ORIGINAL ARTICLE

Pneumonitis in Patients Receiving Thoracic Radiotherapy and Osimertinib: A Multi-Institutional Study

Leou Ismael Banla, MD, PhD,[a] Alice Tzeng, MD, PhD,[b] John P. Baillieul,[c] Melin J. Kandekhar, MD, PhD,[d] Kelly J. Fitzgerald, MD, PhD,[c] Jaclyn LoPiccolo, MD, PhD,[e] Holly A. Poitras,[c] Daniel E. Soto, MD,[d] Julia K. Rotow, MD,[e] Lisa Singer, MD, PhD,[f] Henning Willers, MD,[d] David E. Kozono, MD, PhD,[c] Pasi A. Janne, MD, PhD,[e] Raymond H. Mak, MD,[c] Zofia Piotrowska, MD,[g] Florence K. Keane, MD,[d] Benjamin H. Kann, MD[c,*]

[a]*Harvard Radiation Oncology Program, Boston, Massachusetts*
[b]*Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*
[c]*Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts*
[d]*Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*
[e]*Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*
[f]*Department of Radiation Oncology, University of California San Francisco, San Francisco, California*
[g]*Department of Medicine, Division of Hematology/ Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*

Received 27 June 2023; revised 1 August 2023; accepted 6 August 2023
Available online - 17 August 2023

ABSTRACT

Introduction: Thoracic radiotherapy (TRT) is increasingly used in patients receiving osimertinib for advanced NSCLC, and the risk of pneumonitis is not established. We investigated the risk of pneumonitis and potential risk factors in this population.

Methods: We performed a multi-institutional retrospective analysis of patients under active treatment with osimertinib who received TRT between April 2016 and July 2022 at two institutions. Clinical characteristics, including whether osimertinib was held during TRT and pneumonitis incidence and grade (Common Terminology Criteria for Adverse Events version 5.0) were documented. Logistic regression analysis was performed to identify risk factors associated with grade 2 or higher (2+) pneumonitis.

Results: The median follow-up was 10.2 months (range: 1.9–53.2). Of 102 patients, 14 (13.7%) developed grade

*Corresponding author.

Disclosure: Dr. Rotow reports receiving institutional clinical trial funding from AbbVie, AstraZeneca, Bicycle Therapeutics, BioAtla, Blueprint, Daiichi Sankyo, Enliven, EpimAb, Loxo Oncology, ORIC, and Redcloud; consulting fees from AstraZeneca, AbbVie, Gritstone, Eli Lilly, Takeda, Sanofi Genzyme, Genentech, Guardant, Janssen, G1 Therapeutics, BioAtla, Summit, Jazz, and Amgen; honoraria for lectures/presentations/educational events from Chiatai Tianqing, and AstraZeneca; and support for travel/meetings from AstraZeneca and Eli Lilly. Dr. Janne reports receiving institutional grants/contracts from AstraZeneca, Daiichi Sankyo, PUMA, Eli Lilly, Boehringer Ingelheim, Revolution Medicines, and Takeda Oncology; royalties from LabCorp; consulting fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Roche/Genentech, Chugai Pharmaceuticals, Eli Lilly pharmaceuticals, SFJ Pharmaceuticals, Voronoi, Daiichi Sankyo, Biocartis, Novartis, Takeda Oncology, Mirati Therapeutics, Transcenta, Silicon Therapeutics, Syndax, Nuvalent, Bayer, Esai, Allorion Therapeutics, Accutar Biotech, AbbVie, Monte Rosa, Scorpion Therapeutics, Merus, Frontier Medicines, Hongyun Biotechnology, and Duality; and has stock options from Gatekeeper Pharmaceuticals. Dr. Mak reports receiving grants/contracts from ViewRay; consulting fees from ViewRay, AstraZeneca, Sio Capital Management, and Varian Medical Systems; and honoraria for lectures/presentations/educational events from Novartis. Dr. Piotrowska reports receiving grants/contracts from Novartis, Takeda, Spectrum, AstraZeneca, Tesaro/GlaxoSmithKline, Cullinan Oncology, Daiichi Sankyo, AbbVie, Blueprint, and Janssen; consulting fees from AstraZeneca, Janssen, Sanofi, Taiho, Janssen, Takeda, C4 Therapeutics, Jazz Pharmaceuticals, Cullinan Oncology, and Blueprint Medicines; honoraria for lectures/presentations/educational events from Eli Lilly, Daiichi Sankyo, and Janssen; and travel support from Janssen. The remaining authors declare no conflict of interest.

Address for correspondence: Benjamin Kann, MD, Department of Radiation Oncology, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. E-mail: Benjamin_Kann@dfci.harvard.edu

Cite this article as: Banla LI, Tzeng A, Baillieul JP, et al. Pneumonitis in patients receiving thoracic radiotherapy and osimertinib: a multi-institutional study. *JTO Clin Res Rep*. 2023;4:100559.

ISSN: 2666-3643
https://doi.org/10.1016/j.jtocrr.2023.100559

2+ pneumonitis, with a median time to pneumonitis of 3.2 months (range: 1.5–6.3). Pneumonitis risk was not significantly increased in patients who continued osimertinib during TRT compared with patients who held osimertinib during TRT (9.1% versus 15.0%, $p = 0.729$). Three patients (2.9%) had grade 3 pneumonitis, none had grade 4, and two patients had grade 5 events (2.0%, diagnosed 3.2 mo and 4.4 mo post-TRT). Mean lung dose was associated with the development of grade 2+ pneumonitis in multivariate analysis (OR = 1.19, $p = 0.021$).

Conclusions: Although the overall rate of pneumonitis in patients receiving TRT and osimertinib was relatively low, there was a small risk of severe toxicity. The mean lung dose was associated with an increased risk of developing pneumonitis. These findings inform decision-making for patients and providers.

Keywords: Pneumonitis; Osimertinib; Radiation; Lung cancer; Tyrosine kinase inhibitors

Introduction

Lung cancer is a leading cause of cancer-related mortality, and the use of EGFR inhibitors has transformed the management of patients with advanced NSCLC harboring EGFR mutations.[1,2] Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) that has exhibited remarkable efficacy in the management of patients with metastatic EGFR-mutated NSCLC and resected stage IB to IIIA EGFR-mutated NSCLC and is the recommended first-line systemic agent for metastatic disease.[3–5] Given the high rates of systemic control associated with osimertinib, the use of thoracic radiotherapy (TRT) for patients for oligoprogression or palliation is increasing. A better understanding of the potential risks of TRT in patients receiving osimertinib is, therefore, imperative.

Treatment-related pneumonitis represents a major safety concern in this patient population. Whereas the randomized phase 3 Stereotactic Body Radiation Therapy (SBRT) in Newly Diagnosed Advanced Staged Lung Adenocarcinoma (SINDAS) trial reported a significant improvement in PFS in patients and an encouraging safety signal with the use of SBRT before first-generation TKIs in patients with newly diagnosed oligometastatic EGFR-mutant NSCLC, other studies of concurrent earlier-generation TKIs with RT have reported high rates of severe pneumonitis.[6–9] Osimertinib monotherapy is associated with a 4% to 18% risk of pneumonitis in patients with advanced NSCLC. Although inconsistently reported, grade 2 or higher (2+) pneumonitis rates ranged from 9% to 13.6% and grade 3 or higher pneumonitis ranged from 1.8% to 9.1% with osimertinib alone.[4,10–15] There are no prospective studies assessing the safety of combining osimertinib with TRT. Small, single-institution, retrospective studies have raised safety concerns; however, the limited sample size of these studies suggests the need for further investigation to clarify pneumonitis risk factors in this population.[16,17]

To address this knowledge gap, we conducted a pooled, multi-institutional retrospective study of patients receiving TRT while on treatment with osimertinib. We identified the incidence of pneumonitis and associated risk factors. We specifically evaluated the differential risk of pneumonitis in patients for which osimertinib was held or not during TRT and explored disease progression patterns in this patient population.

Materials and Methods

Study Design and Patient Population

This was a pooled retrospective cohort study conducted at two institutions. Consecutive patients with EGFR-mutant NSCLC who received osimertinib and underwent TRT between April 2016 and July 2022 were identified from institutional data repositories. Patients were eligible for inclusion when they had at least 45 days of follow-up after completion of TRT and received osimertinib within 30 days of TRT initiation. Medical records were abstracted by means of a standardized instrument (Supplementary Appendix A) and reviewed for patient demographics, clinical characteristics, radiation treatment details, and oncologic outcomes. Tumor location was defined as peripheral, central, or ultracentral, with central defined as within 2 cm of the tracheobronchial tree and ultracentral defined as tumor abutment or involvement of the tracheobronchial tree, esophagus, heart, or great vessels. Radiation treatment techniques, dose, and fractionation were determined by the treating radiation oncologist according to institutional guidelines and patients' clinical circumstances. The decision to hold osimertinib and hold timing was determined on a case-by-case basis at the discretion of the treating medical and radiation oncologists. SBRT was defined as the delivery of 5 Gy or more per fraction for the purposes of the study. The intent of treatment was inferred from the radiation dose delivered; SBRT treatments with biological equivalent doses in Gy_{10} (BED10) greater or equal to 100 Gy and non-SBRT treatments with equivalence dose in 2 Gy fractions (EQD2) greater or equal to 60 Gy were considered radical whereas SBRT treatments with BED10 less than 100 Gy and non-SBRT treatments with EQD2 less than 60 Gy were considered palliative.

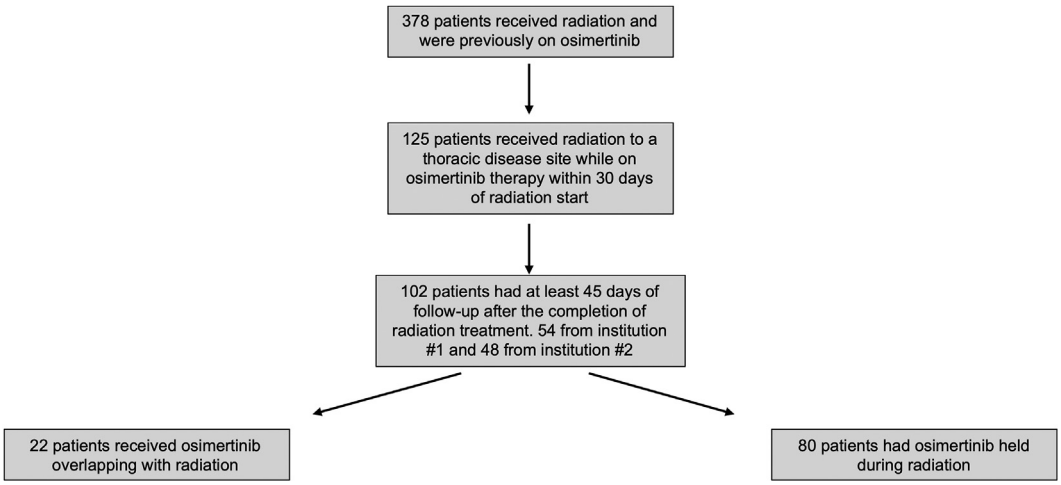

Figure 1. Internal database queries identified patients who received radiation therapy and had a previous or current history of osimertinib use. This population was further narrowed down to patients that were on active osimertinib therapy within 30 days of the start of thoracic radiation therapy. Finally, only patients with at least 45 days of follow-up were retained for analysis. #, number.

The incidence of treatment-related pneumonitis after TRT was recorded, along with the grade of pneumonitis using both Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and Radiation Therapy Oncology Group grading schemas (Supplementary Appendix B).[18,19] Treatment-related pneumonitis was defined as a clinician-reported diagnosis of pneumonitis with radiologic evidence of pneumonitis encompassing the radiation-treated lung region. The study was approved by the institutional review boards at both participating institutions. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (PubMed identifier: 17938396). The study was conducted under a waiver of informed consent.

Statistical Analysis

The primary end point of the study was the rate of clinically impactful pneumonitis occurring post-TRT in the pooled cohort, defined as grade 2 or higher by means of the CTCAE version 5.0 definition. Secondary end points included overall pneumonitis incidence and progression-free survival. Descriptive statistics were used to characterize patient demographics, clinical characteristics, treatment details, and rates of pneumonitis across the cohort. Univariate logistic regression analysis was performed to evaluate the association between patient and treatment factors, including overlapping osimertinib and TRT, and the development of clinically significant pneumonitis. Factors with a p value of 0.150 or less on univariable analysis were included in a multivariable logistic regression model. Dosimetric data were analyzed as continuous variables and were checked for collinearity before inclusion. All statistical analyses were performed using Stata 17.0. A two-sided p value equal to or less than 0.05 was considered statistically significant.

Results

Population and Treatment Characteristics

We identified 378 patients receiving RT to any disease site while on osimertinib from April 2016 to July 2022 at the two participating institutions. Of these, 125 patients received TRT, and 102 patients had at least 45 days of follow-up postradiation and were included in the analyses (Fig. 1). Clinical details of this population are presented in Table 1. Most patients (n = 80, 78.4%) had osimertinib held during radiation. The median age was 64 (range: 31–95), and 71 (69.6%) were women. Radiation treatment sites included 73 lesions (71.6%) in the lungs or mediastinum, and 29 (28.4%) extrapulmonary, intrathoracic sites including thoracic spine, chest wall, scapular, and supraclavicular regions. Pulmonary comorbidities (which included chronic obstructive pulmonary disease, restrictive lung disease, or previous lung surgery) were present in 20 patients (19.6%), nine patients (8.8%) previously received TRT, and one patient had preexisting interstitial lung disease. Of the entire cohort, 44 patients (43.1%) were treated with radical intent—28 patients received SBRT and 16 received non-SBRT treatments—and 58 patients (56.9%) were treated with palliative intent (Table 1). There was a significantly higher proportion of patients receiving TRT to a lung or mediastinal location among patients who continued osimertinib during radiation treatment (Table 1). Though not statistically significant, there was numerically lower use of SBRT and a lower

Table 1. Patient Characteristics and Radiation Treatment Details

Characteristics	Total (N = 102)	Osimertinib Overlapping (n = 22)	Osimertinib Held (n = 80)	*p* Value
Age (y), median [range]	64 [31-95]	63 [31-78]	66 [37-95]	0.165
Sex, n (%)				0.602
Male	31 (30.4)	8 (36.4)	23 (28.8)	
Female	71 (69.6)	14 (63.6)	57 (71.2)	
Tumor location, n (%)				0.016
Lung/mediastinum	73 (71.6)	11 (50.0)	62 (77.5)	
Other	29 (28.4)	11 (50.0)	18 (22.5)	
Pulmonary comorbidity, n (%)				0.553
No	82 (80.4)	19 (86.4)	63 (78.7)	
Yes	20 (19.6)	3 (13.6)	17 (21.3)	
Prior thoracic radiotherapy, n (%)				0.098
No	93 (91.2)	18 (81.8)	75 (93.8)	
Yes	9 (8.8)	4 (18.2)	5 (6.2)	
Prescribed dose (Gy), median [range]	45 [8-70]	30 [24-66]	45 [8-70]	0.322
Number of fractions, median [range]	6 [1-35]	10 [3-33]	5 [1-35]	0.112
Treatment type, n (%)				0.092
SBRT	50 (49.0)	7 (31.8)	43 (53.7)	
Non-SBRT	52 (51.0)	15 (68.2)	37 (46.3)	
Treatment intent,[a] n (%)				0.331
Palliative	58 (56.9)	15 (68.1)	43 (53.7)	
Radical	44 (43.1)	7 (31.8)	37 (46.3)	

Note: p Values comparing each parameter using Wilcoxon rank-sum test or Fisher's exact test.
[a]Radical intent defined as SBRT with BED10 greater than or equal to 100 Gy, or non-SBRT with EQD2 greater than or equal to 60 Gy.
BED10, biological equivalent doses in Gy10; EQD2, equivalence dose in 2 Gy fractions; SBRT, stereotactic body radiotherapy.

proportion of patients who previously received TRT among patients who had osimertinib held during radiation treatment. No other statistically significant imbalance of clinical parameters among the group of patients with held osimertinib and the group with overlapping osimertinib was appreciated.

Pneumonitis and Associated Risk Factors

The median clinical follow-up was 10.2 months (range: 1.9–53.2). A total of 16 patients (15.7%) developed any-grade pneumonitis, and 14 (13.7%) developed CTCAE grade 2+ pneumonitis (Table 2, Radiation Therapy Oncology Group grade breakdown in Supplementary Appendix C). Among the 22 patients who received osimertinib overlapping with TRT, two (9.1%) developed grade 2+ pneumonitis, compared with 12 (15.0%) of the 80 patients for whom osimertinib was held during TRT ($p = 0.729$, Fisher's exact test) (Table 2 and Fig. 2). The median time to grade 2+ pneumonitis was 3.2 months (range: 1.5–6.3 mo).

Table 2. Breakdown of Treatment-Related Pneumonitis Incidence by Grade According to Common Terminology Criteria for Adverse Events Version 5.0

Pneumonitis Grade Category	Total (N = 102)	Osimertinib Overlapping (n = 22)	Osimertinib Held During RT (n = 80)
None or grade 1	88 (86.3)	20 (90.9)	68 (85.0)
Grade 2+	14 (13.7)	2 (9.1)	12 (15.0)
Pneumonitis by grade			
None	86 (84.3)	18 (81.8)	68 (85.0)
Grade 1	2 (2.0)	2 (9.0)	0 (0.0)
Grade 2	9 (8.8)	1 (4.6)	8 (10.0)
Grade 3	3 (2.9)	1 (4.6)	2 (2.5)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5	2 (2.0)	0 (0.0)	2 (2.5)
Time to grade 2+ pneumonitis, median [range] in mo	3.2 [1.5-6.3]	2.2 [1.6-2.7]	3.4 [1.5-6.3]

Note: All values are n (%) unless otherwise specified.
RT, radiotherapy.

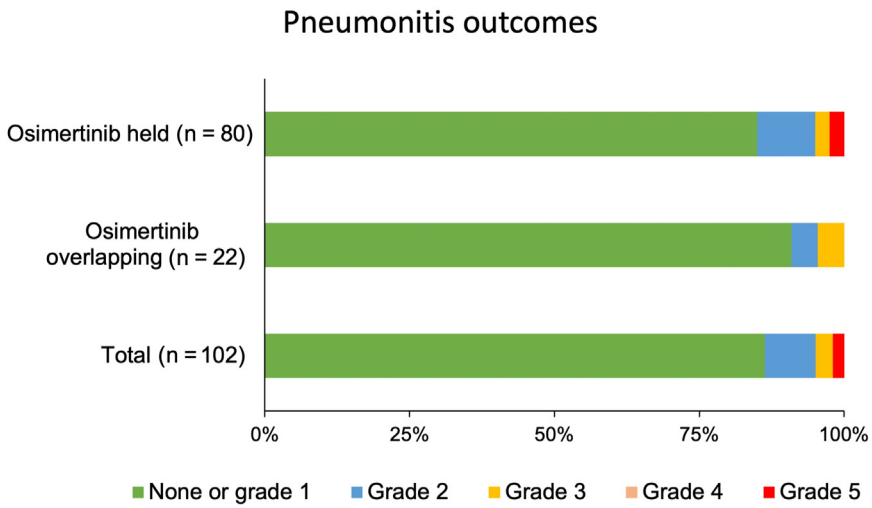

Figure 2. Incidence of radiation pneumonitis by Common Terminology Criteria for Adverse Events version 5.0.

Table 3 provides patient details for those who experienced grade 2+ pneumonitis. Among patients with grade 2+ pneumonitis, 11 (79%) had central or ultracentral tumors, and nine patients (64%) had ultracentral tumors. Two patients (2.9%) experienced fatal (grade 5) pneumonitis; of those, the first was a 20-pack-year former smoker who received SBRT (6 Gy $\times$ 5) to a peripheral lung lesion and the second was a 95-year-old who received SBRT (8 Gy $\times$ 5) to a centrally located tumor (Table 3). They were diagnosed with treatment-related pneumonitis 3.2 and 4.4 months after completion of TRT, respectively. All had osimertinib held during TRT; both patients were treated with steroids but experienced progression of pneumonitis and significant respiratory decline.

On univariable analyses of factors associated with clinically significant pneumonitis, only the mean lung dose (OR = 1.18, 95% confidence interval [CI]: 1.03–1.34, $p = 0.014$) and EQD2 normalized mean lung dose (OR = 1.21, 95% CI: 1.03–1.43, $p = 0.024$) were statistically significant (Table 4). The practice of holding osimertinib (versus overlapping) during TRT was not associated with a significant change in the risk of pneumonitis (OR = 1.76, 95% CI: 0.364–8.55, $p = 0.480$). Tumor location (lung/mediastinum versus other), sex (female versus male), and mean lung dose (continuous) reached the threshold for inclusion in the multivariable model set at a p value of 0.2 or less (of note, lung volume receiving a dose of $\geq$5 Gy, $\geq$20 Gy, and EQD2-normalized mean lung dose were excluded from the multivariate analysis because of collinearity with mean lung dose). On multivariable regression, only mean lung dose was found to be significantly associated with pneumonitis (OR = 1.19, 95% CI: 1.03–1.37, $p = 0.021$).

Oncologic Outcomes

The median progression-free survival was 5.8 months from the start of TRT (95% CI: 3.2–7.5 mo), with most patients experiencing distant progression (Table 5). Of the entire cohort, 78 patients (76.5%) experienced disease progression after TRT, which was mainly distant progression, defined as disease progression beyond the irradiated lesion and draining lymph nodes. Three (2.9%) patients experienced disease progression during TRT, two of whom had osimertinib held during TRT. In all three cases, there was known preexisting central nervous system (CNS) disease and progression occurred in the CNS. Of note, two patients developed rapid and symptomatic leptomeningeal disease (LMD) during radiation. The first patient was receiving SBRT for an oligoprogressive lung lesion, this patient had osimertinib held for 11 days and was restarted on osimertinib after the diagnosis of LMD. The second patient was receiving postoperative radiation to an isolated site of small cell progression in the supraclavicular fossa, they remained on osimertinib during radiation therapy but were started on pemetrexed after LMD diagnosis. Both patients eventually completed TRT as prescribed.

Discussion

To our knowledge, we report the largest and only multi-institutional study to-date characterizing the risk of pneumonitis in patients on osimertinib who receive TRT, an increasingly common yet underinvestigated clinical scenario. In 102 patients across two institutions, we found that TRT in patients receiving osimertinib was relatively safe with a moderate risk of clinically significant pneumonitis. Although most patients held osimertinib during RT, our study found that carefully

Table 3. Clinical and Treatment Details of Patients With Common Terminology Criteria for Adverse Events Version 5.0 Grade 2 or Higher Treatment-Related Pneumonitis

Patient	Pneumonitis grade	Age/Sex	Osimertinib delivery	Tumor location	Prescription	MLD (Gy)	V5	V20	Pulmonary comorbidity	Smoking history	Concurrent chemotherapy	Time to Pneumonitis (mo)
1	5	70/F	Held for RT	Peripheral lung	6 Gy ×5	2.8	9.2	2.8	None	Former (20PY)	No	3.2
2	5	95/F	Held for RT	Central	8 Gy ×5	4.75	25.3	4.0	None	Never smoker	No	4.4
3	3	62/F	Held for RT	Ultracentral	4 Gy ×13	11.2	44.8	17.7	None	Never smoker	No	5.4
4	3	49/F	Held for RT	Ultracentral	2.5 Gy ×12	2.7	12.5	4.8	Prior radiation to the same lung lesion	Never smoker	Yes	4.5
5	3	72/F	Overlapping with RT	Thoracic spine	3 Gy ×10	3.73	19.7	4.7	Prior pneumonectomy	Former (20PY)	No	1.6
6	2	66/F	Held for RT	Ultracentral	2 Gy ×30	18	59.1	29.7	None	Never smoker	Yes	2.1
7	2	53/F	Held for RT	Ultracentral	7.5 Gy ×8	6.8	24.1	10.3	Asthma	Former (25PY)	No	6.3
8	2	74/F	Held for RT	Ultracentral	7.5 Gy ×8	5.3	18.5	8.9	COPD, lobectomy + wedge resection	Former (45PY)	No	3.5
9	2	51/F	Held for RT	Peripheral	18 Gy ×3	1.9	7.0	2.5	None	Never smoker	No	5.3
10	2	72/F	Held for RT	Ultracentral	2 Gy ×33	14.3	43.3	23.6	None	Former (20PY)	Yes	3.1
11	2	46/F	Held for RT	Ultracentral	2 Gy ×33	17.6	63.6	33.0	None	Never smoker	Yes	1.5
12	2	68/F	Overlapping with RT	Central	12 Gy ×5	6	32.3	7.2	Prior pulmonary embolism	Former (45PY)	No	2.7
13	2	63/M	Held for RT	Ultracentral	3 Gy ×10	Unavailable			None	Never smoker	No	2.1
14	2	73/F	Held for RT	Ultracentral	8 Gy ×2	3.01	16.3	0.0	None	Never smoker	No	2.6

F, female; M, male; MLD, mean lung dose; PY, pack-years; RT, radiotherapy; V5, lung volume receiving a dose of ≥5 Gy; V20, lung volume receiving a dose of ≥20 Gy.

selected patients who received osimertinib overlapping with TRT did not seem to have a significantly increased risk of pneumonitis. Whereas robust risk factor analysis is limited by the relatively small cohort, we identified mean lung dose as a strong predictor of pneumonitis. Similarly to Smith et al.,[16] we found that most patients with clinical pneumonitis had at least central, and predominantly ultracentral tumors, which should inform caution when discussing risks in these scenarios.

Several points require further discussion. Pneumonitis is critical toxicity for patients with EGFR-mutant NSCLC, not only because of short-term risks but also the potential for the need for prolonged TKI hold and impact on access to subsequent treatments and/or clinical trials. Although the FLAURA trial reported a low risk of grade 2+ pneumonitis of less than 5% in patients treated with osimertinib, subsequent retrospective series have reported rates of pneumonitis ranging as high as 18% with grade 2+ ranging from 9% to 13.6% and grade 3 or higher ranging from 1.8% to 9.1%. [4,10–15] Our reported incidence of 15.7% (13.7% grade 2+, and 4.9% grade 3 or higher) falls at the higher end of this range, though the historical comparison is difficult to interpret given differences in patient and treatment characteristics.

Currently, there are no prospective series assessing the risk of pneumonitis in patients receiving TRT with osimertinib, although the ongoing NORTHSTAR trial should help address this gap.[20] Historically, trials seeking to combine TRT with earlier-generation TKIs reported significant toxicities, including rates of pneumonitis ranging as high as 44%.[6–8] These trials were characterized by large treatment fields. More recently, the randomized phase 3 SINDAS trial of first-generation TKI with or without SBRT reported encouraging results, with significant improvement in PFS and a rate of grade 3 to 4 pneumonitis of 5% with the use of SBRT in addition to TKI.[21] However, it is important to note that SBRT was delivered before TKI administration, not concurrently. The LAURA trial, currently in progress, also evaluates the use of TRT before TKI and will provide additional insight.[22]

Two small retrospective series of concurrent RT and osimertinib highlight the significant potential risks associated with concurrent use of osimertinib with TRT. Jia et al.[17] reported that 10 out of 11 patients (91%) experienced grade 2 or greater pneumonitis, whereas Smith et al.[16] noted that 9 of 16 patients (56%) receiving TRT while on osimertinib developed grade 2 or greater pneumonitis. It is critical to note that all patients treated in the study by Jia et al.[17] and all but two patients treated in the study by Smith et al.[16] continued osimertinib during RT without a treatment hold and that patients in both studies were treated to relatively high

Table 4. Logistic Regression Analyses for Clinically Significant (Common Terminology Criteria For Adverse Events Version 5.0 Grade 2 or More) Treatment-Related Pneumonitis by Patient and Treatment Characteristics

	Univariable			Multivariable		
Variable	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Sex (male)						
Female	6.72	(0.839-53.9)	0.073	6.34	(0.735-54.8)	0.093
Age[a]	1.02	(0.971-1.07)	0.412			
Osimertinib status (overlapping)						
Held	1.76	(0.364-8.55)	0.480			
Tumor location (other)						
Lung/mediastinum	6.07	(0.756-48.7)	0.090	3.77	(0.442-32.2)	0.225
Pulmonary comorbidity (no)						
Yes	1.14	(0.286-4.54)	0.854			
Previous thoracic radiotherapy (no)						
Yes	0.769	(0.089-6.67)	0.812			
Treatment type (non-SBRT)						
SBRT	1.05	(0.339-3.23)	0.937			
Lung V5[a]	1.03	(0.995-1.06)	0.103			
Lung V20[a]	1.06	(0.996-1.13)	0.066			
Mean lung dose[a]	1.18	(1.03-1.34)	0.014	1.19	(1.03-1.37)	0.021
EQD2 normalized mean lung dose	1.21	(1.03-1.43)	0.024			

Note: Reference variables in parentheses.
[a]Continuous variables per percentage point (for V5, and V20) or per Gy (for mean lung dose).
CI, confidence interval; EQD2, equivalence dose in 2 Gy fractions; SBRT, stereotactic body radiotherapy; V5, lung volume receiving a dose of ≥5 Gy; V20, lung volume receiving a dose of ≥20 Gy.

doses of RT. Both factors may have contributed to the significant rates of pneumonitis reported.

Whereas we did not see an increased risk of pneumonitis in patients who continued osimertinib during RT, it is critical to note that most patients in our study held osimertinib during TRT. In addition, a significantly lower fraction of patients who continued osimertinib during RT received radiation to a lung or mediastinal lesion. Although not statistically significant, the median prescribed radiation dose was numerically lower in our cohort of patients who received osimertinib overlapping with radiation compared with patients for whom osimertinib was held and compared with patients in both the studies of Jia et al.[17] and Smith et al.[16] In carefully selected patients who continued osimertinib, there was no increased risk of pneumonitis.

Holding osimertinib is not without potential risks. In our study, there was a low, though not negligible, rate of disease progression during RT, including a patient who experienced rapid and symptomatic disease progression in the CNS whereas osimertinib was held for TRT. Caution should be taken before holding osimertinib in patients with known extrathoracic metastases.

Our study identified mean lung dose as the only significant factor associated with the development of pneumonitis on multivariate analysis. This finding is consistent with previous studies, which have suggested that higher lung doses are associated with an increased

Table 5. Follow-Up and Oncologic Outcomes

Measured Outcome	Total (N = 102)	Osimertinib Overlapping (n = 22)	Osimertinib Held During RT (n = 80)
Follow-up (mo), median [range]	10.2 [1.9-53.2]	8 [1.9-53.2]	12.7 [2.1-52.3]
Overall survival (mo), median (95% CI)	23.2 (13.7-44)	13.7 (7.5-NR)	23.7 (15.2-44.9)
Progression-free survival (mo), median (95% CI)	5.8 (3.2-7.5)	3.0 (2.2-7.3)	7.0 (3.7-8.9)
Any progression	78 (76.5)	19 (86.4)	59 (73.8)
Local progression	27 (26.5)	7 (31.8)	20 (25.0)
Regional progression	38 (37.3)	10 (45.5)	28 (35.0)
Distant progression	71 (69.6)	16 (72.7)	55 (68.8)
Progression during RT	3 (2.9)	1 (4.6)	2 (2.5)

Note: All values are n (%) unless otherwise specified.
CI, confidence interval; RT, radiotherapy.

risk of developing pneumonitis.[7,23] In addition, we noted an overrepresentation of central and ultracentral tumors among patients who developed clinically significant pneumonitis. This is consistent with the recent work by Smith et al.[16] who noted that severe pneumonitis was limited to patients receiving TRT to central lung lesions, suggesting that central location could represent an additional risk factor for the development of pneumonitis in this patient population.

The disease and mortality outcomes for the patients included in the study were also analyzed. We noted a median overall survival of 23.2 months and progression-free survival of 5.8 months. There was, however, significant variability in each of these outcomes, reflecting the heterogeneity of our patient population. Most patients (76.5%) experienced disease progression, however, the survival post-TRT was observed to be markedly longer than the progression-free survival. This is likely explained by the availability of additional interventions (further radiation, ablation, alternative systemic therapies), and supports the use of radical interventions like TRT for patients with oligoprogressive disease and otherwise well-controlled metastatic disease.

There are several important limitations to this study. First, the retrospective nature of this study introduces inherent biases in our results. Furthermore, the combination of the relatively small sample size and the limited number of pneumonitis events limits our ability to comprehensively analyze the risk factors of pneumonitis. More importantly, there was significant heterogeneity in patient characteristics and treatment conditions including fractionation schemes, which further limits the strength of our conclusions. Finally, the limited number of patients receiving TRT overlapping with osimertinib therapy, and the relatively short median follow-up for patients in this subpopulation (7.7 mo) restricted our ability to capture late pneumonitis events in this cohort and, therefore, limited our ability to make definitive conclusions regarding the safety of this practice across large patient cohorts.

In conclusion, this pooled multi-institutional study represents the largest to-date analysis of patients receiving TRT and osimertinib therapy. It establishes incidence rates of pneumonitis in this population and denotes the relative safety of this approach in carefully selected patients. Furthermore, this work investigates potential risk factors for pneumonitis and identifies mean lung dose and central lung tumor location as potentially associated with an increased risk of clinically significant pneumonitis. Collectively, the study provides important data to inform thoracic oncology providers and patients in their decision-making when discussing the use of thoracic radiation in combination with osimertinib.

CRediT Authorship Contribution Statement

Leou Ismael Banla: Conceptualization, Investigation, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing.

Alice Tzeng: Data curation, Investigation, Methodology, Writing - review & editing.

John P. Baillieul: Investigation, Data curation, Writing - review & editing.

Melin J. Kandekhar: Investigation, Methodology, Writing - review & editing.

Kelly J. Fitzgerald: Investigation, Writing - review & editing.

Jaclyn LoPiccolo: Project administration, Writing - review & editing.

Holly A. Poitras: Investigation, Writing - review & editing.

Dan E. Soto: Investigation, Writing - review & editing.

Julia K. Rotow: Investigation, Methodology, Writing - review & editing

Lisa Singer: Investigation, Methodology, Data curation, Writing - review & editing

Henning Willers: Investigation, Methodology, Data curation, Writing - review & editing.

David E. Kozono: Investigation, Methodology, Writing - review & editing.

Pasi A. Janne: Investigation, Writing - review & editing.

Raymond H. Mak: Investigation, Project administration, Writing - review & editing.

Zofia Piotrowska: Conceptualization, Methodology, Investigation, Writing - review & editing.

Florence K. Keane: Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing.

Benjamin H. Kann: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Project administration, Writing - original draft, Writing - review & editing, Supervision.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100560.

References

1. Marin-Acevedo JA, Pellini B, Kimbrough EO, Hicks JK, Chiappori A. Treatment strategies for non-small cell lung cancer with common *EGFR* mutations: a review of the history of EGFR TKIs approval and emerging data. *Cancers (Basel)*. 2023;15:629.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73:17–48.

3. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR* -mutated advanced NSCLC. *N Engl J Med*. 2020;382:41–50.
4. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR -mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
5. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected *EGFR* -mutated non-small-cell lung cancer. *N Engl J Med*. 2020;383:1711–1723.
6. Wan J, Cohen V, Agulnik J, et al. Unexpected high lung toxicity from radiation pneumonitis in a Phase I/II trial of concurrent erlotinib with limited field radiation for intermediate prognosis patients with Stage III or inoperable Stage IIB non-small-cell lung cancer(NSCLC). *Int J Radiat Oncol Biol Phys*. 2009;75(suppl):S110.
7. Jia W, Gao Q, Wang M, et al. Overlap time is an independent risk factor of radiation pneumonitis for patients treated with simultaneous EGFR-TKI and thoracic radiotherapy. *Radiat Oncol*. 2021;16:41.
8. 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;9:882–885.
9. Wang XS, Bai YF, Verma V, et al. Randomized trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic EGFR-mutated non-small cell lung cancer. *J Natl Cancer Inst*. 2023;115:742–748.
10. Yamamoto G, Asahina H, Honjo O, et al. First-line osimertinib in elderly patients with epidermal growth factor receptor-mutated advanced non-small cell lung cancer: a retrospective multicenter study (HOT2002). *Sci Rep*. 2021;11:23140.
11. Kishikawa T, Kasai T, Okada M, et al. Osimertinib, a third-generation EGFR tyrosine kinase inhibitor: A retrospective multicenter study of its real-world efficacy and safety in advanced/recurrent non-small cell lung carcinoma. *Thorac Cancer*. 2020;11:935–942.
12. Sakata Y, Sakata S, Oya Y, et al. Osimertinib as first-line treatment for advanced epidermal growth factor receptor mutation positive non-small-cell lung cancer in a real-world setting (OSI-FACT). *Eur J Cancer*. 2021; 159:144–153.
13. Lorenzi M, Ferro A, Cecere F, et al. First-line osimertinib in patients with EGFR-mutant advanced non-small cell lung cancer: outcome and safety in the real world: FLOWER study. *Oncologist*. 2022;27:87–e115.
14. Gemma A, Kusumoto M, Sakai F, et al. Real-world evaluation of factors for interstitial lung disease incidence and radiologic characteristics in patients with EGFR T790M–positive NSCLC treated with osimertinib in Japan. *J Thorac Oncol*. 2020;15:1893–1906.
15. Sato Y, Sumikawa H, Shibaki R, et al. Drug-related pneumonitis induced by osimertinib as first-line treatment for epidermal growth factor receptor mutation-positive non-small cell lung cancer a real-world setting. *Chest*. 2022;162:1188–1198.
16. Smith CP, Xiang M, Yoon SM, et al. Brief report: severe pneumonitis after combined thoracic radiotherapy and osimertinib. *JTO Clin Res Rep*. 2023;4:100468.
17. Jia W, Guo H, Jing W, et al. An especially high rate of radiation pneumonitis observed in patients treated with thoracic radiotherapy and simultaneous osimertinib. *Radiother Oncol*. 2020;152:96–100.
18. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE). v5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed March 26, 2023.
19. Cox JD, Stetz J, Pajak TF. Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31:1341–1346.
20. Khan TM, Verbus EA, Gandhi S, Heymach JV, Hernandez JM, Elamin YY. Osimertinib, surgery, and radiation therapy in treating patients with Stage IIIB or IV non-small cell lung cancer with EGFR mutations (NORTHSTAR). *Ann Surg Oncol*. 2022;29:4688–4689.
21. Wang X, Zeng M. First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small cell lung cancer: interim results of a randomized phase III, open-label clinical trial (SINDAS) (NCT02893332). 2020; 38(suppl 15):9508–9508.
22. Lu S, Casarini I, Kato T, et al. Osimertinib maintenance after definitive chemoradiation in patients with unresectable EGFR mutation positive stage III non-small-cell lung cancer: LAURA trial in progress. *Clin Lung Cancer*. 2021;22:371–375.
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;7:807–813.