

Discussion

MDR is the key reason for the poor efficacy of chemotherapy in NSCLC. Several factors are involved in MDR development. The MRP phenotypes of various types of lung cancers are different. The mechanisms of NSCLC MDR remain to be clarified, but are possibly associated with changes in the expression levels of a variety of proteins resulting in the process of tumor formation. p53, MRP and c-erbB2 are three MDR-regulating proteins. In this study, we observed that the three proteins are correlated with the efficacy of surgery and chemotherapy in NSCLC patients.

Table II. Correlation between expression of p53, MRP and c-erbB2 in tumor tissues and survival rates of NSCLC patients.

		NSCLC survival rates (146 cases)					
Variables	No.	1-year (%)	P-value	2-year (%)	P-value	3-year (%)	P-value
MRP							
Negative	82	82.3	0.35	75.8	0.04	54.7	0.04
Positive	64	77.6	60.2	35.6			
c-erbB2							
Negative	81	87.4	0.07	73.3	0.10	50.4	0.03
Positive	65	79.2	65.4	36.1			
p53							
Negative	67	86.5	0.14	71.6	0.11	59.8	0.09
Positive	79	81.3	67.2	54.3			
p53, MRP, c-erbB2							
All negative	28	92.1	0.02	78.5	0.01	63.4	0.00
p53, MRP, c-erbB2							
All positive	23	72.6	54.8	32.2			
p53 and MRP							
All negative	16	88.3	0.08	76.5	0.03	61.8	0.02
p53 and MRP							
All positive	18	75.2	57.1	34.2			
p53 or MRP							
Single positive	35	83.5	69.3	51.2			
p53 and c-erbB2							
All Negative	12	90.2	0.13	74.8	0.07	61.7	0.02
p53 and c-erbB2							
All positive	15	76.4	60.9	35.3			
p53 or c-erbB2							
Single positive	39	84.3	71.4	56.5			
MRP and c-erbB2							
All negative	23	88.6	0.08	76.2	0.03	58.7	0.01
MRP and c-erbB2							
All positive	11	74.2	58.1	32.6			
MRP and c-erbB2							
Single positive	28	82.5	67.3	43.4			

χ^2 test. NSCLC, non-small cell lung cancer; MRP, multidrug resistance proteins.

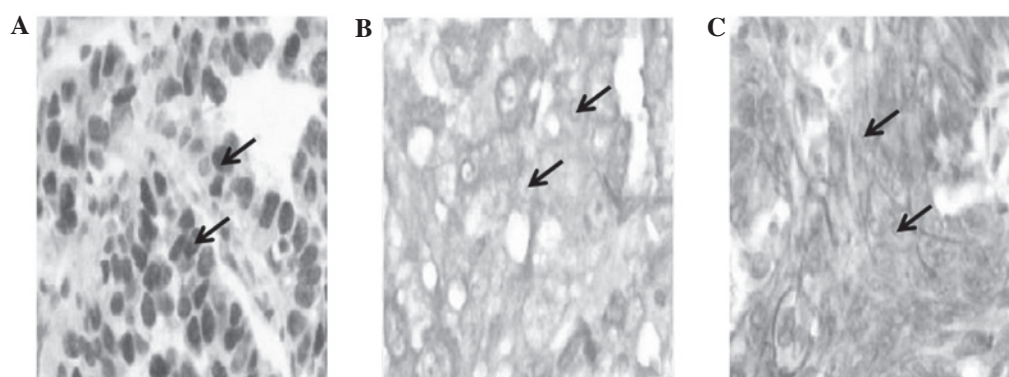


Figure 1. Positive expression (as indicated by arrows) of p53, MRP and c-erbB2 proteins in NSCLC tissues (S-P, magnification, x200). (A) p53, (B) MRP and (C) c-erbB2. NSCLC, non-small cell lung cancer; MRP, multidrug resistance proteins.

Table III. Correlation between expression of p53, MRP and c-erbB2 in tumor tissues and survival rates of NSCLC patients undergoing surgery only or surgery plus chemotherapy.

Variables	Surgery				Surgery and chemotherapy after surgery			
	1-year survival (%)	2-year survival (%)	3-year survival (%)	P-value	1-year survival (%)	2-year survival (%)	3-year survival (%)	P-value
p53								
Positive	79.5	59.0	43.6	0.03	82.5	70.0	62.5	0.82
Negative	84.8	69.7	58.7	94.1	73.5	61.8		
MRP								
Positive	76.4	61.3	34.9	0.04	78.2	58.3	36.9	0.03
Negative	79.7	74.5	49.6	84.6	76.7	59.4		
c-erbB2								
Positive	74.2	62.2	32.7	0.04	83.6	70.7	38.7	0.01
Negative	80.5	72.4	48.9	94.3	74.1	52.9		

χ^2 test. NSCLC, non-small cell lung cancer; MRP, multidrug resistance proteins.

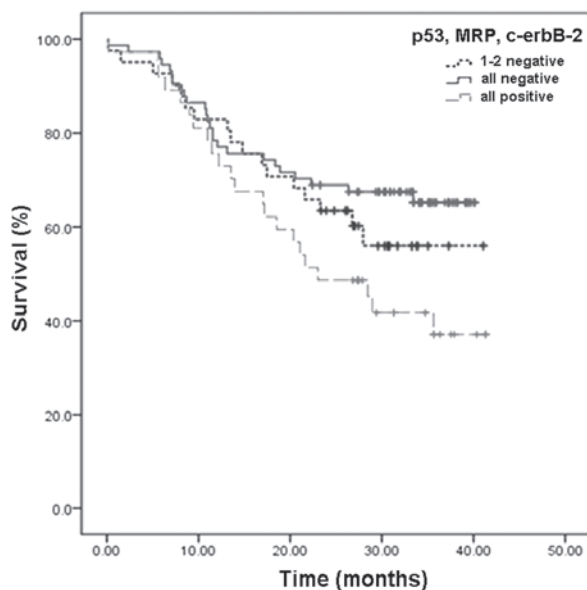


Figure 2. Survival curves of patients who underwent surgery with various expression patterns of p53, multidrug resistance proteins (MRP), and c-erbB-2 proteins. Patients with a negative expression of the three proteins had the highest survival rates, while patients with a positive expression of the three proteins had the lowest survival rates ($P < 0.05$).

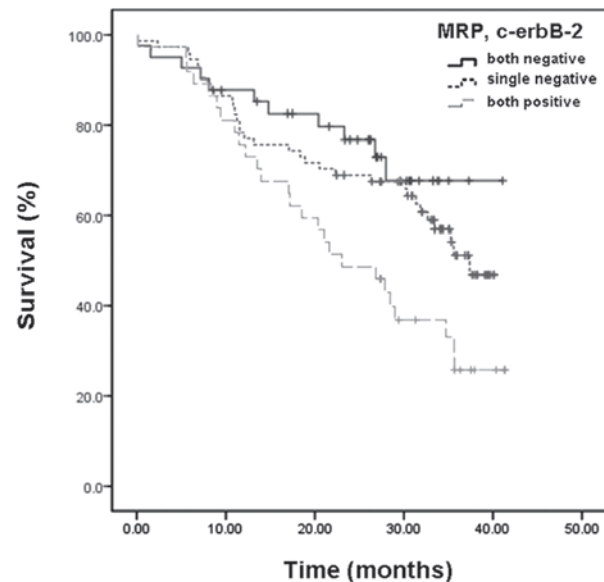


Figure 3. Survival curves of patients who underwent surgery and received chemotherapy with various expression patterns of multidrug resistance (MRP) and c-erbB-2 proteins. Cumulative survival rates of patients with a negative expression of MRP and c-erbB2 were higher compared with those patients with a positive expression of the two proteins. Patients with a positive expression of either MRP or c-erbB2 had cumulative survival rates ($P = 0.01$).

In this study, IHC was used to detect p53 expression in 152 NSCLC cases. The findings show that the positive rate of p53 expression in NSCLC cases was 53.9%. p53 protein expression was correlated with NSCLC patient gender, cytological grades, clinical stages, lymph node metastasis and other clinical characteristics ($P < 0.05$), but did not correlate with pathological types. In their study, Rusch *et al* (10) found that NSCLC patients with a positive expression of p53 protein are less sensitive to cisplatin compared with patients with a negative expression of p53 protein, a negative correlation. Sengupta *et al* (12) reported that overexpression of p53 protein

may affect the efficacy of chemotherapy, leading to poor prognosis of NSCLC. However, Huang *et al* (13) observed that the chemotherapeutic efficacy of late-stage NSCLC patients with a negative expression of p53 protein was less than that of patients with a positive p53 expression, a positive correlation. However, this positive correlation is not adequate to be statistically significant. Our studies showed that 1-, 2- and 3-year survival rates of patients with a positive expression of p53 protein were not statistically different from those of patients with a negative p53 protein expression ($P = 0.82$), indicating that the post-surgery chemotherapeutic efficacy did not correlate with

p53 protein expression. These inconsistencies may be due to the two-way regulation of chemotherapy sensitivity by p53 as reported previously (14). In their study, Lee *et al* (15) reported that a positive expression of p53 protein is a good indicator of early prognosis in resectable NSCLC cases. However, Kwiatkowski *et al* (16) and Ebina *et al* (17) demonstrated that p53 protein overexpression predicts a poor prognosis for NSCLC patients in early stages. In this study, the 1-, 2- and 3-year survival rates of patients, who only underwent surgery and had a positive expression of p53, were lower compared to those of patients with a negative expression of p53. This difference is statistically significant ($P=0.03$). Although a positive p53 expression is negatively correlated with the prognosis of NSCLC, the Cox multi-element analyses indicated that p53 is not an independent predictor of the prognosis of NSCLC patients.

Filipits *et al* (18) found that NSCLC patients suitable for surgery had a positive MRP1 expression rate of 47% and a positive MRP2 expression of 40%. The overall survival rates of NSCLC patients with a positive MRP2 expression were markedly shorter compared with those of patients with a negative MRP2 expression ($P=0.007$), suggesting that MRP2 protein expression may be an indicator of poor prognosis of NSCLC patients suitable for surgery. However, MRP1 expression did not correlate with survival period. MRP1 and MRP2 are not significant for predicting the efficacy of platinum-containing chemotherapy. Our results indicate that in NSCLC tumor tissues, MRP protein had a positive expression rate of 43.4% (66/152), which is markedly correlated with pathological types and lymph node metastasis ($P<0.05$). The positive MRP protein expression rate in lung adenocarcinoma was 67.6% (25/37), markedly higher compared with that of squamous cell carcinoma (33.0%, 32/97), which was markedly different ($P<0.05$). The 1-, 2- and 3-year survival rates of patients with a positive MRP expression were markedly lower compared with those of patients with a negative MRP expression, suggesting poor prognosis of NSCLC patients with a positive MRP expression. However, the Cox multi-element analyses suggest that MRP is not an independent predictor of the prognosis of NSCLC patients.

Our findings suggest that the 1-, 2- and 3-year survival rates of patients, who received surgery and chemotherapy, and had positive c-erbB2 protein expression, were markedly lower compared with those of patients with a negative c-erbB2 expression ($P=0.01$), suggesting that NSCLC patients with a positive c-erbB2 expression may be resistant to platinum-containing chemotherapy. Overexpression of c-erbB2 protein in NSCLC tissues may be a prognostic indicator of tumor progression. Similarly, the Cox multi-element analyses suggest that c-erbB2 is an independent predictor of the prognosis of NSCLC patients.

Findings of this study have shown that a positive expression of the three proteins in NSCLC patients indicates a poor prognosis, as the 1-, 2- and 3-year survival rates were 72.6, 54.8 and 32.2%, respectively, which were markedly lower compared with those of patients with a negative expression of the three proteins (92.1, 78.5 and 63.4%, $P=0.02$, 0.01 and 0.00). The 3-year survival rates of patients with a positive expression of

two proteins were lower compared with those of patients with a positive expression of one protein or a negative expression of the two proteins ($P=0.02$ and $P=0.01$). Utilization of p53, c-erbB2 and MRP as a three-indicator combination or of MRP and c-erbB2 as a two-indicator combination, are useful for the prognostic evaluation of the surgical and chemotherapeutic efficacies of NSCLC patients.

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