

Gefitinib Combination with Radiotherapy in Patients with Local Advanced Non-Small Cell Lung Cancer

Amira Elwan^{*†}, MD, Adel Bakry^{**}, MD, Ahmed Elwan^{***}, MD

^{*}Clinical Oncology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

^{**}Medical Oncology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

^{***}Cardiothoracic Surgery Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Abstract

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors is a crucial agent in EGFR-mutated advanced lung disease. Previous studies have suggested a positive correlation between EGFR overexpression and cellular radioreistance in the treatment of non-small cell lung cancer (NSCLC). Concurrent or sequential Gefitinib with thoracic irradiation showed tolerability and possible efficacy in patients who exhibited EGFR mutation. The aim of this study was to improve treatment outcomes of local advanced NSCLC patients.

Method: A prospective study included stage III NSCLC cases divided in to 30 patients in Arm A and 20 patients in Arm B. The patients received thoracic irradiation concurrently or sequentially with Gefitinib. We used Kaplan-Meier plot and compared results using log-rank test. Percent of categorical variables was compared using Pearson's chi-square test or Fisher's exact test when appropriate. A *P*-value of less than 0.05 was considered to be statistically significant using SPSS 16.0.

Results: Pneumonitis was more observed toxicity in Arm A versus Arm B with statistical significance *P* = 0.039. The median progression-free survival was 10 months with a 95 % confidence interval range of 8.2-11.7 months, 8.5-11.4 months in Arm A and Arm B, respectively. The median overall survival was 18 months versus 16 months with the range at 95 % confidence interval of 12.6-23.3 months versus 13.2-18.7 months in Arm A and Arm B, respectively.

Conclusion: Gefitinib is affordable and effective with thoracic irradiation in stage III NSCLC patients with accepted toxicity profile.

Keywords: Carcinoma, Non-small-cell lung, Mutation, Gefitinib, Pneumonitis

Please cite this article as: Elwan A, Bakry A, Elwan A. Gefitinib Combination with Radiotherapy in Patients with Local Advanced Non-Small Cell Lung Cancer. Middle East J Cancer. 2025; 16(4):346-355. doi: 10.30476/mejc.2024.103982.2161.

Received: September 06, 2024;
Accepted: December 24, 2024

†Corresponding Author:

Amira Elwan, MD
Clinical Oncology Department,
Faculty of Medicine, Zagazig
University, Zagazig, Egypt
Email: toamira_elwan@yahoo.com

Introduction

Lung cancer is the most common neoplasm worldwide. Most patients

are unsuitable for surgery due to medical or technical reasons. Radiotherapy (RT) creates curative



Copyright: ©Middle East Journal of Cancer. This is an open-access article distributed under the terms of the Creative Commons Attribution-No Derivatives 4.0 International License. This license allows reusers to copy and distribute the material in any medium or format in unadapted form only, and only so long as attribution is given to the creator. The license allows for commercial use.

treatment possibilities. Unfortunately, in these scenarios, the prognosis is poor, primarily due to the radioresistance of non-small cell lung cancer (NSCLC).¹

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) is a crucial agent in EGFR-mutated advanced lung disease.^{2,3}

However, in the setting of EGFR mutations in stage III, EGFR-mutant NSCLC could be detected in 17%-30% of patients, especially those with non-squamous tumors.⁴⁻⁷

Gefitinib plus concurrent thoracic irradiation showed tolerability and possible RT efficacy in patients who exhibited EGFR mutation.⁸

Many studies suggested the positive correlation between EGFR overexpression and cellular radioresistance in the treatment of NSCLC.⁹

Nivolumab, pembrolizumab, atezolizumab, and durvalumab immune checkpoint inhibitors (ICIs) reverse the inhibition of T cells, prevent the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) binding to the tumor cells producing anti-tumor effects, with novel treatment innovations. In addition, the exact synergistic effect between immunotherapy and conventional treatment. The PACIFIC trial evaluated the efficacy of ICIs in patients with

local advanced NSCLC and demonstrated unprecedented improvements in overall survival (OS) and progression-free survival (PFS).¹⁰⁻¹⁴

Local irradiation provides local control and provides more proactive alleviate symptoms participation in local advanced NSCLC. Stereotactic Body Radiation Therapy has shown high local control efficacy.¹⁵ The present study aimed to improve treatment outcomes of local advanced NSCLC patients.

Methodology

Study design and participants

A prospective study included 50 cases of NSCLC admitted at Clinical Oncology and Nuclear Medicine, Cardiothoracic, and Medical Oncology departments, all patients with mutated EGFR stage III included in the study from the period of January 2021 up to June 2024. Arm A included 30 patients received Gefitinib concurrently with RT then post irradiation. Arm B included 20 patients received Gefitinib sequentially 8 weeks prior to thoracic irradiation. Then, the patients in both arms continued Gefitinib treatment after the end of RT up to 6 months in responder patients. Gefitinib selection due to its availability and affordability.

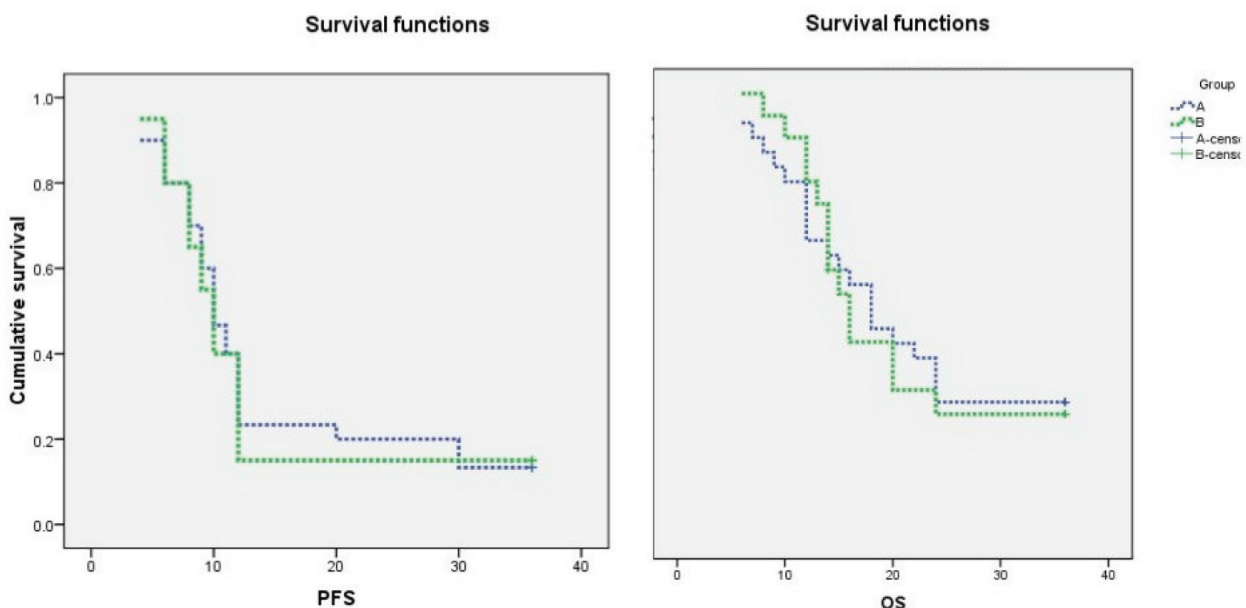


Figure 1. This figure shows the Kaplan Meier plot of PFS and OS of 30 patients in Group A and 20 patients in Group B, respectively. PFS: Progression-free survival; OS: Overall survival; No statistical difference between both arms regards PFS. In Arm A, the median OS was better than Arm B but with no statistical difference

Inclusion criteria

Cases of local advanced NSCLC stage III, no previous thoracic RT history; EGFR-proven mutated patients, objectively measured lesions; Karnofsky Performance Status ≥ 70 ; age ≥ 18 years; without vital organs impairment; explicit written consent, patients who refuse chemotherapy with irradiation.

Exclusion criteria

Cases fit for surgery, cases fit for concurrent chemoradiation, previous target therapy proposal, history of induction chemotherapy, and patients with incomplete data in medical records.

RT: Photon beams with an intensity of 6- 15 MV. The gross tumor volume was the volume of the primary disease and involved regional lymphatic ≥ 10 mm at the short axis on a computed tomography scan. The clinical target volume (CTV) included the primary tumor plus a 10 mm margin and regional lymph nodes electively. The planning target volume = CTV+ 20 mm margin. Radiation oncologist prescribed a dose over four weeks, 40 - 44 Gy (20-22) fractions at 2 Gy (per fraction), beam arrangement was in the anterior-posterior fields. Patients received 16- 20-Gy boost through parallel opposed lateral or oblique portals. The radiation oncologist limited the maximum spinal cord dose to 45 Gy.

Gefitinib: Arm A; started on daily dose of 250 mg orally, Day 1. The treatment continued after RT for up to 6 months if it was effective, while Arm B, the patients received sequential Gefitinib in 8 weeks before RT, and up to 6 months in responsive condition.

The cardiothoracic surgeon repeated thoracentesis plus pleurodesis, which may end with tube thoracostomy in progressive circumstances associated with massive pleural effusion.

Treatment response by Response Evaluation Criteria in Solid Tumors (RECIST) by the end of 12 weeks.¹⁶

We asked the patients for a plain chest x-ray, computed chest and pelvic-abdomen tomography, and bone scan \pm positron emission tomography-computed tomography scan (PET-CT) to assess the disease status. The multidisciplinary team

collected toxicity and survival data from the patient's medical records and by direct patient contact. Toxicity was evaluated by teamwork according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0.¹⁷

Ethics approval and consent to participate

This study was approved by the Faculty of Medicine, Zagazig University, Institutional Review Board (IRB) for human studies and the patients have signed an informed written consent, (Approval No.:8067).

Statistical analysis

Continuous variables are the mean \pm SD and median (range); categorical variables are a number (percentage). OS was the time from diagnosis to death or the most recent follow-up contact (censored). PFS was the most recent follow-up contact in which the patient was free from progression using the method of Kaplan-Meier plot and compared using log-rank test. Percent of categorical variables were compared using Pearson's chi-square test or Fisher's exact test when was appropriate, $P < 0.05$ is statistically significant. The authors performed all statistics using SPSS 16.0 for Windows (IBM Inc., Chicago, IL, USA).

Results

Table 1 shows characteristics of stage III NSCLC of 50 patients Arm A (concurrent Gefitinib) and Arm B (sequential Gefitinib).

Characteristics of patients and tumor

The mean age of the patients was 62.67 ± 3.8 , 61.25 ± 5.6 years old in arm A and B, respectively. The male gender was predominant by 86.7, 85 % in arm A and B, respectively. Also, 27 patients had Karnofsky Performance Status of 70 in Arm A, while 15 patients had Karnofsky Performance Status of 70 in Arm B. A majority of patients, 73.3% in Arm A and 75% in Arm B, had a smoking index ≥ 400 , 53.3 % had < 5 % weight loss within six months before the treatment in Arm A, and 60 % weight loss in Arm B. Clinically, 56.7% of patients in Arm A and 35% in Arm B had T2 disease. In Arm A, 46.7% of patients had

Table 1. Patients' characteristics of stage III non-small-cell lung cancer of 50 patients Arm A (concurrent Gefitinib) and Arm B (sequential Gefitinib)

Characteristics	Arm A (30)		Arm B (20)		P value
Age					0.98 ∞
Mean	62.67 ± 3.8		61.25 ± 5.6		
Range	55 - 70		46 - 68		
	N	%	N	%	
Sex					0.99 ∞
Male	26	86.7	17	85	
Female	4	13.3	3	15	
KPS					0.38 ∞
90	1	3.3	1	5	
80	2	6.7	4	20	
70	27	90	15	75	
Smoking index					0.99 ∞
0	2	6.7	2	10	
1 - 400	6	20	3	15	
≥ 400	22	73.3	15	75	
Weight loss within 6 months prior to the treatment					0.49 ∞
0	5	16.7	5	25	
< 5 %	16	53.3	12	60	
≥ 5 %	9	30	3	15	
T stage					0.52 ∞
T1	3	10	6	30	
T2	17	56.7	7	35	
T3	6	20	5	25	
T4	4	13.3	2	10	
N stage					0.47 ∞
N0	3	10	5	25	
N1	12	40	8	40	
N2	14	46.7	7	35	
N3	1	3.3	0	0	
Clinical stage					0.29 *
IIIA	12	40	11	55	
IIIB	18	60	9	45	
Pathological subtype					0.73 ∞
Squamous cell carcinoma	9	30	8	40	
Adenocarcinoma	20	66.7	12	60	
Others	1	3.3	0	0	

Categorical variables were expressed as numbers (percentages); KPS: Karnofsky performance status; ∞: Fisher's exact test; *: Person chi- square test; T: Tumor; N: Nodal

N2 disease while in Arm B, 40% of patients had N1 disease. Clinical stages included 18 patients as stage III B and 12 as stage III-A, in Arm A, 11 patients had stage III-A and 9 patients had stage III B in arm B. The pathological subtype was adenocarcinoma in 66.7%, 60 % of patients in Arm A and B, respectively. No statistically significant difference was found between both Arms regards patients and tumor characteristics (Table 1).

Table 2 shows the incidence of adverse events among the 50 patients in this study, Arm A (concurrent Gefitinib) and Arm B (sequential Gefitinib).

Adverse events outcome

Pneumonitis was more observed toxicity for

concurrent Gefitinib with thoracic irradiation in Arm A versus sequential Gefitinib administration in Arm B with statistical significance of $P = 0.039$. In Arm A two patients (6.7%) showed Grade 1 Pneumonitis, Six patients (20%) showed Grade 2 Pneumonitis and 3 patients (10%) had Grade 3 Pneumonitis. On the other hand, only 3 patients in Arm B had Grade 1 Pneumonitis. Seven patients (23.4%) showed G1 increased Alanine transaminase (ALT), six patients (20%) showed G1 + G2 increased aspartate transaminase (AST) in Arm A while in Arm B, 5 patients (25%) had Grade 1, 2 patients (10%) had Grade 2 increased ALT and AST without significance. In Arm A, six patients (20%) showed dermatitis, and only one patient showed Grade 3 dermatitis,

Table 2. Incidence of adverse events among 50 patients, Arm A (concurrent Gefitinib) and Arm B (sequential Gefitinib)

	Arm A (30)										Arm B (20)										P value
	Overall				G1		G2		G3		Overall				G1		G2		G3		
	Absent		Present								Absent		Present								
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Skin rash	25	76.6	5	16.7	3	10	2	6.7			16	80	4	20	2	10	2	10		0.99 ∞	
Dermatitis	24	80	6	20	5	16.7			1	3.3	15	75	5	25	4	20	1	5		0.80 ∞	
Leucopenia	27	90	3	10	3	10					15	75	5	25	5	25				0.24 ∞	
Anemia	25	83.3	5	16.7	5	16.7					14	70	6	30	5	25	1	5		0.36 ∞	
Thrombocytopenia	28	93.3	2	6.7	2	6.7					16	80	4	20	3	15	1	5		0.23 ∞	
Increased ALT	23	76.6	7	23.4	7	23.4					13	65	7	35	5	25	2	10		0.23 ∞	
Increased AST	24	80	6	20	3	10	3	10			13	65	7	35	5	25	2	10		0.34 ∞	
Increased creatinine	27	90	3	10	3	10					15	75	5	25	5	25				0.24 ∞	
Nausea	25	83.3	5	16.7	5	16.7					14	70	6	30	5	25	1	5		0.36 ∞	
Vomiting	26	86.7	4	13.4	2	6.7	2	6.7			14	70	6	30	4	20	2	10		0.33 ∞	
Diarrhea	24	80	6	20	3	10	3	10			13	65	7	35	6	30	1	5		0.20 ∞	
Esophagitis	23	76.6	7	23.4	4	13.4	3	10			15	75	5	25	5	25				0.24 ∞	
Pneumonitis	19	63.3	11	36.7	2	6.7	6	20	3	10	17	85	3	15	3	15				0.039*∞	

Categorical variables were expressed as numbers (percentage); G1: Grade 1 toxicity; G2: Grade 2 toxicity; G3: Grade 3; ∞: Fisher's exact test; **P* <0.05 is statistically significant; ALT: Alanine transaminase; AST: Aspartate transaminase

five patients showed Grade 1 dermatitis. In Arm B, no Grade 3 dermatitis, 4 patients had Grade 1 and one patient had Grade 2 dermatitis without significance. Five patients (16.7%) showed skin rash Grade 1+2 in Arm A versus 4 patients had Grade 1+2 in Arm B, without statistical difference. Seven patients (23.4%) showed Grade 1+2 esophagitis, and six (20%) showed Grade 1+2 diarrhea versus 5 patients (25%) showed Grade 1 esophagitis and 7 patients (35%) showed Grade 1+2 diarrhea in Arm A and B respectively without statistical significance (Table 2). Gefitinib was tolerable with RT for the Arm A patients and the sequential Gefitinib administration in Arm B. Teamwork controlled all manifestations by medical treatment.

Table 3 shows the response and survival outcome among the studied 50 patients, Arm A (concurrent Gefitinib) and Arm B (sequential Gefitinib).

Response and survival data

In this study, 15 patients had partial response (PR) and 11 patients had SD in Arm A versus 12 patients had PR and 8 patients had SD, and four patients in Arm A showed a progressive disease and none in Arm B at 12 weeks post-treatment protocol. After three years, only 4 cases in Arm A had no progressive disease versus 3 cases in Arm B. Also, 14 patients showed a distant metastasis, 8 had a mediastina progression, and 2 had a loco-regional progression site in Arm A while in Arm B, five patients had a mediastina progression and another five had a distant

metastasis. The median PFS was 10 months with a 95 % confidence interval (CI) range of 8.2-11.7 months, 8.5-11.4 months in Arm A and Arm B, respectively. The median OS was 18 months versus 16 months with the range at 95 % CI of 12.6-23.3 months versus 13.2-18.7 months in Arm A and Arm B respectively. The two-year PFS rate in Arm A and Arm B was 20 % and 15%, while the two-year OS rate in Arm A and arm B was 30 % and 27%, respectively. The 3-year PFS rate in Arm A and Arm B was 13 % and 15 %, while the three-year OS rate was 30 % in Arm A versus 27% in Arm B. No statistically significant difference between Arm A and Arm B regards response data, progression, progression site, death and survival data (Table 3) (Figure 1).

Discussion

The present study found that pneumonitis was more observed toxicity for concurrent Gefitinib with thoracic irradiation in Arm A versus sequential Gefitinib administration in Arm B with statistical significance. In Arm A, two patients (6.7%) showed Grade 1 Pneumonitis, six patients (20%) showed Grade 2 Pneumonitis and 3 patients (10%) had Grade 3 Pneumonitis, on other side only 3 patients in Arm B had Grade 1 Pneumonitis. Seven patients (23.4%) showed G1 increased ALT, six patients (20%) showed G1 + G2 increased AST in Arm A while in Arm B, 5 patients (25%) had Grade 1, 2 patients (10%) had Grade 2 increased ALT and AST without

Table 3. The response and survival outcome among 50 patients, Arm A (concurrent Gefitinib) and Arm B (sequential Gefitinib)

	Arm A (N=30)		Arm B (N=20)		P value
Response					0.28 ∞
PR	15	50	12	60	
SD	11	36.7	8	40	
PD	4	13.3	0	0	
Progression					0.86 ∞
Absent	4	13.3	3	15	
Present	26	86.7	17	85	
Progression site					0.39 ∞
Loco regional	2	6.7	4	20	
Supraclavicular	2	6.7	3	15	
Mediastina	8	26.7	5	25	
Distant metastasis	14	46.6	5	25	
Death					0.99 *
Absent	9	30	6	30	
Present	21	70	14	70	
OS					0.88 ‡
Median OS	18 months		16 months		
Range at 95 % Confidence Interval	12.6 - 23.3 months		13.2 – 18.7 months		
PFS					0.92‡
Median PFS	10 months		10 months		
Range at 95 % Confidence Interval	8.2 – 11.7 months		8.5 – 11.4 months		

Continuous variables were expressed as median (95%CI); Categorical variables were expressed as numbers (percentage); PR: Partial response; SD: Stable disease; PD: Progressive disease; PFS: Progression-free survival; OS: Overall survival; ‡: Log rank (Mantel-Cox); *: Person chi-square test; ∞: Fisher's exact test

significance. In Arm A, six patients (20%) showed dermatitis, and only one patient showed Grade 3 dermatitis, five patients showed Grade 1 dermatitis. In Arm B, no Grade 3 dermatitis, 4 patients had Grade 1 and one patient had Grade 2 dermatitis without significance. Five patients (16.7%) showed skin rash Grade 1+2 in Arm A versus 4 patients had Grade 1+2, without statistical difference. Seven patients (23.4%) showed Grade 1 + 2 esophagitis, and six (20%) showed Grade 1 + 2 diarrhea versus 5 patients (25%) showed Grade 1 esophagitis and 7 patients (35%) showed Grade 1+ 2 diarrhea in Arm A and B without statistical significance, respectively. Gefitinib administration concurrently with thoracic irradiation associated with accepted controlled adverse events either concurrently or sequentially.

Fu et al. stated that the most common acute side effects mainly \leq grades 2, only 7.1% of patients showed a grade 3 critical adverse event, and no patients showed a grade 4 acute adverse event; one patient (3.6%) showed Grade 3 elevated hepatic enzymes, esophagitis, and diarrhea, respectively. Seven patients (25.0%) showed grade 2 pneumonitis without grade 3 pneumonitis. These results are consistent with our results and emphasize that RT with the gefitinib combination

was well tolerated.¹⁸

Zheng et al. observed grade 3 radiation pneumonitis (20%) and (10%) rash in TIK combination with RT as first-line therapy for metastatic NSCLC patients harboring EGFR active mutations. Advanced NSCLC patients with thoracic Rth should undergo monitoring, considering radiation pneumonitis.¹⁹

Akamatsu et al. observed pneumonitis frequent liver dysfunction with increased ALT and AST.⁸

K. Haslett, P. Koh, A. Hudson, et al. studied selumetinib mitogen-activated protein kinase inhibitor (MEK inhibitor) in combination with chest irradiation in NSCLC and revealed one patient showed grade 3 diarrhea/fatigue and one showed grade 1 pulmonary embolism. They reported 3-4 adverse events, such as lymphopenia in 19 patients and hypertension in 7 patients, which are different from our results and may be due to induction chemotherapy, MEK inhibitor combination, and other underlying medical conditions. One patient showed grade 3 esophagitis without grade 3 radiation pneumonitis.^{20, 21}

J. Shimizu et al. observed grade 3 adverse events: fatigue, skin reaction, and appetite loss, respectively. Pneumonitis was the most reported

toxicity, with grade 1 (59.2%) and grade 2 (29.6%); these results are similar to the current notified toxicity.²²

In the present study, 15 patients had PR and 11 patients had SD in Arm A versus 12 patients had PR and 8 patients had SD, and four patients in Arm A showed a progressive disease and none in Arm B at 12 weeks post-treatment protocol. After three years, only 4 cases in Arm A had no progressive disease versus 3 cases in Arm B. Fourteen patients showed a distant metastasis, 8 had a mediastina progression, and 2 had a loco-regional progression site in Arm A while in Arm B, five patients had a mediastina progression and another five had a distant metastasis. The median PFS was 10 months with a 95% CI range of 8.2-11.7 months, 8.5-11.4 months in Arm A and Arm B, respectively. The median OS was 18 months versus 16 months with the range at 95 % CI of 12.6-23.3 months versus 13.2-18.7 months in Arm A and Arm B, respectively. The two-year PFS rate in Arm A and Arm B was 20 % and 15%, while the two-year OS rate in Arm A and arm B was 30 % and 27%, respectively. The three-year PFS rate in Arm A and Arm B was 13% and 15%, while the three-year OS rate was 30 % in Arm A versus 27% in Arm B.

Fu et al. observed that in the treatment response, 21 (75.0%) achieved (PR), 5 (17.9%) had (SD), and 2 (7.1%) had a progressive disease (PD). None of the patients showed a complete response (CR) in agreement with the stated study. Also, 25 patients (89.3%) showed a relapse; 19(67.9%) showed a local relapse, and 16 (57.1%) showed a distant relapse, including ten patients (35.7%) who underwent both a local and a distant relapse. The median PFS was 11 months, and the three-year survival rates were 39.0. The 3-year PFS rates were 14.3.¹⁸

Zheng et al. nearly demonstrated similar results and reported that the 1-year PFS rate was 57.1%, and the median PFS was 13 months in TKI combination with radiation as first-line treatment for stage IV NSCLC patients who have active mutated.¹⁹

K. Haslett, P. Koh, A. Hudson, et al. followed local advanced NSCLC; the 2-year survival was

31%, the 1-year PFS was 23.8%, and the 2-year PFS was 9.5%. The median OS was 9.7 months, and the median PFS was 6.9 months.²¹

J. Shimizu et al. reported that the PFS rate at two years was 29.6%. The overall response rate was 81.5%, the median PFS was 28.6 months (95%CI: 12.0 to 24.5 months), and the median OS was 61.1 months; Gefitinib in combination with thoracic RT did not improve the PFS rate at two years. EGFR inhibitors with thoracic radiation significantly improved OS emphasized that Non-oligometastatic NSCLC patients with EGFR mutations benefited from thoracic RT while using EGFR inhibitors,²² which is in agreement with the objectives of the study.

F. Hsu et al. observed 264 patients with EGFR mutated metastatic NSCLC who received palliative RT in comparison with progressed patients after do novo benefit from TKI, with documentation that do novo TKI intake in patients with mutated EGFR showed significant response efficacy compared with RT alone. Acquired resistance to TKI treatment results from neoplasm cross-resistance to palliative RT.²³

Spanish researchers studied 90 patients with stage III NSCLC who received RT with erlotinib or RT alone. The median OS was 8.9 and 11.4 months, respectively. Consistent with the present study, the median PFS was 12.9 and 15.3 months, respectively.²⁴

The median PFS in Akamatsu et al.'s study was 18.6 months, and PFS rates at 1 and 2 years were 66.7% and 33.3%, respectively. OS among the overall population was 61.1 months, three patients had CR, and 19 had PR8 these results differ from the present study due to using Gefitinib 250 mg orally for 2-year duration and receiving concurrent thoracic irradiation with 64 Gy total dose.⁸

Thoracic RT plus EGFR-TKIs in patients with nonoligometastatic advanced non-small-cell lung cancer revealed survival benefits by F Zhou, Y Qin, et al.²⁵

Combining radiation therapy and ICIs is a promising treatment approach and should be tailored in large randomized trials.^{26,27}

Donata. Von Reibnitz et al. reported more

adverse events and were Grade ≥ 2 after thoracic radiation therapy and immunotherapy, including five patients (6%) with Grade ≥ 2 pneumonitis (4 patients showed Grade 2, and one showed Grade 4), 14 patients (18%) showed pneumonia, five patients (6%) showed upper respiratory infections, three patients showed dyspnea, two patients showed cough, three patients showed pleural effusions. six patients (8%) showed Grade ≥ 2 esophagitis. Eight patients (10%) showed \geq grade dermatitis, and 13 patients (16%) showed fatigue. Treatment timing (concurrent/sequential) may impact toxicity rates. Patients received palliative RT, stereotactic body, or conventionally fractionated RT.²⁸ The data are in agreement with the present study.

Durvalumab therapy was combined with RT and discovered safety and high therapeutic response of immune strategy with thoracic irradiation for elderly NSCLC stage III patients.²⁹

The present study has certain limitations including: small sample size, data bias, lack of biomarker analysis and lack of advanced RT techniques. Further large-scale comparative studies could offer a better promising bridge for treatment outcome benefits allow proper gefitinib-acquired resistance and disease cross-resistance understanding.

Conclusion

EGFR-TKI Concurrently or sequentially with thoracic RT is crucial to disease biology directions with acceptable findings but with treatment timing consideration. Gefitinib is affordable and tolerable with thoracic irradiation in NSCLC patients.

Availability of data and materials

All data analyzed and generated during this study are included in this published article.

Funding

None declared.

Acknowledgments

We would like to thank the patients who participated as well as the members of the research.

Authors' Contributions

A.E: Study design, data gathering, drafting and reviewing the manuscript; A.B: Study design, and reviewing the manuscript; Ah. E: Study design, and reviewing the manuscript; A.E: Data gathering, drafting; A.B: Data gathering, drafting; Ah. E: Data gathering, drafting; All authors have read and approved the final manuscript and agree to be 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.

Conflict of Interest

None declared.

References

1. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol.* 2015;16(2):187-99. doi: 10.1016/S1470-2045(14)71207-0. PMID: 25601342; PMCID: PMC4419359.
2. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-25. doi: 10.1056/NEJMoa1713137. PMID: 29151359.
3. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med.* 2020;382(1):41-50. doi: 10.1056/NEJMoa1913662. PMID: 31751012.
4. Tanaka K, Hida T, Oya Y, Oguri T, Yoshida T, Shimizu J, et al. EGFR mutation impact on definitive concurrent chemoradiation therapy for inoperable stage III adenocarcinoma. *J Thorac Oncol.* 2015;10(12):1720-5. doi: 10.1097/JTO.0000000000000675. PMID: 26743855.
5. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, et al. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2015;91(1):140-8. doi: 10.1016/j.ijrobp.2014.08.344. PMID: 25442336.
6. Nakamura M, Kageyama SI, Niho S, Okumura M, Hojo H, Motegi A, et al. Impact of EGFR mutation

- and ALK translocation on recurrence pattern after definitive chemoradiotherapy for inoperable stage III non-squamous non-small-cell lung cancer. *Clin Lung Cancer*. 2019;20(3):e256-e264. doi: 10.1016/j.clcc.2019.02.021. PMID: 30926356.
7. Akamatsu H, Kaira K, Murakami H, Serizawa M, Koh Y, Ono A, et al. The impact of clinical outcomes according to EGFR mutation status in patients with locally advanced lung adenocarcinoma who received concurrent chemoradiotherapy. *Am J Clin Oncol*. 2014;37(2):144-7. doi: 10.1097/COC.0b013e31826e04f9. PMID: 23211219.
 8. Akamatsu H, Murakami H, Harada H, Shimizu J, Hayashi H, Daga H, et al. Gefitinib with concurrent thoracic radiotherapy in unresectable locally advanced NSCLC with EGFR mutation; West Japan Oncology Group 6911L. *J Thorac Oncol*. 2021;16(10):1745-52. doi: 10.1016/j.jtho.2021.05.019. PMID: 34116229.
 9. Wang M, Kern AM, Hülskötter M, Greninger P, Singh A, Pan Y, et al. EGFR-mediated chromatin condensation protects KRAS-mutant cancer cells against ionizing radiation. *Cancer Res J*. 2014;74(10):2825-34. doi:10.1158/0008-5472.CAN-13-3157. PMID: 24648348 PMCID: PMC4278592.
 10. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-50. doi: 10.1056/NEJMoa1809697. PMID: 30280658.
 11. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919-29. doi: 10.1056/NEJMoa1709937. PMID: 28885881.
 12. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. *J Thorac Oncol*. 2020;15(2):288-93. doi: 10.1016/j.jtho.2019.10.002. PMID: 31622733; PMCID: PMC7244187.
 13. Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. *J Thorac Oncol*. 2021;16(5):860-7. doi: 10.1016/j.jtho.2020.12.015. PMID: 33476803.
 14. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: Durvalumab After chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. 2022;40(12):1301-11. doi: 10.1200/JCO.21.01308. Erratum in: *J Clin Oncol*. 2022;40(17):1965. doi: 10.1200/JCO.22.01023. PMID: 35108059; PMCID: PMC9015199.
 15. Zhou Y, Yu F, Zhao Y, Zeng Y, Yang X, Chu L, et al. A narrative review of evolving roles of radiotherapy in advanced non-small cell lung cancer: from palliative care to active player. *Transl Lung Cancer Res*. 2020;9(6):2479-93. doi: 10.21037/tlcr-20-1145. PMID: 33489808; PMCID: PMC7815368.
 16. Ruchalski K, Braschi-Amirfarzan M, Douek M, Sai V, Gutierrez A, Dewan R, et al. A primer on RECIST 1.1 for oncologic imaging in clinical drug trials. *Radiol Imaging Cancer*. 2021;3(3):e210008. doi: 10.1148/rycan.2021210008. PMID: 33988475 PMCID: PMC8183261.
 17. Chung AE, Shoenbill K, Mitchell SA, Dueck AC, Schrag D, Bruner DW, et al. Patient free text reporting of symptomatic adverse events in cancer clinical research using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Am Med Inform Assoc*. 2019;26(4):276-85. doi: 10.1093/jamia/ocy169. PMID: 30840079 PMCID: PMC6402312.
 18. Fu Z, Yang X, Wang W, Deng L, Zhang T, Bi N, et al. Radiotherapy combined with gefitinib for patients with locally advanced non-small cell lung cancer who are unfit for surgery or concurrent chemoradiotherapy: a phase II clinical trial. *Radiat Oncol*. 2020;15(1):155. doi: 10.1186/s13014-020-01596-2. PMID: 32563259; PMCID: PMC7305585.
 19. Zheng L, Wang Y, Xu Z, Yang Q, Zhu G, Liao XY, 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-e612. doi: 10.1634/theoncologist.2019-0285. PMID: 31040256; PMCID: PMC6693693.
 20. Chen F, Niu J, Wang M, Zhu H, Guo Z. Re-evaluating the risk factors for radiation pneumonitis in the era of immunotherapy. *J Transl Med*. 2023;21(1):368. doi: 10.1186/s12967-023-04212-5. PMID: 37287014; PMCID: PMC10246421.
 21. Haslett K, Koh P, Hudson A, Ryder WD, Falk S, Mullan D, et al. Phase I trial of the MEK inhibitor selumetinib in combination with thoracic radiotherapy in non-small cell lung cancer. *Clin Transl Radiat Oncol*. 2021;28:24-31. doi: 10.1016/j.ctro.2021.02.008. PMID: 33748440; PMCID: PMC7970011.
 22. Shimizu J, Akamatsu H, Murakami H, Harada H, Hayashi H, Daga H, et al. A single-arm phase II study of gefitinib with concurrent thoracic radiotherapy in unresectable locally-advanced non-small cell lung cancer patients with EGFR mutation (West Japan Oncology Group 6911L). *Ann Oncol J*. 2020;31(S4):S803. doi:10.1016/j.annonc.2020.08.109.
 23. Hsu F, Sit D, Pastuch A, Dingler A, Atwal P. Lung cancer epidermal growth factor receptor mutations and radiotherapy response: A multicentre clinical study. *Clin Transl Radiat Oncol*. 2021;30:15-8. doi: 10.1016/j.ctro.2021.06.006. PMID: 34278010; PMCID: PMC8267427.

24. Martínez E, Martínez M, Rico M, Hernández B, Casas F, Viñolas N, et al. Feasibility, tolerability, and efficacy of the concurrent addition of erlotinib to thoracic radiotherapy in locally advanced unresectable non-small-cell lung cancer: a Phase II trial. *Onco Targets Ther.* 2016;9:1057-66. doi: 10.2147/OTT.S89755. PMID: 27042098; PMCID: PMC4780183.
25. Zhou F, Qin Y, Liu X, Huang J, Wu B, Zhang Z, et al. Survival benefit of thoracic radiotherapy plus EGFR-TKIs in patients with non-oligometastatic advanced non-small-cell lung cancer: a single-center retrospective study. *Ther Adv Med Oncol.* 2023;15:17588359231161411. doi: 10.1177/17588359231161411. PMID: 36970112; PMCID: PMC10031612.
26. Rajeev-Kumar G, Pitroda SP. Synergizing radiotherapy and immunotherapy: Current challenges and strategies for optimization. *Neoplasia.* 2023;36:100867. doi: 10.1016/j.neo.2022.100867. PMID: 36563632; PMCID: PMC9798173.
27. Hsieh K, Dickstein DR, Runnels J, Lehrer EJ, Rosenzweig K, Hirsch FR, et al. Radiotherapy and immunotherapy in lung cancer. *Biomedicines.* 2023;11(6):1642. doi: 10.3390/biomedicines11061642. PMID: 37371737; PMCID: PMC10295589.
28. von Reibnitz D, Chaft JE, Wu AJ, Samstein R, Hellmann MD, Plodkowski AJ, et al. Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition. *Adv Radiat Oncol.* 2018;3(3):391-8. doi: 10.1016/j.adro.2018.05.001. PMID: 30202807; PMCID: PMC6128092.
29. Bozorgmehr F, Chung I, Christopoulos P, Krisam J, Schneider MA, Brückner L, et al. Thoracic radiotherapy plus Durvalumab in elderly and/or frail NSCLC stage III patients unfit for chemotherapy - employing optimized (hypofractionated) radiotherapy to foster durvalumab efficacy: study protocol of the TRADE-hypo trial. *BMC Cancer.* 2020;20(1):806. doi: 10.1186/s12885-020-07264-8. Erratum in: *BMC Cancer.* 2023;23(1):740. doi: 10.1186/s12885-023-11270-x. PMID: 32842974; PMCID: PMC7447611.