



# Prognostic role of epidermal growth factor receptor mutation status in patients with de novo lung adenocarcinoma

Bo Li<sup>1#</sup>, Xiaolu Ren<sup>1#</sup>, Hongxia Guo<sup>2</sup>, Yi Guo<sup>3</sup>, Fei Han<sup>4</sup>, Xiaolian Wen<sup>5</sup>, Jing Wu<sup>1</sup>, Xiaomin Li<sup>1</sup>, Yuejun Ren<sup>1</sup>, Xiaoyun Hu<sup>6</sup>, Zhihong Liu<sup>6,7</sup>

<sup>1</sup>Department of Radiation Oncology, Shanxi Cancer Hospital, Taiyuan, China; <sup>2</sup>Department of Oncology, Shanxi Bethune Hospital, Taiyuan, China; <sup>3</sup>Department of Respiration, Shanxi Cancer Hospital, Taiyuan, China; <sup>4</sup>Department of Thoracic Surgery, Shanxi Cancer Hospital, Taiyuan, China; <sup>5</sup>Department of Hematology, Shanxi Cancer Hospital, Taiyuan, China; <sup>6</sup>Department of Respiration, First Hospital of Shanxi Medical University, Taiyuan, China; <sup>7</sup>Shanxi Medical University, Taiyuan, China

**Contributions:** (I) Conception and design: B Li, X Ren, Z Liu; (II) Administrative support: J Wu, X Li, Y Ren; (III) Provision of study materials or patients: B Li, H Guo; (IV) Collection and assembly of data: B Li, H Guo, Y Guo, F Han; (V) Data analysis and interpretation: X Ren, X Hu, X Wen, Z Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Zhihong Liu. First Hospital of Shanxi Medical University, 56th Xinjian South Road, Taiyuan 030001, China. Email: liuzhdoc@163.com.

**Background:** To explore the relationship between the status of epidermal growth factor receptor (EGFR) and overall survival (OS) in de novo lung adenocarcinoma.

**Methods:** We retrospectively analyzed 291 lung adenocarcinoma subjects with exact EGFR status. The cases were divided into a mutant-type group (124 patients) and wild-type group (167 patients) according to the status of EGFR. The general information, OS, and possible risk factors influencing the OS were also evaluated.

**Results:** The EGFR mutation rate was 42.6% (124/291 patients), and there were statistically significant differences in gender, smoking history, and OS ( $P < 0.05$ ), but no significant difference in diagnosed age, alcohol history, TNM stage, clinical stage, and immunohistochemistry between the two groups ( $P > 0.05$ ). The most common subtypes of EGFR mutations were exon 19 and exon 21. The median OS of the total population was 30.20 months [95% confidence interval (CI): 25.94–34.46 months] and the OS in the mutant-type group was better than in the wild-type group ( $P < 0.001$ ). Cox regression demonstrated that N stage, M stage, and EGFR status were the risk factors for OS in de novo lung adenocarcinoma patients ( $P < 0.001$ ), and the relative risk were 1.398 (95% CI: 1.214–1.609), 2.427 (95% CI: 1.780–3.310), and 2.030 (95% CI: 1.528–2.699), respectively.

**Conclusions:** The OS of EGFR mutant individuals was better than that of wild-type patients in de novo lung adenocarcinoma patients. EGFR mutation may be a useful prognostic indicator in lung adenocarcinoma.

**Keywords:** Lung adenocarcinoma; epidermal growth factor receptor (EGFR); overall survival (OS)

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## Introduction

Lung cancer is the most common malignant tumor with high morbidity and mortality worldwide (1,2). Lung adenocarcinoma is the most frequent pathological type of non-small cell lung cancer (NSCLC) and carries a poor

prognosis (3). Epidermal growth factor receptor (EGFR) is a glycoprotein belonging to the ErbB family and has been shown to play an important role in tumorigenesis (4,5). EGFR mutations are mainly found in patients with lung adenocarcinoma and several clinical trials (6-8) have

confirmed that the application of EGFR tyrosine kinase inhibitors (TKIs) improves the prognosis of patients with positive EGFR mutations. Thus, EGFR-TKIs have been approved as a first-line therapeutic method for metastatic NSCLC with EGFR mutation (9). The advent of novel targeted therapies provides options for treatment strategies. However, there are few studies on the relationship between overall survival (OS) and the status of EGFR outside clinical trials. Therefore, 291 lung adenocarcinomas with known exact status of EGFR were retrospectively analyzed. The relationship between the status of EGFR and general clinical characteristics was explored in de novo lung adenocarcinoma and further investigation on the outcomes and the status of EGFR was also performed.

We present the following article in accordance with the REMARK reporting checklist (available at <http://dx.doi.org/10.21037/tcr-21-402>).

## Methods

### *Patients and clinical information*

The clinical details of 291 patients with primary lung adenocarcinoma diagnosed between January 2011 and December 2013 at the Shanxi Cancer Hospital were collected. The study was approved by the Ethics Committee of the Shanxi Cancer Hospital (ethical ID: 201835). All procedures performed in studies involving human participants followed the ethical standards of the institutional research committee of Shanxi Cancer hospital (Ethical ID: 201835) and the Helsinki declaration (as revised in 2013). Formal consent was not required for this retrospective study and the study did not involve animal experiments.

All patients were diagnosed as primary lung adenocarcinoma by either cytopathology or histopathology and EGFR status was confirmed. Patients with an unknown EGFR status or with mixed pathological types were excluded. Follow-up was provided by the Medical Records Department of our hospital. All cases were divided into a mutant-type group and wild-type group according to their EGFR status and the definition of metastatic status and TNM stage were based on the IASLC 8th TNM Lung Cancer Staging System. Initially, 337 cases were identified, and of these, 291 patients were ultimately selected. In addition, 396 individuals were excluded for the following reasons: (I) 23 patients had been treated before their EGFR status was determined; (II) 12 cases had a history of another

malignancy or mixed pathological types; (III) three cases had incomplete laboratory data; and (IV) eight individuals had incomplete follow-up data.

### *Detection of EGFR*

DNA extraction procedures of tissue specimens were performed as follows. Paraffin-embedded wax blocks were cut into four slices with 7  $\mu$ m thickness, then after dewaxing, benzol removal, and dyeing, the slices were placed into an Eppendorf tube. DNA was extracted according to the experimental steps of the QIAamp DNA FFPE Kit (Qiagen Company, Germany), then the concentration of DNA was adjusted to 20–30 ng/ $\mu$ L and stored at  $-20^{\circ}\text{C}$  to reserve.

The DNA extraction procedures of cytological specimens were as follows: Samples of lung adenocarcinoma patients scraped cancer cells were placed into an Eppendorf tube, and the number of cancer cells was not less than 200. DNA was extracted according to the instructions of the DNA extraction kit (Xiamen amoydx Technology Co., Ltd.) and stored at  $-20^{\circ}\text{C}$  to reserve.

### *Detection of EGFR gene mutation*

The primers for polymerase chain reaction (PCR) amplification and sequencing were designed by AstraZeneca (Shanghai R&D Center) and synthesized by the Shanghai Biological Company. Mutations in exons 18–21 of the EGFR gene were detected by amplification refractory mutation system (ARMS) and all experimental steps were completed according to the instructions of the ADx -EGFR detection kit.

### *Survival time*

All subjects were followed up by telephone and follow-up records and the end point was death or the last follow-up date. The survival time of the dead patients was defined as the date from diagnosis to death or last follow-up and the survival time was calculated in monthly units.

### *Statistical analysis*

All data were analyzed using SPSS 22.0 for Windows (IBM, Armonk, NY, USA). Continuous data were presented as means  $\pm$  standard deviation and were analyzed using the Student t test and categorical data were analyzed using the chi-square test or Fisher's exact test. Statistically significant

differences were defined as two-sided P values <0.05. Log-Rank test was used to assess the survival time and Cox regression was used to analyze the prognostic factors. Variables with P<0.05 in the Log-Rank test were analyzed by Cox regression.

## Results

### Basic information between the two groups

General information regarding the two groups is summarized in *Table 1*. Among involved patients, 124 had

the EGFR mutation, 167 had wild-type EGFR, and the mutation rate was 42.6% (124/291). The gender ratio was 146 males and 145 females, the median age was 58 years old, 121 cases were smokers, and 170 cases were non-smokers. Distant metastases at the initial diagnosis were present in 147 cases, 95 cases underwent surgical resection at the initial treatment, and 11 cases underwent initial treatment after neoadjuvant chemotherapy. Radiotherapy and chemotherapy were provided in 133 cases, 13 cases used TKIs, and 39 cases received best supportive treatment. The 1-, 2-, 3-, and 5-year survival rates were 75.9%,

**Table 1** Basic information between the two groups

Characteristics	EGFR		Total	P
	Mutant (N=124)	Wild (N=167)		
Age (years), mean ± SD [range]	57.52±10.21 [26–82]	59.21±11.11 [29–88]	58.49±10.75 [26–88]	0.186
Gender (n, %)				<0.001
Male	46 (37.1)	100 (59.9)	146 (50.2)	
Female	78 (62.9)	67 (40.1)	145 (49.8)	
Smoking status (n, %)				<0.001
Never smoked	87 (70.2)	83 (49.7)	170 (58.4)	
Current or previous smoker	37 (29.8)	84 (50.3)	121 (41.6)	
Drinking status (n, %)				0.399
Never drinker	111 (89.5)	144 (86.2)	255 (87.6)	
Current of previous drinker	13 (10.5)	23 (13.8)	36 (12.4)	
Tumor statement (n, %)				0.622
1	31 (25.0)	32 (19.2)	63 (21.6)	
2	43 (34.7)	59 (35.3)	102 (35.1)	
3	29 (23.4)	41 (24.6)	70 (24.1)	
4	21 (16.9)	35 (21.0)	56 (19.2)	
Nodal involvement (n, %)				0.569
0	38 (30.6)	46 (27.5)	84 (28.9)	
1	18 (14.5)	33 (19.8)	51 (17.5)	
2	39 (31.5)	45 (26.9)	84 (28.9)	
3	29 (23.4)	43 (25.7)	72 (24.7)	
Metastatic statement (n, %)				0.698
0	63 (50.8)	81 (48.5)	144 (49.5)	
1	61 (49.2)	86 (51.5)	147 (50.5)	

**Table 1** (continued)

Table 1 (continued)

Characteristics	EGFR		Total	P
	Mutant (N=124)	Wild (N=167)		
Stage (n, %)				0.550
I	22 (17.7)	20 (12.0)	42 (14.4)	
II	15 (12.1)	20 (12.0)	35 (12.0)	
III	26 (21.0)	41 (24.6)	67 (23.0)	
IV	61 (49.2)	86 (51.5)	147 (50.5)	
TTF-1 (n, %)				0.048
Negative	0 (0)	8 (12.3)	8 (8.1)	
Positive	34 (100.0)	57 (87.7)	91 (91.9)	
NaspinA (n, %)				0.199
Negative	2 (7.7)	11 (21.6)	13(16.9)	
Positive	24 (92.3)	40 (78.4)	64 (83.1)	
CK7 (n, %)				0.526
Negative	0 (0)	2 (13.3)	2 (8.7)	
Positive	8 (100.0)	13 (86.7)	21 (91.3)	
Ki67 score, mean $\pm$ SD	43.35 $\pm$ 21.13	35.97 $\pm$ 19.43	10.81 $\pm$ 20.75	0.109
Survival (n, %)				<0.001
Yes	48 (39.0)	33 (20.1)	81 (28.2)	
No	75 (61.0)	131 (79.9)	206 (71.8)	
Survival time (n, %)				<0.001
<12 months	17 (13.7)	53 (31.7)	70 (24.1)	
12–24 months	18 (14.5)	39 (23.4)	57 (19.6)	
25–36 months	24 (19.4)	18 (10.8)	42 (14.4)	
37–60 months	39 (31.5)	40 (24.0)	79 (27.1)	
$\geq$ 60 months	26 (21.0)	17 (10.2)	43 (14.8)	
Survival rate (%)				
1-year	86.3	68.3	75.9	0.024
2-year	71.8	44.9	56.3	0.387
3-year	52.4	34.1	41.9	0.254
5-year	21.0	10.2	14.8	0.770
EGFR mutations (n, %)				
Exon 18	7 (5.6)			
Exon 19	56 (45.2)			
Exon 20	4 (3.2)			
Exon 21	52 (41.9)			
Exon18 and 20	4 (3.2)			
Exon 18 and 21	1 (0.8)			

EGFR, epidermal growth factor receptor.

56.3%, 41.9%, and 14.8%, respectively, and 42, 35, 67, and 147 cases had stage I, stage II, stage III and stage IV, respectively. KRAS was detected in 93 patients, including nine mutations and 84 non-mutations.

There were no significant differences in age, drinking exposure, TNM stages, clinical stages, and immunohistochemical results between mutant-type and wild-type patients ( $P>0.05$ ). The EGFR mutation was more common in females and non-smokers ( $P<0.001$ ), and showed a survival time of between 37 and 60 months, while the survival time of patients with the EGFR wild-type was less than 12 months ( $P<0.001$ ). By the end of follow-up, among the 81 surviving patients, 48 were mutant-type and 33 were wild-type. The 1-, 2-, 3- and 5-year survival rates of mutant-type patients were 86.3%, 71.8%, 52.4%, and 21.0%, respectively and the 1-, 2-, 3- and 5-year survival rates of wild-type patients were 68.3%, 44.9%, 34.1%, and 10.2%, respectively.

#### *The subtypes of EGFR mutations*

Exon 19 mutations were the most common, accounting for 45.2% of all mutations, followed by 21 exon mutations, accounting for 41.9%. Exon 18 mutations were detected in seven cases (5.6%) and exon 20 mutations in four cases (3.2%). There were four patients with exon 18 combined with exon 20 mutation (3.2%), and one patient with exon 18 combined with exon 21 mutation (0.8%). Simultaneous mutations in both EGFR and KRAS were not detected.

#### *OS between the two groups*

By the end of follow-up, 210 patients had died. The median OS was 30.20 months (95% CI: 25.94–34.46 months), the median OS of mutant-type patients was 41.60 months (95% CI: 27.51–55.69 months), and that of the wild-type patients was 19.87 months (95% CI: 15.35–24.39 months), respectively. The OS of mutant-type patients was better than that of wild-type patients ( $P<0.001$ ). The OS in global patients and wild-type patients was significantly correlated with TNM stages and clinical stages ( $P<0.001$ ), yet the OS of mutant-type individuals was only associated with N and M stages and clinical stages ( $P<0.001$ ) and not with T stages ( $P=0.137$ ) (Table 2). To further confirm the risk factors for OS, Cox regression was performed, which included TNM stages, clinical stages, and the status of EGFR. The results showed that N stage, M stage, and EGFR mutation were risk factors for OS ( $P<0.001$ ), and the relative risk was 1.398

(95% CI: 1.214–1.609), 2.427 (95% CI: 1.780–3.310), and 2.030 (95% CI: 1.528–2.699), respectively (Figure 1).

## **Discussion**

NSCLC is prone to be diagnosed in its advanced stages when the prognosis is poor (10). EGFR belongs to the ErbB family which has tyrosine kinase activity, and its abnormal function can lead to unusual cell proliferation, adhesion, and migration variation, which promotes the invasion and metastasis of cancer cells (11). Some studies showed EGFR mutation was more likely to respond to EGFR-TKIs in lung adenocarcinomas patients and led to longer progression-free survival (PFS) (12,13). In the present study, we observed the relationship between the status of EGFR and outcomes in lung adenocarcinomas. The rate of EGFR mutations has varied in previous studies and a higher rate has been found in Asians, females, and non-smokers (14), while in Europe, the rate of EGFR mutations was only 16.6% in Spain (7) and 4.9% in Germany (15).

Studies analyzing lung adenocarcinoma patients in areas of Southeast Asia (14) showed that the mutation frequency of EGFR varied from region to region. The mutant rate of the EGFR gene in China was 50.2%, and the mutant rate in females (61.1%) was higher than that of males (44.0%), while age had no effect on the mutation of EGFR. The results of our study support these findings.

EGFR mutations are most common in lung adenocarcinomas and are associated with particular clinical features. Some researchers have analyzed the relationship between EGFR mutation and clinical and pathological features (16) and showed higher mutant rates were found in Asians, females, and non-smokers (17), which is consistent with our study. We retrospectively analyzed 291 lung adenocarcinomas with exact status of EGFR and the results showed that the mutant rate was 42.6%, and OS of mutant-type patients was better than that of wild-type patients.

Some studies have found that exon 19 and exon 21 were more common in all EGFR mutations (18,19), which is consistent with our research. However, while there was no difference in OS between exon 19 mutations and exon 21 mutations after gefitinib treatment (20), other studies have shown opposing results. The OS in patients with exon 19 deletion mutation was better than that with exon 21 L858R mutation, and first-line treatment did not affect OS (21,22). In contrast, in the present study, there was no difference in OS with each subtype of EGFR mutations. Fewer deaths occurred in the mutant-type group and the different clinical

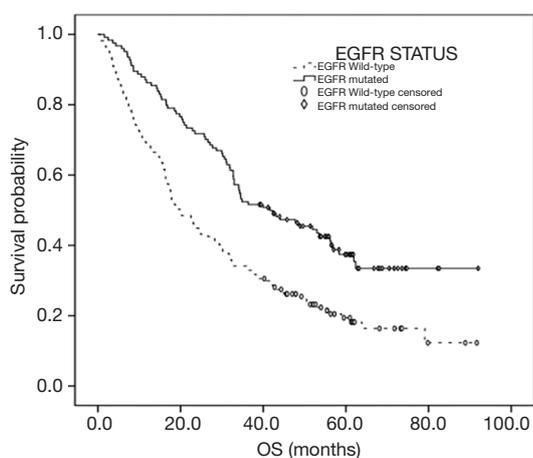
Table 2 Kaplan-Meier survival analysis

Characteristics	Total population (n=210)				EGFR wild-type (n=134)				EGFR mutant(n=76)						
	n	Median (month)	95% CI (month)	SD (month)	P	n	Median (month)	95% CI (month)	SD (month)	P	n	Median (month)	95% CI (month)	SD (month)	P
Age (years)					0.086					0.598					0.203
<60	110	32.33	28.38–36.29	2.02		66	18.80	12.80–24.81	3.06		44	48.63	32.41–64.85	8.28	
≥60	100	26.63	19.01–34.17	3.84		68	19.87	12.54–27.20	3.74		32	33.00	24.29–41.71	4.45	
Gender					0.090					0.904					0.193
Male	111	25.73	18.75–32.72	3.56		79	19.87	14.15–25.58	2.92		32	34.10	22.43–45.77	5.95	
Female	99	33.00	26.55–39.45	3.29		55	17.87	9.12–26.61	4.46		44	44.07	24.18–63.96	10.15	
Smoking status					0.173					0.964					0.508
Never smoker	119	32.00	27.32–36.69	2.39		67	18.57	10.90–26.24	3.91		52	44.07	25.07–63.07	9.69	
Current or previous smoker	91	24.37	16.68–32.05	3.92		67	19.87	15.38–24.36	2.29		24	34.10	19.72–48.48	7.34	
Drinking status					0.090					0.561					0.153
Never drinker	180	31.17	26.70–35.63	2.28		113	17.87	13.21–22.52	2.38		67	44.07	28.30–59.84	8.05	
Current of previous drinker	30	22.97	14.34–31.59	4.40		21	24.37	10.69–38.04	6.97		9	19.80	6.53–33.07	6.77	
Stage					<0.001					<0.001					<0.001
I	18	63.87				12	44.50	13.06–75.94	16.04		6				
II	17	58.90				10	56.07	32.38–79.76	12.09		7				
III	45	36.23	24.80–47.66	5.83		31	31.87	15.39–48.34	8.41		14	53.53	23.86–83.21	15.14	
IV	130	17.13	13.99–20.28	1.60		81	12.77	8.40–17.13	2.23		49	25.97	14.52–37.41	5.84	
Tumor statement					0.005					0.007					0.137
1	38	44.50	28.63–60.37	8.10		20	43.23	27.42–59.05	8.07		18	47.77	26.52–69.02	10.84	
2	72	31.70	19.77–43.63	6.09		51	17.83	14.89–20.77	1.50		21	58.37			
3	54	25.97	18.04–33.89	4.04		34	17.80	13.45–22.15	2.22		20	30.63	22.02–39.25	4.40	
4	46	18.80	12.81–24.79	3.06		29	15.67	6.78–24.55	4.53		17	33.00	30.27–35.73	1.39	
Nodal involvement					<0.001					<0.001					<0.001
0	47	56.37	42.75–69.98	6.95		31	32.63	19.89–45.37			16	61.93			
1	31	39.93	22.88–56.98	8.70		23	32.50	10.93–54.07			8				

Table 2 (continued)

Table 2 (continued)

Characteristics	Total population (n=210)					EGFR wild-type (n=134)					EGFR mutant(n=76)				
	n	Median (month)	95% CI (month)	SD (month)	P	n	Median (month)	95% CI (month)	SD (month)	P	n	Median (month)	95% CI (month)	SD (month)	P
2	64	29.77	21.44-38.09	4.25		38	19.87	12.20-27.53			26	34.10	23.25-44.95	5.54	
3	68	11.73	6.09-17.38	2.88		42	9.10	2.16-16.04			26	14.43	6.11-22.76	4.25	
Metastasis					<0.001					<0.001					<0.001
0	80	39.00-62.07	5.89			53	41.70	33.56-49.84	4.15		27				
1	130	13.99-20.28	1.60			81	12.77	8.40-17.13	2.23		49	25.97	14.52-37.41	5.84	
Mutational status					<0.001										
Wild	76	19.87	15.35-24.39	2.31											
Mutant	134	41.60	27.51-55.69	7.19											
Exon															0.134
18											2				
19											35	41.60	20.23-62.94		
20											2	25.97			
21											33	36.37	19.46-53.27		
18 and 20											3	28.67	0.00-60.55		
18 and 21											1	10.53			



**Figure 1** Kaplan-Meier Survival curve of EGFR mutated patients (continuous line) versus EGFR wild-type patients (dotted line). P value<0.001. EGFR, epidermal growth factor receptor.

treatments may have contributed to this. In the LUX-Lung6 clinical trial (23), OS in a mutant-type group was 9 months longer than that in a wild-type group. However, in a cross-sectional study of phase IV lung adenocarcinoma patients using second-generation sequencing (22), the OS of wild-type patients was better than that of mutant-type patients. In our study, the OS of both wild-type and mutant-type patients was slightly higher than that reported in clinical trials, although this disparity may be due to a loss of follow-up following premature death.

In addition, some studies (24) have revealed that the response to chemotherapy was better in EGFR mutant-type patients than that of wild-type patients, which may also lead to longer survivals. Some studies (25) demonstrated that there was no survival difference between EGFR mutations treated with TKIs and those which were not. However, patients with mutant-type usually choose surgery or radiotherapy and chemotherapy as first-line treatment, and if these treatments fail or the disease progresses, EGFR-TKIs treatment can be used to prolong the OS of these patients. At the same time, with the wide application of TKIs and immunotherapy, there are more choices for a therapeutic strategy. Finally, the economic status and desire for treatment of patient's is also related to OS. Although most EGFR mutations occurred in non-smoking women with lung adenocarcinoma, there was still no difference in OS. In this study, N stage, M stage, clinical staging, and EGFR mutation were the risk factors of OS in lung adenocarcinomas.

There are some limitations to our study. Firstly, the nature of retrospective studies causes selection bias. In addition, specific treatment methods and other gene mutations were not included in this study. Finally, because of the heterogeneity of malignancy, multi-center studies using larger cohorts are required to confirm the results.

In conclusion, EGFR mutation is more likely to be detected in adenocarcinomas, females, and non-smokers. In addition to the clinical stage, EGFR mutation is a prognostic factor in lung adenocarcinoma.

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### Footnote

*Reporting Checklist:* The authors have completed the REMARK reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-21-402>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/tcr-21-402>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-21-402>). 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. The study was approved by the Ethics Committee of the Shanxi Cancer Hospital (ethical ID: 201835). All procedures performed in studies involving human participants followed the ethical standards of the institutional research committee of Shanxi Cancer hospital (Ethical ID: 201835) and the Helsinki declaration (as revised in 2013). Formal consent was not required for this retrospective study and the study did not involve animal experiments.

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