Original Article

Pooled analysis on image-guided moderately hypofractionated thoracic irradiation in inoperable node-positive/recurrent patients with non–small cell lung cancer with poor prognostic factors and severely limited pulmonary function and reserve

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BACKGROUND: The objective of this study was to investigate the feasibility and efficacy of image-guided moderately hypofractionated thoracic radiotherapy (hypo-IGRT) in patients with non–small cell lung cancer (NSCLC) with poor performance status and severely limited pulmonary function and reserve. **METHODS:** Consecutive inoperable patients who had node-positive, stage IIB-IIIC (TNM, 8th edition) or recurrent NSCLC, had an Eastern Cooperative Oncology Group performance status ≥1, and had a forced expiratory volume in 1 second (FEV_1) ≤1.0 L, had a single-breath diffusing capacity of the lung for carbon monoxide (DLCO-SB) ≤40% and/or on long-term oxygen therapy were analyzed. All patients received hypofractionated IGRT to a total dose of 42.0 to 49.0 Gy/13 to 16 fractions (2.8-3.5 Gy/fraction) (equivalent dose in 2-Gy fractions/biologically effective dose [α/β = 10] = 45.5-55.1 Gy/54.6-66.2 Gy) alone. Patients were monitored closely for nonhematological toxicity, which was classified per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. **RESULTS:** Between 2014 and 2021, 47 consecutive patients with a median age of 72 years (range, 52.2-88 years) were treated. At baseline, the median FEV_1, vital capacity, and DLCO-SB were 1.17 L (range, 0.69-2.84 L), 2.34 L (range, 1.23-3.74 L), and 35% predicted (range, 13.3%-69.0%), respectively. The mean and median planning target volumes were 410.8 cc (SD, 267.1 cc) and 315.4 cc (range, 83.4-1174.1 cc). With a median follow-up of 28.9 months (range, 0.5-90.6 months) after RT, the median progression-free survival (PFS)/overall survival (OS) and 6- and 12-month PFS/OS rates were 10.4 months (95% CI, 7-13.8 months)/18.3 months (95% CI, 9.2-27.4 months), 70%/89.4%, and 38.8%/66%, respectively. Treatment was well tolerated with only 1 case each of grade 3 pneumonitis and esophagitis. No toxicity greater than grade 3 was observed. **CONCLUSIONS:** Patients with inoperable node-positive NSCLC, a poor performance status, and severely limited lung function can be safely and effectively treated with individualized moderately hypofractionated IGRT. The achieved survival rates for this highly multimorbid group of patients were encouraging. ***Cancer* 2022;128:2358-2366**.

KEYWORDS: hypofractionation, image-guided radiotherapy, non–small cell lung cancer (NSCLC), pulmonary function, thoracic radiotherapy.

INTRODUCTION

Non–small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide.[1] In recent years, consolidation PD-L1 inhibition with durvalumab after concurrent chemoradiation (CRT) has been established as the new standard of care for inoperable node-positive stage IIB (N1)/III NSCLC.[2] However, the seminal trial that established this treatment paradigm enrolled patients with favorable baseline performance status. In patients with poor prognostic factors (frailty, poor baseline performance status, multimorbidity), concurrent CRT is not an option and patients are often referred for palliative radiotherapy (RT) alone or best supportive care.[3]

Accelerated hypofractionated RT (AHRT) is an alternative strategy ensuring delivery of higher biologically effective doses (BEDs) while minimizing the overall treatment time and thus promoting reduced repopulation of tumor cells.[4] In previous series investigating AHRT alone in locally advanced NSCLC, patients with favorable risk factors were evaluated,[5-7] as were patients with unfavorable risk factors.[8-11] More recently, the first randomized trial on AHRT in patients with poor performance status was published.[12] However, there is a knowledge gap in a distinct subpopulation with poor prognostic

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factors and, importantly, severely limited pulmonary function and reserve (forced expiratory volume in 1 second [FEV_1] ≤1 L and/or single-breath diffusing capacity of the lung for carbon monoxide [DLCO-SB] ≤40% predicted and/or on long-term oxygen therapy). Previously, we demonstrated our initial experience with this protocol.[13,14] Here, we present a pooled analysis of all patients treated at our institution with this concept from 2014 onward. To our best knowledge, this report represents the first application of hypofractionated thoracic RT (hypo-IGRT) in patients with not only poor prognostic factors, but also severely compromised pulmonary function and reserve.

MATERIALS AND METHODS

Patients

We reviewed the medical charts of consecutive patients treated at our department from January 2014 through July 2021. Inclusion criteria included patients with cytologically/histologically confirmed NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥1, inoperable node-positive clinical stage IIB/III (TNM 8th edition), or recurrent disease ineligible for concurrent CRT. All patients had FEV_1 ≤1.0L and/or DLCO-SB ≤40% and/or were on long-term oxygen therapy (LTOT).

Initial workup comprised positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (CT) scan or CT of the chest/upper abdomen and a contrast-enhanced CT or magnetic resonance imaging of the brain and pulmonary function tests (PFTs). The Ludwig Maximilian University of Munich institutional review board approved this analysis (reference numbers 17-230 and 17-233). Patients from August 2017 onward were prospectively enrolled.

Radiotherapy

Patients without isolated lymph node recurrence underwent a 4-dimensional CT scan as previously described.[14] Target delineation and treatment planning were previously described; importantly, tighter planning target volume (PTV) margins of 5 mm customarily used in stereotactic RT planning were used to account for patients' limited pulmonary reserve.[14] All patients received 3-dimensional CRT/intensity-modulated RT over a course of 13 to 16 once-daily fractions given 5 days per week to a total dose of 42.0 to 49.0 Gy/13 to 16 fractions (2.8-3.5 Gy/fraction) (equivalent dose in 2-Gy fractions/BED [$\alpha/\beta = 10$] = 45.5-55.1 Gy/54.6-66.2 Gy). This was estimated as follows:

$$BED = nd\ \left(1 + \mathrm{d}/\left[\alpha/\beta\right]\right)$$

$$EQD2 = nd\left(\frac{d + \left[\alpha/\beta\right]}{2 + \left[\alpha/\beta\right]}\right)$$

where n is the number of fractions, d is dose per fraction, and the α/β for lung cancer was set at 10 with no correction for time.[15] Induction systemic therapy was permitted. Radiotherapy was delivered on a linear accelerator (Elekta Synergy/Versa HD, Stockholm, Sweden) with 6/15-MV photons. Image guidance was performed with kilovoltage-cone beam CT. Normal tissue dose-volume constraints were based on Radiation Therapy Oncology Group 0937.[16]

Study Objectives and Statistical Analysis

The primary objective was median progression-free survival (PFS). Secondary objectives included locoregional PFS, distant metastasis-free survival, overall survival (OS), and toxicity. Treatment response was assessed on the first follow-up imaging (approximately 3 months) after IGRT according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria. Progressive disease within or adjacent to the RT field was considered to be locoregional failure at the date of progression. PFS was defined as the time to locoregional/systemic progression or death. Locoregional PFS and distant metastasis-free survival were defined as the time to locoregional recurrence/progression and time to distant progression, respectively. Overall survival was defined as the time to death from any cause or last follow-up. Furthermore, median follow-up was calculated as the time from the last day of hypo-IGRT to the last or loss of follow-up using the reverse Kaplan-Meier method. Time to event was calculated using the Kaplan-Meier method and compared using the log-rank test.

Univariate analysis was performed to determine (borderline) significant clinical and treatment-related factors using the log-rank test. Lung function parameters and PTV were dichotomized based on median values. Variables that demonstrated (borderline) significance in the univariate analysis ($P < .1$) were included in the multivariate Cox regression analysis to identify predictors of PFS and OS after hypo-IGRT. In addition, PFTs were performed after radiotherapy if clinically indicated. Changes in PFT were calculated by subtracting the baseline value from the follow-up and were evaluated using the paired Wilcoxon signed-rank test. A P value < .05 was considered statistically significant. All statistics were performed using IBM SPSS version 27 (IBM, Armonk, New York).

Follow-Up and Data Collection

Patients were assessed before treatment and at least twice per week during the course of treatment as well as 4 to 6 weeks after hypo-IGRT to monitor acute toxicity. A whole-body PET/CT or CT scan of the chest/upper abdomen was performed every 3 months for the first 2 years, every 6 months for the following 2 years, and annually thereafter. Acute nonhematological toxicity was classified per Common Terminology Criteria for Adverse Events version 5.0 during and up to 3 months posttreatment (6 months posttreatment for pneumonitis where applicable).

RESULTS

We reviewed the medical history of eligible patients treated at our department from January 2014 through July 2021 based on the previously described criteria. The median follow-up was 28.9 months (range, 0.5-90.6) months. The median age was 72 years (range, 52.2-88). In 34 of 39 (87.2%) patients, DLCO-SB was ≤40% predicted, 18 of 47 (38.3%) were on LTOT, and 18 of 47 patients (38.3%) had an FEV_1 ≤1 L. Before treatment, median baseline DLCO-SB was 35% predicted (range, 13.3-69.0), median FEV_1 was 1.17 L (range, 0.69-2.84 L), median vital capacity was 2.34 L (range, 1.23-3.74 L), and the mean (SD) and median PTV were 410.8 cc (267.1 cc) and 315.4 cc (range, 83.4-1174.1 cc). Nineteen of 47 patients (40.4%) received induction systemic therapy: platinum-doublet in all but 1 patient who had nodal recurrence while on nivolumab monotherapy (Table 1). All 47 patients were deemed ineligible for concurrent CRT at the multidisciplinary tumor board and thus referred for hypo-IGRT.

Following hypo-IGRT, complete remission, partial remission/stable disease, and progressive disease were observed in 1 of 47 (2.1%), 36 of 47 (76.6%), and 7 of 47 (14.9%) patients, whereas in 3 of 47 (6.4%) patients, the follow-up was too short, or death occurred before first follow-up imaging.

Locoregional and distant failure were observed in 18 of 47 (38.3%) and 14 of 47 (29.8%) patients, respectively. The median and the 6- and 12-month locoregional-PFS rates were 19.4 months (95% CI, 6.9-31.9 months), 88%, and 61.7%, respectively, and the median DMFS and the 6- and 12-month DMFS rates were not reached, 82%, and 71%, respectively (Figs. 1 and 2); 10 of the 47 (21.3%) patients received salvage systemic treatment. At the cutoff date of December 31, 2021, 19 of 47 (40.4%) patients were still alive. The median PFS and the 6- and 12-month PFS rates

TABLE 1. Patient and Treatment Characteristics

	No. (%)
Total	47 (100)
Age, y	
Median	72 (52.2-88)
Mean (SD)	71.9 (8.6)
Age >70 y	
Yes	27 (57.4)
No	20 (42.6)
Sex	
Male	27 (57.4)
Female	20 (42.6)
T category	
Tx	8 (17)
T1	1 (2.1)
T2	8 (17)
T3	13 (27.7)
T4	17 (36.2)
N category	
N1	9 (19.1)
N2	24 (51.1)
N3	14 (29.8)
Stage	
IIB	2 (4.3)
IIIA	8 (17)
IIIB	17 (36.2)
IIIC	12 (25.5)
Recurrent (stage III)	8 (17)
CCI	
4-6	30 (63.8)
≥7	17 (36.2)
Staging PET-CT	
Yes	42 (89.4)
No	5 (10.6)
RT modality	
3D-CRT	6 (12.8)
IMRT/VMAT	41 (87.2)
PTV, cc	
Median (range)	315.4 (83.4-1174.1)
Mean (SD)	410.8 (267.1)
Histology	
SCC	20 (42.6)
ACC	22 (46.8)
NOS	5 (10.6)
Induction systemic therapy	
Yes	19 (40.4)
No	28 (59.6)
Salvage systemic therapy	
Yes	10 (21.3)
No	37 (78.7)
Baseline FEV_1	
Median (range), L	1.17 (0.69-2.84)
Mean (SD), L	1.28 (0.5)
Median (range), %	47.5 (27.9-96.4)
Mean (SD), %	51 (17.1)
Vital capacity	
Median (range), L	2.34 (1.23-3.74)
Mean (SD), L	2.25 (0.64)
Median (range), %	67.8 (33-110)
Mean (SD), %	67.7 (14)
Baseline DLCO-SB	
Median, mmol/min/kPa	2.59 (1-4.7)
Mean (SD), mmol/min/kPa	2.7 (0.88)
Median predicted (range), %	35 (13.3-69)
Mean (SD), %	34.51 (10.46)
LTOT	
Yes	18 (39.3)

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; ACC, adenocarcinoma; CCI, Charlson Comorbidity Index; DLCO-SB, single-breath diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; IMRT, intensity-modulated radiation therapy; NOS, not otherwise specified; PET/CT, positron emission tomography/computed tomography; PTV, planning target volume; RT, radiotherapy; SCC, squamous cell carcinoma; VMAT, volumetric-modulated arc therapy.

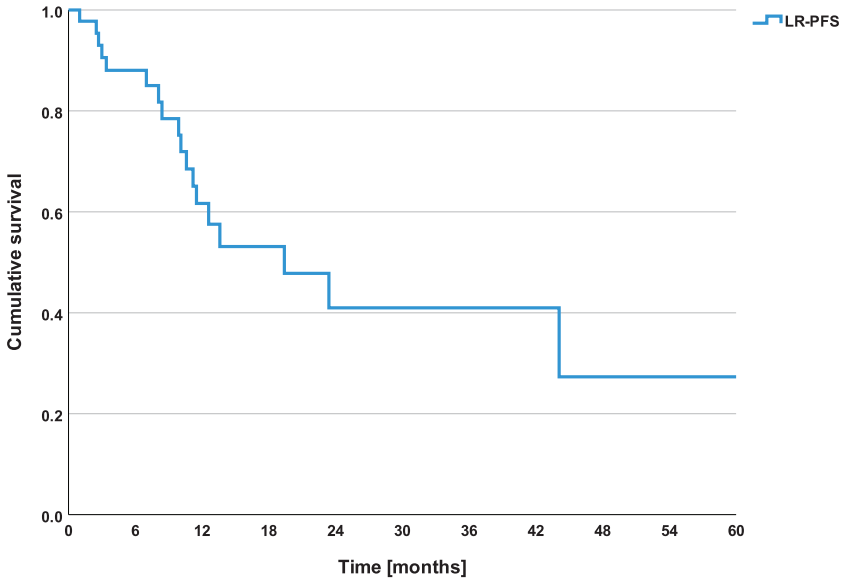

FIGURE 1. Locoregional progression-free survival (LR-PFS).

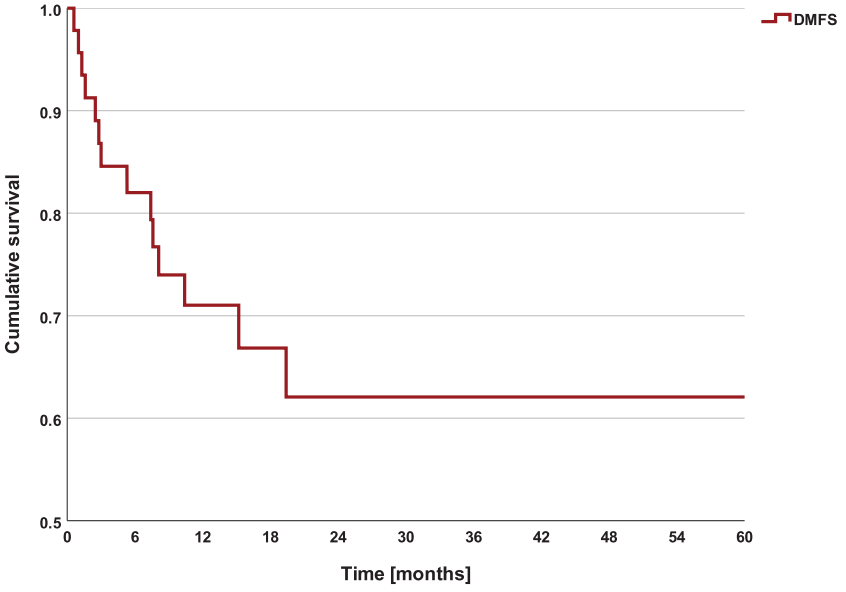

FIGURE 2. Distant metastasis-free survival (DMFS).

were 10.4 months (95% CI, 7-13.8 months), 70%, and 38.8%, respectively. The median and the 6- and 12-month OS rates were 18.3 months (95% CI, 9.2-27.4 months), 89.4%, and 66%, respectively (Fig. 3). Dosimetric parameters were as follows: median mean lung and heart doses were 9.27 Gy (range, 5.26-14.33 Gy) and 5.26 Gy (range, 0.56-13.32 Gy), respectively. The median percentage of normal lung volume receiving at least 20 Gy was 15.2% (range, 6.19%-30.14%); the median mean esophageal dose was 13.96 Gy (range, 0.93-24.3 Gy).

On univariate analysis, ECOG-PS (P = .014), baseline FEV_1 (P = .01), and PTV (P = .013) were identified as significant prognosticators of OS, whereas histological subtype (P = .081) was a borderline prognosticator of OS. Furthermore, tumor histological

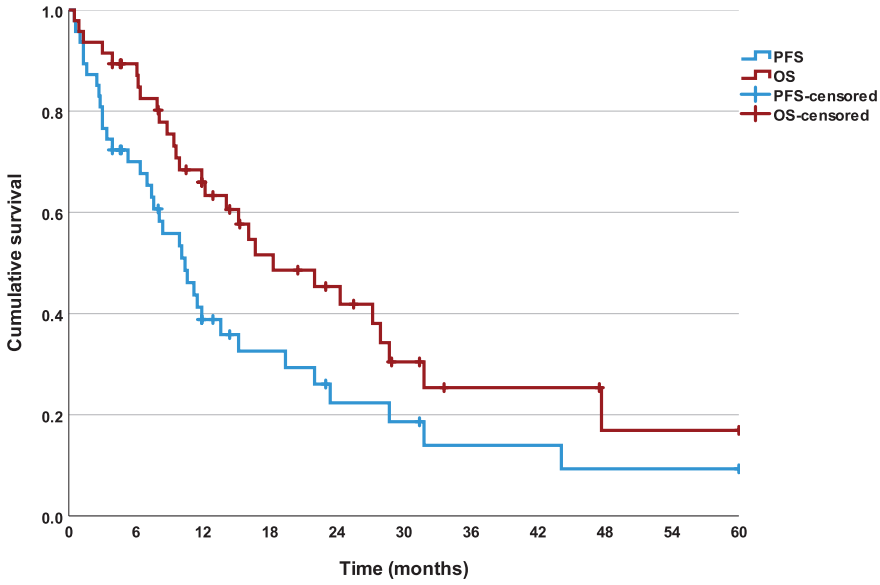

FIGURE 3. Progression-free survival and overall survival (PFS and OS).

subtype ($P = .03$), salvage systemic therapy ($P = .032$), and PTV ($P = .008$) were identified as significant predictors for PFS. On multivariate analysis, ECOG-PS (hazard ratio [HR], 2.575; 95% CI, 1.021-6.493; $P = .045$) and PTV (HR, 2.419; 95% CI, 1.036-5.647; $P = .041$) remained significant prognosticators of OS. Furthermore, only PTV (HR, 2.080; 95% CI, 0.916-4.724; $P = .08$) resulted in borderline statistical significance for PFS outcome. The univariate and multivariate analyses with corresponding HRs and P values are presented in Table 2.

Postradiotherapy PFT Changes

PFT changes were assessed after radiotherapy. PFT availability (mean [SD] = 3.3 [2.9] months) after RT was 62% (29 of 47). The reasons for nonavailability of PFTs were the result of 1) the deterioration of patients' general condition, 2) compliance issues, and 3) death before first follow-up. After RT, mean DLCO-SB (absolute and %Predicted) declined by 5.9% and 8.1%, respectively. However, all PFT changes were not statistically significant ($P > .05$); Table 3.

Toxicity

At baseline, because of underlying chronic obstructive pulmonary disease, 37 of 47 patients (79%) presented with some form of dyspnea. Baseline symptoms and treatment-related acute toxicity are presented in Supporting Table 1 and only treatment-related acute toxicity are shown in Supporting Table 2 (there were some cases of aggravation of baseline cough and dyspnea). Overall, treatment was well tolerated with only 1 case each of grade 3 pneumonitis and esophagitis. No greater than grade 3 acute adverse event was observed.

DISCUSSION

In this analysis, we report on our long-term experience in managing multimorbid locally advanced/recurrent node-positive patients with NSCLC and severely compromised lung function who were ineligible for definitive concurrent chemoradiation. The results of our findings are relevant, providing a clinical pathway for the management of these high-risk patients. To our best knowledge, although other series assessing hypofractionated RT enrolled patients with adverse prognostic factors, the distinct feature of our analysis is the inclusion of patients with severely limited pulmonary function and reserve. All treated patients had an $FEV_1 \leq 1.0$ L and/or DLCO-SB $\leq 40\%$ and/or were on LTOT. Other studies on AHRT in borderline patients do not disclose information on patients' pulmonary status,[8-11] except for a dose-escalation study, in which the mean FEV_1 and DLCO (%Predicted) was approximately 60% in both cases.[11] In our study, mean FEV_1 and DLCO were significantly lower at 51% and 34.5%, respectively.

The majority (60%) of patients were enrolled prospectively and the majority (78.7%) did not receive any salvage systemic treatment after radiotherapy, which was not a significant predictor for PFS/OS on multivariate

TABLE 2. Univariate and Multivariate Analysis

		Univariate Analysis: *P*		Multivariate Analysis			
	No. of Patients	OS	PFS	OS, HR (95% CI)	*P*	PFS, HR (95% CI)	*P*
Age, y							
≥70	27	.682	.849				
<70	20						
Sex							
Male	27	.422	.517				
Female	20						
T category							
Tx-T2	17	.365	.308				
T3-T4	30						
N category							
N1	9	.167	.415				
N2	24						
N3	14						
Stage IIIC/recurrent							
Yes	20	.455	.637				
No	27						
ECOG-PS							
1	27	.014	.181				
2-3	20			2.575 (1.021-6.493)	.045		
CCI							
4-6	30	.464	.535				
≥7	17						
Histology							
SCC	20	.081	.030	1.830 (0.827-4.051)	.136	1.834 (0.884-3.803)	.103
Non-SCC	27						
Induction systemic therapy							
Yes	19	.778	.845				
No	28						
Salvage systemic therapy							
Yes	10	.835	.032			1.883 (0.855-4.149)	.116
No	37						
Vital capacity >2.34 L							
Yes	22	.136	.386				
No	22						
Baseline FEV_1 >1.17 L							
Yes	22	.01	.231	1.572 (0.615-4.017)	.344		
No	25						
Baseline DLCO-SB >35% of predicted							
Yes	19	.675	.506				
No	20						
LTOT							
Yes	18	.438	.764				
No	29						
PTV >315 cc							
Yes	24	.013	.008	2.419 (1.036-5.647)	.041	2.080 (0.916-4.724)	.08
No	23						

Abbreviations: CCI, Charlson Comorbidity Index; DLCO-SB, single-breath diffusing capacity of the lung for carbon monoxide; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; LTOT, long-term oxygen therapy; OS, overall survival; PFS, progression-free survival; PTV, planning target volume; SCC, squamous cell carcinoma.

TABLE 3. PFT Distribution

	Baseline (n = 47)		Post-RT (n = 29)		Relative Δ From Baseline, % (SD)	Paired Wilcoxon Signed-Rank Test: No. of Pairs (*P*)
	No.	Mean (SD)	No.	Mean (SD)		
FEV_1, L	47	1.28 (0.50)	29	1.3 (0.51)	0.46 (22.94)	29 (.9)
FEV_1, %Predicted	46	51.04 (17.09)	27	51.40 (16.32)	3.28 (25.54)	27 (.61)
VC, L	44	2.25 (0.64)	24	2.35 (0.86)	0.53 (21.87)	22 (.59)
VC, %Predicted	44	67.72 (14.04)	24	67.42 (16.52)	3.53 (24.84)	22 (.97)
DLCO-SB, mmol/min/kPa	31	2.70 (0.88)	13	2.73 (0.78)	–5.90 (17.33)	11 (.2)
DLCO-SB, %	39	34.51 (10.46)	15	34.07 (7.35)	–8.12 (19.40)	12 (.13)

Abbreviations: DLCO-SB, single-breath diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; PFT, pulmonary function test; RT, radiotherapy; VC, vital capacity.

analysis. Notably on multivariate analysis, ECOG-PS ($P = .045$) and PTV ($P = .04$) were significant prognosticators for OS, whereas only PTV ($P = .08$) was a borderline statistical significant prognosticator for PFS outcome. Furthermore, most patients presented in advanced age (median, 72 years), the absolute majority of patients had an age-adjusted Charlson Comorbidity Index score >4 and presented with more advanced disease: 8, 17, and 12 patients with stage IIIA, IIIB, and IIIC disease (TNM 8th edition) and 8 patients with regional nodal recurrence.

The present analysis fares favorably in comparison to other studies. With a median follow-up of 28.9 months, the median PFS and 6- and 12-month PFS rates were 10.4 months and 70% and 38.8%, respectively. The median and 6- and 12-month OS rates were 18.3 months and 89.4% and 66%. Previously, the randomized phase 3 Japan Clinical Oncology Group 0301 trial investigating conventional thoracic irradiation with or without low-dose carboplatin in elderly patients (median age, 77 years) with inoperable stage III NSCLC reported a median OS of 16.9 (13.4-20.3) months in the radiotherapy alone group. Importantly, the study included patients with ECOG 0-2 and reported 4% treatment-related deaths in the radiotherapy group.[17] More recently, the first phase 3 randomized controlled trial comparing hypofractionated versus conventional radiotherapy alone for stage II/III NSCLC and poor performance status was published. The study was powered to detect a 15% improvement in 1-year survival rate from 45% to 60% between the experimental (60.0 Gy/15 fractions) and the control (60.0 Gy/30 fractions) arm, respectively. After a planned interim analysis demonstrated futility, the study was closed, and 103 patients were randomized with 96 evaluable. At a median follow-up of 8.7 months, the primary end point of 1-year OS was 37.7% versus 44.6% in the experimental and control arms, respectively. In addition, median PFS/OS was 6.4/8.2 months in the hypofractionation arm and 7.3/10.6 months in the normofractionation arm.[12] Another retrospective analysis from one of the participating centers of the previous study retrospectively analyzed 300 stage III patients with NSCLC treated with either AHRT (arm A, 45.0 Gy/15 fractions) or conventionally fractionated RT (arm B, 60.0-63.0 Gy; arm C, >63.0 Gy). Interestingly, despite more patients significantly presenting with adverse risk factors in the AHRT arm (performance status, weight loss, and stage IIIB disease [TNM, 7th edition]), there was no significant benefit in terms of tumor control and OS.[8] Another study reported on patients with mostly metastatic/recurrent disease (64%) and baseline ECOG rating of 2 to 3 (37%) treated with hypofractionated RT to a total dose of 52.5 to 60.0 Gy/15 fractions. At a median follow-up of 13 months, median OS was 15.1 months. In addition, 12-month OS and PFS rates were 63% and 22.5%. Interestingly, no significant survival difference between patients with or without metastases was observed.[9] Westover et al previously published a phase 1 dose-escalation trial with allocation to 50.0/55.0/60.0 Gy in 15-fraction arms. Forty-two percent presented with a PS ≥ 2 and the majority with stage III disease. With a median follow-up of 12.5 months, median survival time was 6 months and no significant differences between the different dose levels was observed.[11] Furthermore, an Italian group recently updated and analyzed its cohort of 76 patients (76.3% with stage III disease) who were ineligible for concurrent chemoradiation (52.6% with Karnofsky Index <70%) and amenable to moderately hypofractionated RT of 60.0 Gy/20 fractions. With a median follow-up of 50 months, the median OS was 17 months.[10]

Overall, in this analysis, treatment was well tolerated with only 1 case each of grade 3 pneumonitis and esophagitis. No greater than grade 3 acute adverse event was observed. Noteworthy was, because of patients' underlying chronic obstructive pulmonary disease, 37 of 47 patients (79%) presented with some form of dyspnea at baseline. Furthermore, we assessed changes in PFT parameters after radiotherapy and only observed a nonsignificant decline in DLCO-SB (absolute and %Predicted) by 5.9% and 8.1%, respectively.

In terms of tumor control, our analysis revealed that locoregional relapse occurred in 18 of 47 patients (38.3%). This is in accordance with previously published radiotherapy alone series. To improve local control, dose escalation had widely been considered a promising strategy. However, randomized controlled trials in unresectable stage III NSCLC treated with concurrent chemoradiation failed to demonstrate a survival benefit.[18,19] Indeed, as used in NRG-Radiation Therapy Oncology Group 1106/American College of Radiology Imaging Network 6697, further refinement of PET in this setting with the advent of immuno-PET tracers might be promising.[20]

Another promising strategy is the use of immune-checkpoint inhibitors in these high-risk patients. Indeed, the Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small

Cell Lung Cancer trial (PACIFIC) and real-word data support this notion with a marked improvement in locoregional control and patient outcome.[2,21] Several studies have been initiated exploring conventionally/hypofractionated RT in combination with PD-L1 inhibition in patients with adverse prognostic factors (SWOG S1933 [NCT04310020], ARCHON-1 [Accelerated Hypofractionated or Conventionally Fractionated Radiotherapy and Durvalumab in Treating Patients With Stage II-III Non-Small Cell Lung Cancer; NCT03801902], TRADE-hypo [Thoracic Radiotherapy Plus Durvalumab in Elderly and/or Frail NSCLC Stage III Patients Unfit for Chemotherapy trial[22]; NCT04351256], and SPIRAL-RT [Phase 2 Trial of Durvalumab in Stage 3 Chemoradiotherapy Ineligible NSCLC Patients Following Radiation Therapy Alone; JMA-IIA00434][23]).

In acknowledgment of the limitations of the current analysis, the results reflect the experience at a single tertiary cancer center and although the prospectively enrolled cohort represented the majority (60%) of patients included in this study, selection bias cannot be excluded for the retrospective cohort. In addition, postradiotherapy PFTs were analyzed, and we observed a decrease in available PFTs. However, this is to be expected in the real-world setting.

Recruitment to an updated institutional protocol for treatment of this distinct cohort on a magnetic resonance–guided radiotherapy treatment platform is ongoing (Ludwig Maximilian University of Munich reference number: 20-793) and could potentially ensure isotoxic dose-escalation strategies. Indeed, a technical report on the first enrolled patient was recently published.[24]

In conclusion, inoperable node-positive NSCLC in patients with a poor performance status and severely limited lung function can be safely and effectively treated with individualized moderately hypofractionated IGRT. The achieved survival rates for this multimorbid group of patients were encouraging.

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CONFLICT OF INTEREST DISCLOSURES

Chukwuka Eze reports receiving consulting fees from Novartis, outside the submitted work. Claus Belka reports receiving grants or contracts from ViewRay, Brainlab, and Elekta; payment or honoraria from Bristol-Myers Squibb, Roche, Merck, AstraZeneca, Elekta, and ViewRay; receiving support for attending meetings or travel from Bristol-Myers Squibb, Roche, Merck, AstraZeneca, Elekta, and ViewRay; and having a leadership or fiduciary role with ESTRO, all outside the submitted work. Farkhad Manapov reports receiving a research grant from AstraZeneca; consulting fees from AstraZeneca, Elekta, Roche, Lilly, Novartis, and Brainlab; receiving payment or honoraria from AstraZeneca; receiving payment for expert testimony from AstraZeneca and Novartis; and participating on data safety monitoring boards for AstraZeneca and Novartis, all outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Chukwuka Eze: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Julian Elias Guggenberger:** Data curation, formal analysis, investigation, methodology, validation, visualization, writing–original draft; and writing–review and editing. **Nina-Sophie Schmidt-Hegemann:** Conceptualization, formal analysis, investigation, methodology, validation, and writing–review and editing. **Saskia Kenndoff:** Data curation, formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Julian Taugner:** Conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Lukas Käsmann:** Conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Stephan Schönecker:** Data curation, formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Benedikt Flörsch:** Data curation, formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Minglun Li:** Conceptualization, formal analysis, investigation, methodology, validation, and writing–review and editing. **Claus Belka:** Conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, and writing–review and editing. **Farkhad Manapov:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, roles/writing–original draft, and writing–review and editing.

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