Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Clinical outcomes and radiation pneumonitis after concurrent EGFR-tyrosine kinase inhibitors and radiotherapy for unresectable stage III non-small cell lung cancer

Kunpeng Xu[1], Jun Liang[2], Tao Zhang[1], Zongmei Zhou[1], Dongfu Chen[1], Qinfu Feng[1], Zefen Xiao[1], Zhouguang Hui[1], Jima Lu[1], Xin Wang[1], Lei Deng[1], Wenyang Liu[1], Jianyang Wang[1], Yirui Zhai[1], Jie Wang[3], Nan Bi[1†] & Luhua Wang[1,2†]

1 Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

2 Department of Radiation Oncology, National Cancer Center/ Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

3 Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Keywords

ErbB-1; non-small-cell lung carcinoma; protein kinase inhibitors; radiation pneumonitis; radiotherapy.

Correspondence

Luhua Wang, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 113 Baohe Road, Longgang District, Shenzhen, Guangdong Province 518116, China.
Tel: +86 755 6661 8228
Fax: +86 755 6661 8154
Email: wlhwq@yahoo.com

Nan Bi, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College,
No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China.
Tel: +86 10 8778 8995
Fax: +86 10 8771 6559
Email: binan_email@163.com

†These authors contributed equally to this paper.

Received: 19 October 2020;
Accepted: 14 December 2020.

doi: 10.1111/1759-7714.13816

Thoracic Cancer **12** (2021) 814–823

Abstract

Background: Concurrent epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) with radiotherapy in patients with *EGFR*-mutant unresectable stage III non-small cell lung cancer (NSCLC) might improve survival. However, both treatments carry a potential risk of pneumonitis.

Methods: Between May 2012 and December 2017, patients with unresectable stage III NSCLC treated with concurrent radiotherapy and EGFR-TKI were enrolled in this retrospective study. The baseline characteristics were evaluated to determine correlations with toxicity development.

Results: Among 45 eligible patients, 20 (44.4%) had an *EGFR* mutation and 44 (97.8%) received 50–66 Gy of radiotherapy. The median follow-up was 62.7 months. The median progression free survival (PFS) and overall survival (OS) for patients with *EGFR*-mutations were 27.9 (95% CI: 18.7–37.2) and 49.7 (95% CI: 27.7–71.8) months, and 13.8 (95% CI: 8.8–18.9) and 31.1 (95% CI: 9.8–52.4) months for *EGFR* wild-type/unknown patients. A total of 17 patients (37.7%) developed radiation pneumonitis/pneumonitis (14 grade 2, 3 grade 3). In 16 patients, pneumonitis occurred within the radiation field and one patient had bilateral pneumonitis. The median time from the initial radiotherapy to pneumonitis was 74 days. Logistic regression analysis revealed a trend between the time of EGFR-TKI and the development of G2+ pneumonitis. For late toxicity, only two patients had G2+ fibrosis. The daily dyspnea symptoms of patients with G2+ pneumonitis recovered significantly after the phase of pneumonitis ($P = 0.007$).

Conclusions: Combined EGFR-TKI and radiotherapy showed favorable survival in *EGFR*-mutant patients with inoperable stage III NSCLC, with a 6.7% incidence of grade 3 radiation pneumonitis/pneumonitis, despite a higher incidence of mild-to-moderate radiation pneumonitis.

Key points

Significant findings of the study: We evaluated the outcomes and radiation pneumonitis after EGFR-TKI during interval radiotherapy. EGFR-TKI plus radiotherapy increased survival in patients with *EGFR*-mutant inoperable stage III NSCLC. The mild-to-moderate radiation pneumonitis incidence increased but no grade 4–-5 adverse events occurred.

What this study adds: The combination of EGFR-TKI and radiotherapy might carry a risk of pneumonitis; however, there are limited data concerning dose constraints. Our results showed a slightly higher incidence of mild or moderate radiation pneumonitis by strict dose limitation.

Introduction

Approximately 30% of non-small lung cancer (NSCLC) patients have locally advanced disease upon initial diagnosis. Despite ongoing efforts to improve the survival in this cohort, concurrent chemoradiotherapy (CRT) remains the standard care. However, the five-year overall survival (OS) rate for these patients is only 20%–30%.[2,3]

Activating mutations of *EGFR* (encoding the epidermal growth factor receptor, also known as ERBB1) are associated with a high response to targeted therapy using EGFR-tyrosine kinase inhibitors (TKIs), and have drastically changed the decision-making for patients with advanced NSCLC.[4,5] For unselected patients, adding EGFR-TKIs to radiotherapy (RT) failed to demonstrate superior survival related to historical data of CRT.[6,7] In patients with *EGFR*-mutations, a multicenter phase II trial showed that concurrent erlotinib and radiotherapy provided a significant improvement in progression free survival (PFS) compared with CRT.[8] However, the lung toxicity of the combination of RT and EGFR-TKI is a particular concern. A preliminary study of concurrent thoracic RT and erlotinib showed that 37.5% of patients had grade 2 or higher of pneumonitis after treatment, including 8.3% grade 3 and 12.5% fatal (grade 5) pneumonitis.[9]

Therefore, we conducted a retrospective analysis in which we collected information from patients with unresectable stage III NSCLC treated with concurrent radiotherapy and EGFR-TKI, to assess the outcomes, especially focusing on lung toxicities, for this combined strategy.

Methods

Patient eligibility

We retrospectively reviewed the data of patients with stage III NSCLC treated with concurrent radiotherapy and EGFR-TKI from our institution between May 2012 and December 2017. Eligibility required patients (age > 18 years) to have histologically and cytologically, or both, confirmed unresectable locally advanced disease. The patients included were unsuitable for, or had refused, concurrent chemoradiotherapy. Patients who received reradiation or surgical treatment were ineligible for inclusion. Furthermore, patients whose disease was complicated by a second malignancy must have been cured for at least five years. This study was approved by the ethical review boards of our institution.

The following information was gathered for analysis: Patient characteristics (age, sex, the Charlson Comorbidity Index (CCI), smoking history, Karnofsky performance status (KPS), tumor information (stage status, location, histology, and type of *EGFR* mutation), and treatment details (radiation, EGFR-TKI, and chemotherapy).

Activating *EGFR* mutations were detected in tissue biopsy samples using polymerase chain reaction (PCR) amplification. The *EGFR* status was assessed in tissue specimens before treatment.

Treatment

All patients underwent intensity-modulated radiation therapy (IMRT) or volumetric intensity-modulated arc therapy (VMAT).[10]All patients received integrated boost IMRT (SIB-IMRT) or conventional IMRT. The gross tumor volume included the primary disease as well as any involved regional lymph nodes, which were defined as those with a short-axis diameter of at least 1 cm on a computed tomography (CT) scan or with high fluorodeoxyglucose uptake on a positron emission tomography (PET)–CT scan. The clinical tumor volume included the primary tumor plus a margin of 0.6 to 0.8 cm, with ipsilateral hilum and mediastinal nodal stations involved. The mean dose to the lungs (MLD) was optimally 17 Gy or less; the lung volumes, minus the gross tumor volume, receiving more than 20 Gy (V20) and 30 Gy (V30) were limited to less than 30% and less than 20%, respectively. The esophageal volume receiving more than 50 Gy was limited to less than 50% (V50 < 50%) and the maximum dose (Dmax) received less than 105% of the prescription dose. The heart volume receiving more than 30 and 40 Gy was limited to less than 40% and less than 30 (V30 < 40%, V40 < 30%), respectively. The spinal cord Dmax was less than 40 Gy (Dmax < 40 Gy), and the Dmax of cord planning organ at risk volume (PRV) was less than 45 Gy (Dmax < 45 Gy).

EGFR-TKIs were administered to patients during the interval of radiotherapy, and those undergoing induction EGFR-TKI or chemotherapy and concurrent chemotherapy treatment were also eligible for inclusion. The EGFR-TKIs administered consisted of gefitinib, icotinib, and erbtinib. Platinum-based doublet agent regimens were used for concurrent or sequential chemotherapy, including etoposide,

Table 1 Patient and tumor characteristics of the overall cohort

Characteristics	Total *N* = 45	*EGFR*-mutant *N* = 20	*EGFR*-mild/unknown *N* = 25
Age			
Median	63	62	65
Range	42–79	42–79	45–79
≥65	21 (46.7)	8 (40.0)	13 (52.0)
<65	24 (53.3)	12 (60.0)	12 (48.0)
Sex			
Female	16 (35.6)	13 (65.0)	3 (12.0)
Male	29 (64.4)	7 (35.0)	22 (88.0)
Sides			
Right	25 (55.6)	12 (60)	13 (52.0)
Left	20 (44.4)	8 (40)	12 (48.0)
Location			
Upper	29 (64.4)	13 (65.0)	16 (64.0)
Middle/lower	15 (33.3)	7 (35)	8 (32,0)
Main bronchus	1 (2.2)	0	1 (4.0)
KPS			
≥80	43 (95.6)	20 (100)	23 (92.0)
<80	2 (4.4)	0	2 (8.0)
Smoking			
Yes	26 (57.8)	4 (20.0)	22 (88.0)
No	19 (42.2)	16 (80.0)	3 (12.0)
Loss weight (≥5%)			
Yes	8 (17.8)	2 (10.0)	6 (24.0)
No	37 (82.2)	18 (90.0)	19 (76.0)
CCI			
0	30 (66.7)	15 (75.0)	15 (60.0)
1	13 (28.9)	4 (20.0)	9 (36.0)
2	2 (4.4)	1 (5.0)	1 (4.0)
PET-CT staging			
Yes	24 (53.3)	13 (65.0)	11 (44.0)
No	21 (46.7)	7 (35.0)	14 (56.0)
Stage (seventh)			
IIIA	14 (31.1)	6 (30.0)	8 (32.0)
IIIB	31 (68.9)	14 (70.0)	17 (68.0)
EGFR mutation			
19DEL	9 (20.0)	9 (45.0)	0
L858R	10 (22.2)	10 (50.0)	0
21L861Q + 18G719X	1 (2.2)	1 (5.0)	0
Histology			
Adenocarcinoma	29 (64.4)	20 (100)	9 (36.0)
Squamous	15 (33.3)	0	15 (60.0)
NSCLC	1 (2.2)	0	1 (4.0)
Baseline PFT (*N* = 40)			
FEV1	1.97 (0.8–3.7)	1.96 (0.80–3.62)	1.98 (0.83–3.87)
FVC	2.50 (1.05–4.65)	2.46 (1.2–4.65)	2.50 (1.05–4.29)

CCI, Charlson comorbidity index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.; KPS, Karnofsky performance status; PFT, pulmonary function test.

paclitaxel, pemetrexed, and gemcitabine (only for sequential CRT).

Evaluation and follow-up

Follow-up evaluation of all patients including symptom assessment, physical examination, and CT was performed in the first months after the end of radiotherapy, sequentially every 2–3 months during the first two years, and every six months thereafter.

The National Cancer Institute Common Toxicity criteria (NCICTC) version 4.0 was used to assess treatment-related toxicities including radiation pneumonitis and fibrosis. The modified Medical Research Council (mMRC) questionnaire

Table 2 Treatment details of the overall cohort

Characteristics	Overall	*EGFR*-mutant	*EGFR*-mild/unknown
Radiotherapy dose (Gy)			
Median (range)	60.0	60.0	60.0
Range	34.0–66.0	50.0–66.0	34.0–66.0
GTV volume (mL)			
Median (range)	29.18	22.09	80.63
Range	2.57–366.26	2.57–98.16	3.58–366.26
PTV volume (mL)			
Median	431.86	370.62	466.93
Range	191.40–846.66	191.40–497.81	204.39–846.66
V5 (%)			
Median	55.2	58.3	51.7
Range	35.3–83.0	41.2–83.0	35.3–79.7
V20 (%)			
Median	24.3	25.4	23.6
Range	10.2–29.10	18.5–29.1	10.2–28.8
V30 (%)			
Median	18.5	19.1	18.2
Range	3.5–22.7	15.7–22.7	3.5–20.4
MLD (Gy)			
Median	14.83	15.58	13.88
Range	7.92–18.40	11.86–18.40	7.92–16.61
Induction chemotherapy			
Yes	21 (46.7)	7 (35.0)	14 (56.0)
No	24 (53.3)	13 (65.0)	11 (44.0)
Consolidation chemotherapy			
Yes	3 (6.7)	1 (5.0)	2 (8.0)
No	42 (93.3)	19 (95.0)	23 (92.0)
The cycle of chemotherapy			
≥4	16 (35.6)	4 (20)	12 (48.0)
<4	29 (64.4)	16 (80.0)	13 (52.0)
Technology			
IMRT	33 (73.3)	14 (70.0)	19 (76.0)
VMAT	12 (26.7)	6 (30.0)	6 (24.0)
Induction EGFR-TKI			
Yes	11 (24.4)	8(40)	2 (8.0)
No	34 (75.6)	12 (60)	23 (92.0)
Consolidation EGFR-TKI			
Yes	22 (48.9)	19 (95.0)	22 (88.0)
No	23 (51.1)	1 (5.0)	3 (12.0)
Time of EGFR-TKI concurrent with RT (days)			
Median	40	39	40
Range	10.0–51.0	10–47	10–51
Total time of EGFR-TKI (months)			
Median	2.1	28.4	1.34
Range	0.3–79.4	1.33–79.4	0.33–49.9
EGFR-TKI			
Gefitinib	36 (80.0)	14 (70.0)	22 (88.0)
Icotinib	8 (17.8)	5 (25.0)	3 (12.0)
Erlotinib	1 (2.2)	1 (5.0)	0

GTV, Gross target volume; MLD, mean lung dose; PTV, Planning target volume; V5, V20, V30, The volume of normal lung receiving >5, 20, 30 Gy.

with grade 0–4 scales (mild to severe symptom) was used to evaluate the extent of dyspnea symptoms.[11,12]

PFS was calculated from the time of diagnosis to death, progression, or most recent follow-up. OS was defined as the period between diagnosis initiation and death, or last follow-up if alive. Locoregional failure was defined as involved lobe and/or regional lymph node progression.

Table 3 Relevant toxicities of the overall cohort

Toxicity	Overall (%)	Grades 2 (%)	Grades 3 (%)	Grades 4 (%)	Grades 5 (%)
Neutropenia	6 (13.3)	5 (11.1)	1 (2.2)	0	0
Thrombocytopenia	1 (2.2)	1 (2.2)	0	0	0
ALT/AST elevated	1 (2.2)	0	1 (2.2)	0	0
Nausea and vomiting	4 (8.9)	3 (6.7)	1 (2.2)	0	0
Diarrhea	1 (2.2)	0	1 (2.2)	0	0
Pneumonitis	17 (37.7)	14 (31.1)	3 (6.7)	0	0
Pneumonia	4 (8.9)	3 (6.6)	1 (2.2)	0	0
Radiation dermatitis	1 (2.2)	1 (2.2)	0	0	0
Radiation esophagitis	11 (24.4)	10 (22.2)	1 (2.2)	0	0

Statistical analysis

Data were compared via chi-squared and *t*-tests or non-parametric Mann–Whitney U tests. The analysis of the lung toxicity grade included Pearson's chi-squared test of independence, as well as logistic regression analysis. PFS, OS, and follow-up time were assessed using Kaplan–Meier analysis. All tests were two-sided. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 45 patients with NSCLC were included in this study. The median age at diagnosis was 63 years (range: 42–79). Among them, 29 (64.4%) were male, and 26 (57.8%) were current or former smokers. A total of 14 (31.1%) patients presented with stage IIIA disease and 31 (68.9%) patients presented with stage IIIB disease. One patient had high grade neuroendocrine tumors and 29 (64.4%) patients had adenocarcinoma.

In total, 29 (64.4%) patients had undergone *EGFR* testing before treatment and among them, 20 (44.4%) had *EGFR* mutations. All patients with *EGFR* mutations had adenocarcinoma. Among these 20 patients, nine (45.0%) had an exon 19 deletion, 10 (50.0%) had L858R mutation, and one (5.0%) had a compound 21-L861Q + 18-G719X mutation. There were 16 (35.6%) patients including three with adenocarcinomas in which insufficient specimens were provided and these were not subjected to gene testing. The patient characteristics are shown in Table 1.

Treatment

A total of 21 (46.7%) patients received induction chemotherapy and 11 (24.4%) received induction EGFR-TKI before radiotherapy. There were 33 (73.3%) patients who received IMRT and 12 (26.7%) who received VMAT. A total of 10 (22.2%) patients received SIB-IMRT, and 44 (97.8%) patients received ≥50 Gy. In one patient with grade 3 infectious pneumonia, RT was discontinued at 34 Gy. Only one patient received concurrent CRT and another received concurrent RT and EGFR-TKI.

The MLD was 14.83 Gy (range: 7.92–14.80 Gy). The median volume of normal lung receiving >5 Gy (V5) was 55.2% (range: 35.3%–83.0%), V20 was 24.3% (range: 10.2%–29.1%), and V30 was 18.5% (range: 3.5%–22.7%). The median volume of GTV was 29.18 mL (range: 2.57–366.26 mL), and the median volume of PTV was 431.86 mL (range 191.40–846.66 mL). The information regarding treatment is shown in Table 2.

Toxicity

The grade ≥ 2 adverse events are summarized in Table 3. Grade 2/3 neutrophils/granulocytes were observed in six (13.3%) patients. Grade 2/3 nausea and vomiting were reported in four (8.8%) patients. A total of 11 (24.4%) patients suffered from grade 2/3 radiation esophagitis, and the median time from the initial radiotherapy to radiation esophagitis was 27 days (range: 19–48). There was no grade 4 or higher related adverse events.

With regard to lung toxicity, 17 (37.7%) patients developed radiation pneumonitis/pneumonitis of grade 2 or higher (14 grade 2, 3 grade 3, and no grade 5), and in most patients (16) the pneumonitis occurred within the radiation field and only one patient had bilateral pneumonitis. The median time from the beginning of RT to diagnosis of pneumonitis was 74 days (range: 42–156) days. Two patients who developed pneumonitis exceeded 90 days after the end of RT. Data for the patients with grade 3 pneumonitis are shown in Table S1 and Figure S1.

As shown in Table 4, selected patient, tumor, and treatment characteristics, such as age, sex, smoking, CCI, stage, *EGFR*-mutation, prescribed dose, dosimetry parameters, and time of EGFR-TKI were evaluated using univariate logistic regression analysis to determine their impact on the development of grade 2+ pneumonitis. We did not identify a significant correlation between dose volumes

Table 4 Risk analysis of the incidence of pneumonitis for EGFR-TKI and radiotherapy

Characteristics	Grades 0–1	Grades 2–3	*P*-value*
Patients			
Age			0.677
≥65	12 (42.9)	9 (52.9)	
<65	16 (57.1)	8 (47.1)	
Sex			0.977
Female	10 (35.7)	6 (35.3)	
Male	18 (64.3)	11 (64.7)	
Sides			0.373
Right	17 (60.7)	8 (47.1)	
Left	11 (39.3)	9 (52.9)	
Location			0.504
Upper	17 (60.7)	12 (70.6)	
Other location	11 (39.3)	5 (29.4)	
KPS			0.718
≥80	27 (96.4)	16 (94.1)	
<80	1 (3.6)	1 (5.9)	
Smoking			0.609
Yes	17 (60.7)	9 (52.9)	
No	11 (39.3)	8 (47.1)	
CCI			0.237
0	21 (75.0)	9 (52.9)	
1–2	7 (25.0)	8 (47.1)	
Tumor			
Stage[a]			
IIIA	10 (35.7)	4 (23.5)	0.395
IIIB	18 (64.3)	13 (76.5)	
EGFR mutation			0.783
Yes	12 (42.9)	8 (47.1)	
No/unknown	16 (57.1)	9 (52.9)	
Adenocarcinoma			0.540
Yes	19 (67.9)	10 (58.8)	
No	9 (32.1)	7 (41.2)	
Treatment			
Radiation dose (Gy)			0.387
≥60	20 (71.4)	10 (58.8)	
<60	8 (28.6)	7 (41.2)	
GTV, mL, median	27.07	59.79	0.341
PTV, mL, median	430.72	448.02	0.518
V5, %, median	54.9	56.8	0.815
V20, %, median	24.2	25.2	0.957
V30, %, median	19.3	18.7	0.398
MLD, mL, median	1447	1492.5	0.832
The cycle of chemotherapy			0.504
≥ 4	11 (39.3)	5 (29.4)	
< 4	17 (60.7)	12 (70.6)	
Time of EGFR-TKI concurrent with RT (days)	39	41	0.982
Total time of EGFR-TKI (Months)	1.78	7.5	0.095

*For logistic regression. [a]Tumor stage was determined according to the American Joint Committee on Cancer, seventh edition. CCI, Charlson comorbidity index; GTV, gross target volume; KPS, Karnofsky performance status; MLD, mean lung dose; PTV, planning target volume; V5, V20, V30, The volume of normal lung receiving >5, 20, 30 Gy.

(MLD, V20, V30, and V5) and the development of G2+ pneumonitis. A trend was found between the time of EGFR-TKI and the development of G2+ pneumonitis ($P = 0.095$).

For late lung toxicity, only two patients developed G2+ fibrosis based on the CT, both of whom received long-term consolidation EGFR-TKI. The total time of application of EGFR-TKI was 52.9 months and 79.4 months, respectively.

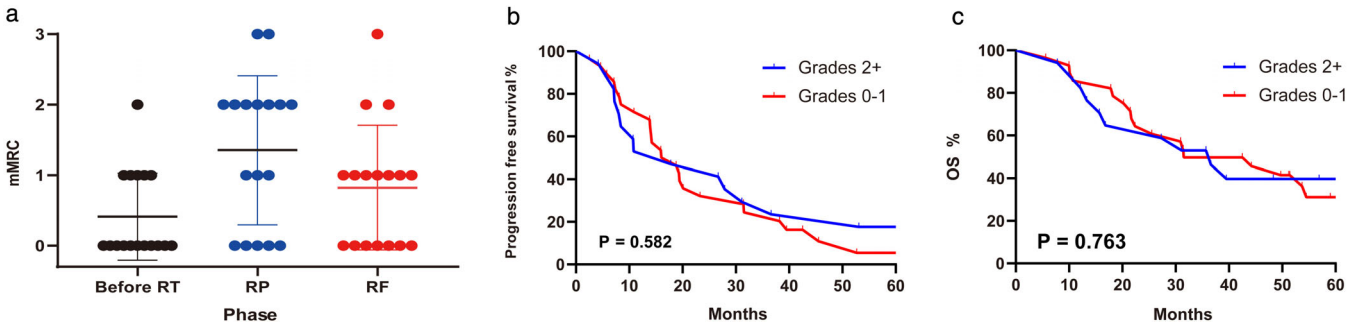

Figure 1 (**a**) The modified Medical Research Council (mMRC) scores of the 17 patients with radiation pneumonitis of grade 2 or higher in different phases. RT, radiotherapy; RP, radiation pneumonitis; RF, radiation fibrosis. (**b**, **c**) The progression-free survival (PFS) and overall survival (OS) for grades 2+ and grades 0–1 radiation pneumonitis/pneumonitis.

However, both patients achieved good survival and were still alive with OS 73.7 and 80.1 months, respectively, at the end of follow-up. The mMRC scale was used to evaluate symptoms of daily dyspnea. As shown in Figure 1a, patients who developed G2+ pneumonitis reported a significantly higher score compared with the baseline score (P = 0.024). The mMRC score then recovered significantly after the phase of pneumonitis (P = 0.007), which suggested only mild late symptoms of dyspnea remained.

Survival and failure patterns

The median follow-up was 62.7 months (interquartile range [IQR] 51.4–74.2 months). A total of 36 (80.0%) patients developed tumor recurrence after treatment and 29 (64.4%) patients died. Among the patients who died, four died of other causes and 25 died as a result of their cancer. The median PFS and OS of the overall cohort were 17.8 (95% confidence interval [CI]:11.6–24.5) and 36.6 (95% CI: 20.5–52.7) months, respectively. The patients with *EGFR*-mutations had a median PFS of 27.9 (95% CI: 18.7–37.2) months and an OS of 49.7 months (95% CI: 27.7–71.8), respectively. The median PFS and OS of the patients with *EGFR* wild-type/unknown was 13.8 months (95% CI: 8.8–18.9) and 31.1 months (95% CI: 9.8–52.4) months, respectively. Neither OS nor PFS were different between patients with G2+ radiation pneumonitis or those without (P = 0.763 for OS and P = 0.582 for PFS, Fig 1b,c).

Among patients with *EGFR*-mutations, the only distant failure was most prominent at the first site of progression (65%) relative to the only locoregional progression (10.0%). However, distant (32.0%) and locoregional failure (40.0%) were also common sites of progression for patients with EGFR-wild-type/unknown.

Table 5 Studies of concurrent EGFR-TKI and radiotherapy for stage III/IV non-small cell lung cancer (NSCLC)

Study	Phase	Number	Stage	EGFR-TKIs	Radiotherapy dose (Gy)	Grade 2 pneumonitis	Grade 3 pneumonitis	Grades 4–5 pneumonitis
Ready *et al.*[6]	II	60	III	Gefitinib	66/2	NR	4 (6.7)	5 (8.3)
Niho *et al.*[7]	II	38	III	Gefitinib	60/2	1 (2.6)	1 (2.6)	0
Komaki *et al.*[15]	II	46	III	Erlotinib	63/2	5 (10.9)	2 (4.3)	1 (2.2)
Okamoto *et al.*[24]	Prospective	9	III	Gefitinib	60/2	0	1 (11.1)	0
Center *et al.*[25]	I	16	III	Gefitinib	70/2	NR	1 (6.25)	2 (12.5)
Antonin *et al.*[26]	II	16	III	Gefitinib	66/2	NR	NR	1 (6.3)
Lilenbaum *et al.*[27]	II	75	III	Erlotinib	66/2	NR	1 (1.3)	0
Wang *et al.*[28]	Prospective	26	III/IV	Gefitinib/ erlotinib	42–82/2	NR	1(4)	0
Zhuang *et al.*[9]	Prospective	24	III/V	Erlotinib	46–66/2	4 (16.7)	2 (8.3)	3 (12.5)
Pooled data	-	310	-	-	-	10.3	4.2	3.9

Discussion

The results of the present study revealed superior survival in patients with *EGFR*-mutations treated with combination EGFR-TKI and radiotherapy and patients had comparable outcomes to those with *EGFR*-wild-type/unknown; however, the mild or moderate grade radiation pneumonitis/pneumonitis reported might be a cause for concern.

Our results showed that the strategy of adding EGFR-TKI to radiotherapy to increase survival is feasible. Compared to treatment with first-generation EGFR-TKIs, treatment with second-generation targeted drugs (such as dacomitinib) and third-generation osimertinib prolonged PFS by 5.5 and 8.7 months, respectively. The median PFS and OS of patients treated with osimertinib increased to 18.7 and 38.6 months, respectively.[13,14] Treatment with a combination of EGFR-TKI with radiotherapy is essential in patients with locally advanced NSCLC, and the strategy might be a promising choice to treat those patients with locally advanced NSCLC who have *EGFR*-mutations. A previous single-arm phase II study provided the first indication that combining erlotinib and chemoradiation could increase OS in local advanced NSCLC (median OS 36.5 months, five-year OS, 35.9%); however, the PFS failed to meet expectations.[15] A stratified phase II trial, CALGB 30106, showed that the survival of a poor-risk cohort treated with sequential chemoradiation with gefitinib was favorable; however, the outcomes for the good-risk group, including those with *EGFR*-mutations, was unsatisfactory.[6] Unfortunately, compared with the historical data from trials using traditional chemoradiation, the above results of radiation and EGFR-TKI failed to improve survival in patients with wild-type *EGFR* or *EGFR* status unknown.[16,17] A phase II trial using concurrent erlotinib with radiotherapy compared with EP (etoposide and cisplatin) regimen showed significant and superior PFS (24.5 vs. 9.0 months, $P < 0.001$) in patients with *EGFR*-mutations.[8] In our study, the combination of EGFR-TKIs and radiotherapy also achieved a promising PFS (27.9 months) for the *EGFR*-mutation subcohort, and the OS was 49.7 months. However, the survival in *EGFR* wild-type/unknown was similar to that in the above- mentioned trials.

However, the related lung toxicity was a cause for concern. Based on some large-scale reports, the incidence of interstitial lung disease (ILD) induced by gefitinib was 3.5%–5.8% in Asian patients.[18,19] More importantly, ILD was associated with higher grade radiation pneumonitis (grade > 2) in patients receiving radiotherapy.[20] Despite the unclear potential internal mechanism, pulmonary interstitial changes might be the primary cause of radiation pneumonitis after radiotherapy and EGFR-TKI. In a group of 145 patients with *EGFR* mutations with oligometastatic NSCLC, radiation pneumonitis was induced by consolidation radiotherapy followed by EGFR-TKIs in 7%.[21] Moreover, life-threatening pneumonitis has also been observed in several studies. A phase II trial of concurrent EGFR-TKIs and radiotherapy (54–60 Gy) for patients with advanced NSCLC with *EGFR* mutations showed that grade 3 and fatal radiation pneumonitis occurred in 10%.[22] A previous prospective study researched the prevalence of radiation pneumonitis in patients with NSCLC treated with concurrent radiotherapy and erlotinib. Grade 2 or higher radiation pneumonitis occurred in 37.5% (9/24) of patients, grade 3 in 8.7%, and three (12.5%) developed grade 5 radiation pneumonitis.[9] However, bilateral imaging changes occurred in these three patients with fatal pneumonitis, and not confined to the radiation yield. More importantly, the lung-related radiation dose parameters of the patients who died did not exceed the routine dose limits. The risk analysis from this trial revealed that the V20 > 22%,v30 > 17% was associated with increased radiation pneumonitis.[23] These previous analyses indicate that grade 3 pneumonitis rates occurred in 1.3%–11.1% (pooled rate: 4.2%) of patients, with an incidence of grade 4 or higher pneumonitis of 2.2%–12.5% (pooled rate: 3.9%, Table 5). According to strict dose limits in our series, 37.7% of patients developed symptomatic radiation pneumonitis (grades 2+) and 6.7% had severe (grade 3) pneumonitis. Furthermore, pneumonia (grades 2+) was also observed in 8.9% patients, However, no grade 4–5 adverse events and limited late lung toxicity were observed. Overall, our results confirmed that we should pay careful attention to pulmonary toxicity when combining radiotherapy and EGFR-TKIs to treat NSCLC. The risk factors of severe pneumonitis should be further explored in prospective trials.

The present study had several limitations. First, the findings were restricted by the single institution and retrospective nature of the study. Furthermore, the prevalence of *EGFR* mutations in locally advanced NSCLC limited the size of the sample.[29,30] Our findings should be further verified by a large-scale and multicenter cohort study. Importantly, the application of *EGFR*-mutation testing is not routinely recommended in squamous cell lung cancer. Therefore, we could not acquire the information for all patients with an *EGFR* mutation. Finally, the clinical decision-making concerning EGFR-TKIs may differ according to the doctor or the patient's personal situation. For example, compared with gefitinib therapy, erlotinib is associated with a lower incidence of ILD.[31] Similarly, our study also showed that most radiation pneumonitis was associated with gefitinib therapy (14/17, 82.4%).

In conclusion, we explored the survival and toxicity of radiotherapy combined with EGFR-TKI. Combined EGFR-TKI and radiotherapy were associated with superior

survival in patients with *EGFR*-mutations with inoperable stage III NSCLC. These patients experienced a slightly higher incidence of mild or moderate radiation pneumonitis. Overall, applying EGFR-TKI during interval radiotherapy should be further assessed and studied in prospective research.

Acknowledgments

This work was supported by the CAMS Innovation Fund for Medical Sciences (2017-I2M-1-009), the Beijing Hope Run Special Fund of Cancer Foundation of China (LC2018A04), and the Sanming Project of Medicine in Shenzhen (SZSM201612063).

Disclosure

All authors have no conflict of interest to disclose.

References

1 Yang P, Allen MS, Aubry MC *et al.* Clinical features of 5,628 primary lung cancer patients: Experience at Mayo Clinic from 1997 to 2003. *Chest* 2005; **128** (1): 452–62.
2 Yamamoto N, Nakagawa K, Nishimura Y *et al.* Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan thoracic oncology group WJTOG0105. *J Clin Oncol* 2010; **28** (23): 3739–45.
3 Aupérin A, Le Péchoux C, Rolland E *et al.* Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28** (13): 2181–90.
4 Lynch TJ, Bell DW, Sordella R *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350** (21): 2129–39.
5 Fukuoka M, Wu YL, Thongprasert S *et al.* Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011; **29** (21): 2866–74.
6 Ready N, Jänne PA, Bogart J *et al.* Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: Cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. *J Thorac Oncol* 2010; **5** (9): 1382–90.
7 Niho S, Ohe Y, Ishikura S *et al.* Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: A multicenter feasibility study (JCOG 0402). *Ann Oncol* 2012; **23** (9): 2253–8.
8 Xing L, Wu G, Wang L *et al.* Erlotinib vs etoposide/cisplatin with radiotherapy in unresectable stage III epidermal growth factor receptor mutation-positive non-small-cell lung cancer: A multicenter, randomized, open-label, phase 2 trial. *Int J Radiat Oncol Biol Phys* 2020. https://doi.org/10.1016/j.ijrobp.2020.11.026.
9 Zhuang H, Yuan Z, Chang JY *et al.* Radiation pneumonitis in patients with non-small-cell lung cancer treated with erlotinib concurrent with thoracic radiotherapy. *J Thorac Oncol* 2014; **9** (6): 882–5.
10 Liang J, Bi N, Wu S *et al.* Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: A multicenter randomized phase III trial. *Ann Oncol* 2017; **28** (4): 777–83.
11 Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54** (7): 581–6.
12 Suzuki Y, Karayama M, Uto T *et al.* Assessment of immune-related interstitial lung disease in patients with NSCLC treated with immune checkpoint inhibitors: A multicenter prospective study. *J Thorac Oncol* 2020; **15** (8): 1317–27.
13 Ramalingam SS, Vansteenkiste J, Planchard D *et al.* Overall survival with Osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 2020; **382** (1): 41–50.
14 Soria JC, Ohe Y, Vansteenkiste J *et al.* Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018; **378** (2): 113–25.
15 Komaki R, Allen PK, Wei X *et al.* Adding Erlotinib to chemoradiation improves overall survival but not progression-free survival in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2015; **92** (2): 317–24.
16 Senan S, Brade A, Wang L-H *et al.* PROCLAIM: Randomized phase III trial of Pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2016; **34** (9): 953–62.
17 Ahn JS, Ahn YC, Kim J-H *et al.* Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol* 2015; **33** (24): 2660–6.
18 Chang S-C, Chang C-Y, Chang S-J *et al.* Gefitinib-related interstitial lung disease in Taiwanese patients with non-small-cell lung cancer. *Clin Lung Cancer* 2013; **14** (1): 55–61.
19 Ando M, Okamoto I, Yamamoto N *et al.* Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006; **24** (16): 2549–56.

20 Goodman CD, Nijman SFM, Senan S *et al.* A primer on interstitial lung disease and thoracic radiation. *J Thorac Oncol* 2020; **15** (6): 902–13.
21 Xu Q, Zhou F, Liu H *et al.* Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs. *J Thorac Oncol* 2018; **13** (9): 1383–92.
22 Zheng L, Wang Y, Xu Z *et al.* Concurrent EGFR-TKI and thoracic radiotherapy as first-line treatment for stage IV non-small cell lung cancer harboring EGFR active mutations. *Oncologist* 2019; **24** (8): 1031–e1612.
23 Zhuang H, Hou H, Yuan Z *et al.* Preliminary analysis of the risk factors for radiation pneumonitis in patients with non-small-cell lung cancer treated with concurrent erlotinib and thoracic radiotherapy. *Onco Targets Ther* 2014; **7**: 807–13.
24 Okamoto I, Takahashi T, Okamoto H *et al.* Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor. *Lung Cancer* 2011; **72** (2): 199–204.
25 Center B, Petty WJ, Ayala D *et al.* A phase I study of gefitinib with concurrent dose-escalated weekly docetaxel and conformal three-dimensional thoracic radiation followed by consolidative docetaxel and maintenance gefitinib for patients with stage III non-small cell lung cancer. *J Thorac Oncol* 2010; **5** (1): 69–74.
26 Levy A, Bardet E, Lacas B *et al.* A phase II open-label multicenter study of gefitinib in combination with irradiation followed by chemotherapy in patients with inoperable stage III non-small cell lung cancer. *Oncotarget* 2017; **8** (9): 15924–33.
27 Lilenbaum R, Samuels M, Wang X *et al.* A phase II study of induction chemotherapy followed by thoracic radiotherapy and erlotinib in poor-risk stage III non-small-cell lung cancer: Results of CALGB 30605 (Alliance)/RTOG 0972 (NRG). *J Thorac Oncol* 2015; **10** (1): 143–7.
28 Wang J, Xia TY, Wang YJ *et al.* Prospective study of epidermal growth factor receptor tyrosine kinase inhibitors concurrent with individualized radiotherapy for patients with locally advanced or metastatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; **81** (3): e59–65.
29 Qin Q, Peng B, Li B. The impact of epidermal growth factor receptor mutations on the efficacy of definitive chemoradiotherapy in patients with locally advanced unresectable stage III non-small cell lung cancer: A systematic review and meta-analysis. *Expert Rev Anticancer Ther* 2019; **19** (6): 533–9.
30 Park SE, Noh JM, Kim YJ *et al.* EGFR mutation is associated with short progression-free survival in patients with stage III non-squamous cell lung cancer treated with concurrent chemoradiotherapy. *Cancer Res Treat* 2019; **51** (2): 493–501.
31 Hotta K, Kiura K, Takigawa N *et al.* Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese patients with non-small cell lung cancer: The Okayama Lung Cancer Study Group experience. *J Thorac Oncol* 2010; **5** (2): 179–84.

Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1. The computed tomography (CT) images of three cases with grades 3 radiation pneumonitis/pneumonitis.

Table S1. The case of grades 3 of radiation pneumonitis

