Clinical and Translational Radiation Oncology 27 (2021) 8–14

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Prospectively scored pulmonary toxicities in non-small cell lung cancer: Results from a randomized phase II dose escalation trial

Christina M. Lutz [a,*], Marianne M. Knap [a], Lone Hoffmann [a], Ditte S. Møller [a], Olfred Hansen [b], Carsten Brink [b], Tine Schytte [b], Christa H. Nyhus [c], Tine McCulloch [d], Svetlana Borissova [e], Markus Alber [f], Azza A. Khalil [a]

[a] Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Oncology, Odense University Hospital, Odense, Denmark
[c] Department of Oncology, Vejle Hospital, Vejle, Denmark
[d] Department of Oncology, Aalborg Hospital, Aalborg, Denmark
[e] Department of Oncology, Herlev Hospital, Herlev, Denmark
[f] Heidelberg Institute for Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany

ARTICLE INFO

Article history:
Received 9 June 2020
Revised 19 November 2020
Accepted 21 November 2020
Available online 26 November 2020

Keywords:
Prospective
Radiation pneumonitis
Locally-advanced non-small cell lung cancer

ABSTRACT

Purpose: Prospectively scored radiation pneumonitis (RP) observed in a national, randomized phase II dose-escalation trial for patients with locally advanced non-small cell lung cancer (NSCLC) was investigated.
Methods: Patients with stage IIB-IIIB histologically proven NSCLC were treated with concomitant chemoradiotherapy (oral Vinorelbine 3times/week) at 60 Gy/30fx (A–59pts) and 66 Gy/33fx (B–58pts) from 2009 to 2013 at five Danish RT centers. Grade 2 RP (CTCAEv3.0) was investigated with univariate analysis for association with clinical and dosimetric parameters, including dyspnea and cough at baseline and during RT. Multivariable logistic regression and Cox regression with regularization were used to find a multivariable model for RP $\geq$ G2.
Results: Despite a tendency of higher mean lung dose in the high-dose arm (median[range] A = 14.9 Gy[5.8,23.1], B = 17.5 Gy[8.6,24.8], p = 0.075), pulmonary toxicities were not significantly different (RP $\geq$ G2 41%(A) and 52%(B), p = 0.231). A Kaplan Meier analysis of the time to RP $\geq$ G2 between the two arms did not reach statistical significance (p = 0.180). Statistically significant risk factors for RP $\geq$ G2 were GTV size (OR = 2.091/100 cm3, p = 0.002), infection at baseline or during RT (OR = 8.087, p = 0.026), dyspnea at baseline (OR = 2.184, p = 0.044) and increase of cough during RT (OR = 2.787, p = 0.008). In the multivariable logistic regression and the Cox regression analysis, the deviances of the most predictive models were within one standard deviation of the null model.
Conclusion: No statistical difference between the high- and low dose arm was found in the risk of developing RP. The univariate analysis identified target volume, infection, dyspnea at baseline, and increase of cough during RT as risk factors for RP. The number of patients was too small to establish a statistically sound multivariable model.

1. Introduction

The current standard treatment of locally-advanced non-small cell lung cancer (LA-NSCLC) consists of concomitant chemoradiotherapy (CRT) at 60–66 Gy in 30–33 fractions (fx). However, both local control and overall survival are poor [1,2], calling for drastic advancements in treatment. During the past decades, several attempts of intensifying RT have been launched. These include increase in radiation dose and decrease in overall treatment time [3–6]. Beyond RT, adjuvant immunotherapy (Duvalumab) following CRT has shown promising progression-free and overall survival in the phase III PACIFIC trial [7,8]. Unfortunately, any treatment intensification is restricted by the severe and sometimes lethal toxicities observed in the standard treatment [2,9]. Severe pulmonary toxicities often have a measurable impact on the quality of life of patients after treatment [10,11]. The most prominent pulmonary toxicity in RT for lung cancer is radiation pneumonitis (RP). RP occurs within nine months after RT. The risk of RP has been linked to a variety of both clinical and dosimetric factors. The most widely acknowledged are age, smoking status, chemotherapy, previously

* Corresponding author at: Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: chrilutz@rm.dk (C.M. Lutz).

https://doi.org/10.1016/j.ctro.2020.11.013

existing pulmonary disease, and (mean) dose to the lungs [12,13]. However, intensifying treatment according to the patient-individual risk for toxicity, though very appealing, requires detailed pre-treatment knowledge of the link between patient and treatment characteristics, and toxicity. In a retrospectively collected patient cohort, detailed baseline information is often difficult, if not impossible, to obtain. A prospectively scored, multi-center trial, build with the intent to follow toxicities closely, is therefore a rare possibility. The multi-center randomized phase II trial (Navalbine And Radiotherapy in Locally Advanced Lung cancer - NARLAL) was designed to determine the effect of the radiosensitizer Vinorelbine (without platinum compound) administered concurrently with RT. The secondary purpose of this trial was to change the national treatment standard from (at the time predominantly used) 60 Gy to a (at the time) moderately escalated 66 Gy schedule. Local control, overall survival, and overall toxicities were published in 2017 by Hansen et al. [14], and the 66 Gy schedule has since been adopted as the standard treatment in Denmark. With the intent to observe the combined effect of the radiosensitizer Vinorelbine and moderate dose escalation on toxicities, an extensive visitation schedule included frequent and detailed pulmonary function and toxicity reporting. The purpose of this study was to investigate the prospectively scored pulmonary toxicities observed in the NARLAL trial and explore the association between RP and clinical factors.

2. Material and methods

Approval for the NARLAL trial was granted by the regional scientific ethical committee and the national board of health. Written informed consent was obtained from all patients. The protocol is registered at clinicaltrials.gov (NCT00887783). Patients were included between 2009 and 2013 at five RT centers in Denmark. All patients had histologically proven LA-NSCLC stage IIB-IIIB (American Joint Committee on Cancer, 7th Edition), Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 1. Before randomization, RT plans with adequate dose coverage and adhering to the organ at risk (OAR) criteria described below were obtained. Detailed exclusion criteria are presented by Hansen et al. in [14] but included forced expiratory volume in 1 s (FEV1) < 1.0L, symptomatic heart disease or myocardial infarction < 6 months prior to treatment, any unstable systemic disease, pleural effusion, previous chemotherapy or RT for lung cancer as well as other active malignancy within the last five years. The number of patients available for analysis is 117.

2.1. Chemotherapy

All patients were treated with two cycles of neoadjuvant chemotherapy (Carboplatin (AUC5) day1 and oral Vinorelbine day1 + 8 (60 mg/m^2 first cycle and 80 mg/m^2 second cycle) [14]) at six and three weeks before RT. Concomitant chemotherapy (oral Vinorelbine 50 mg) was administered three times/week during the whole course of RT.

2.2. Radiotherapy

Before inclusion, a 4D-CT scan with contrast of the chest and upper abdomen, and a whole-body PET-scan were available for all patients. The patients were randomized into two groups, the standard dose arm at 60 Gy in 30 fx (arm A – 59 patients) and the high dose arm at 66 Gy in 33 fx (arm B – 58 patients). All treatments were delivered with five fractions per week. The start of RT was two to five weeks after the last induction chemotherapy. The gross tumor volume (GTV), including tumor and involved mediastinal lymph nodes, was defined on the CT scan guided by the diagnostic PET scan. Elective lymph nodes were not treated. The clinical target volume (CTV) included the GTV with a 5–10 mm margin and was adjusted to anatomical boundaries such as great vessels and bones. The internal target volume (ITV) and the planning target volume (PTV) were center-specific (5–10 mm). Delineation of OARs was also center-specific. The PTV dose coverage was between 95 and 107% of the prescribed dose with a mean dose of 100%. A maximum of 40% of the lung volume (minus GTV) was allowed to receive more than 20 Gy ($V_{20} \leq 40\%$), and a maximum of 20% of the heart volume was allowed to receive more than 50 Gy ($V_{50} \leq 20\%$). Additional constraints on the dose to the lung, e.g. mean dose to the lung and the lung colume allowed to receive more than 5 Gy (V_5), varied with center and time. Both conventional RT, intensity-modulated RT (IMRT), and volumetric modulated arc therapy (VMAT) were used. Treatments were delivered with linear accelerators at energies of 6-10MV.

2.3. Data collection and pulmonary toxicity

All treatment plans were collected in The Danish National RT Data bank [15,16]. The dose-volume histograms (DVHs) of the lungs minus GTV, heart, PTV, and GTV were centrally recalculated [15], based on the original delineations. Smoking status and pulmonary function measures (forced expired volume in the first second (FEV1), forced vital capacity (FVC)) were recorded at baseline. During RT, patients were followed in weekly consultations. Patients were followed with a consultation and a CT scan every three months until relapse or for the first two years. The follow-up interval was then increased to every six months for the next three years. Furthermore, all patients received a PET/CT scan at nine months. Pulmonary toxicities were reported as RP within the first nine months, scored according to CTCAE v3.0. The maximum grade of RP and the date of the first symptoms were reported as part of the trial. Dyspnea and cough were scored (CTCAE v3.0) at baseline, weekly during RT and when available during follow-up. Dyspnea and cough data during follow-up were infrequent and naturally highly correlated to RP and are therefore not used in this analysis.

2.4. Data analysis

The outcome RP was for analysis dichotomized as an event for RP $\geq$ G2. G2 was used as a cutpoint instead of G3 to reduce the scoring uncertainty, as G2 RP clinically is easier to distinguish from G1 than from G3 RP. Dyspnea and cough at baseline and during RT were tested as clinical predictors for RP. After review, the extensive records of dyspnea and cough during RT were reduced to the maximal observed grade. This resulted in two values for dyspnea and cough, one at baseline (*B*) and one during RT (*RT*). Changes in dyspnea and cough (Δdyspnea and Δcough) were calculated by subtracting the baseline value from the maximal observed grade during RT (RT-B) to determine whether an increase in dyspnea or cough during treatment (whether from G1 to G2 or G1 to G3) would occur more frequently in patients who later developed RP. The variable infection at baseline or during RT is binary and includes any infection G1-3 (CTCAE v3.0) observed.

2.5. Statistics

All statistical analysis was done in Matlab (version: 2019a) and R (version 3.6.1). The significance level for all tests was 0.05. Differences in clinical and dosimetric parameters between the two arms were investigated with a Chi2 test for categorical variables and a Mann-Whitney *U* test for continuous variables. In an actuarial time-to-event analysis of RP $\geq$ G2 (One minus the $\geq$G2-free

Kaplan-Meier survival) the arms A and B were compared using the log-rank test, applying loco-regional recurrences and death as censoring events. The time to event analysis of RP $\geq$ G2 was repeated for mean lung dose (MLD) above and below the median MLD, irrespective of treatment arm, to determine whether MLD was the actual driver. Differences in clinical and dosimetric parameters between RP $\geq$ G2 and $\leq$G1 were investigated with a Chi2 test for categorical variables and a Mann Whitney *U* test for continuous variables.

For multivariable analysis, eleven variables were pre-selected for the prediction model based on clinical rationales and completeness of data. These variables were smoking before and during RT, infection at baseline and during RT, sex, PS, age, histology, stage, GTV size, MLD, mean heart dose (MHD), and high volume center (centers that included $\geq$20 patients). Correlations between these variables were investigated with Chi2 tests (categorical), boxplots and logistic regression (categorical vs continuous) and the Spearman correlation method (continuous). A prediction model for RP $\geq$ G2 was made as a multivariable logistic regression with regularization based on 5-fold cross-validation (Least Absolute Shrinkage and Selection Operator - LASSO) to limit overfitting [17]. The selected model is the simplest model (fewest included variables), which has deviance within one standard deviation of the lowest calculated deviance – the "one-standard-error rule" [17 page: 214]. The rationale behind this is that all models within one standard deviation describe the data almost equally good. This analysis was repeated as a Cox regression with regularization and 5-fold cross-validation to determine whether the inclusion of time to event would change the model.

Table 1
Descriptive analysis for arm A and B.

Variable [unit]	Missing	A (59 (patients)	B (58 (patients)	p-value
Sex				
Male		61.0 (36)	55.2 (32)	
Female		39.0 (23)	44.8 (26)	0.522
Any (former) smoking	3			
Never smoker		5.1 (3)	5.2 (3)	
Formersmoker + smoker		94.9 (56)	89.7 (52)	0.930
Performance status				
=0		44.1 (26)	62.1 (36)	
=1		55.9 (33)	37.9 (22)	0.051
High volume centre				
No		30.5 (18)	37.9 (22)	
Yes		69.5 (41)	62.1 (36)	0.397
Histology				
Non-Adenocarcinoma		52.5 (31)	36.2 (21)	
Adenocarcinoma		47.5 (28)	63.8 (37)	0.075
Infection	2			
No infection		93.2 (55)	91.4 (53)	
Infection G1-3		3.4 (2)	8.6 (5)	0.252
Stage	1			
IIA		10.2 (6)	5.2 (3)	
IIIA		54.2 (32)	58.6 (34)	
IIIB		33.9 (20)	36.2 (21)	0.581
Dyspnea Baseline	4			
No (G0)		52.5 (31)	62.1 (36)	
Yes (G1-3)		44.1 (26)	34.5 (20)	0.284
ΔDyspnea Baseline-RT	4			
No change or decrease		52.5 (31)	51.7 (30)	
Increase		44.1 (26)	44.8 (26)	0.931
Cough Baseline	3			
No (G0)		55.9 (33)	58.6 (34)	
Yes (G1-2)		40.7 (24)	39.7 (23)	0.849
ΔCough Baseline-RT	3			
No change or decrease		50.8 (30)	44.8 (26)	
Increase		45.8 (27)	53.4 (31)	0.454
Age [yrs]				
Median Range		66.6 [44.7;82.0]	64.6 [44.4;79.4]	0.026
FEV1 [L]	2			
Median Range		2.3 [1.1;4.0]	2.4 [1.3;4.7]	0.843
FVC [L]	4			
Median Range		3.5 [1.6;6.9]	3.6 [2.3;7.2]	0.322
FEV1/FVC	4			
Median Range		68.7 [46.1;146.4]	66.4 [42.0;90.7]	0.336
GTV volume [cm^3]				
Median Range		44.4 [4.3;406.2]	37.8 [1.8;292.2]	0.588
MLD				
Median Range		14.9 [5.8;23.1]	17.5 [8.6;24.8]	0.075
V_{5Gy} [%]				
Median Range		52.7 [22.6;91.6]	54.5 [23.7;89.0]	0.871
V_{20Gy} [%]				
Median Range		25.2 [6.6;38.6]	30.3 [13.0;40.0]	0.341
MHD				
Median Range		7.4 [0.6;22.2]	6.9 [0.6;32.0]	0.868

FEV1: forced expired volume in the first second, FVC: forced vital capacity, GTV: gross tumor volume, MLD: mean lung dose, MHD: mean heart dose, V_{20Gy}: volume of the lung receiving 20 Gy or more, V_{5Gy}: volume of the lung receiving 5 Gy or more.

3. Results

Characteristics for the patients in this study are displayed in Table 1. Patients in arm B were generally younger with better performance status than patients in arm A. A borderline-significant higher MLD for patients in arm B was observed, as no principle of equality for MLD between the trial arms was applied (Table 1). There were no statistically significant differences between dyspnea, cough, and changes thereof during RT between the two trial arms (Table 1).

Table 2
Radiation pneumonitis.

Observation	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Arm A (60 Gy)	44.1 (26)	15.3 (9)	22.0 (13)	16.9 (10)	1.7 (1)	–
Arm B (66 Gy)	39.7 (23)	8.6 (5)	25.9 (15)	24.1 (14)	–	1.7 (1)

Table 3
Univariate analysis for RP $\leq$ 1 and RP $\geq$ 2.

Variable [unit]	Missing	RP $\leq$ 1 (63 patients)	RP $\geq$ 2 (54 patients)	OR	p-value
Trial arm					
A (59 patients)		55.6 (35)	44.4 (24)		
B (58 patients)		44.4 (28)	55.6 (30)	1.563	0.231
Sex					
Male		57.1 (36)	59.3 (32)		
Female		42.9 (27)	40.7 (22)	0.917	0.817
Any (former) smoking	3				
Never smoker		1.6 (1)	9.3 (5)		
(Former)smoker		95.2 (60)	88.9 (48)	0.160	0.063
Performance status					
=0		54.0 (34)	51.9 (28)		
=1		46.0 (29)	48.1 (26)	1.089	0.819
High volume centre					
No		33.3 (21)	35.2 (19)		
Yes		66.7 (42)	64.8 (35)	0.921	0.833
Histology					
Non-Adenocarcinoma		36.5 (23)	53.7 (29)		
Adenocarcinoma		63.5 (40)	46.3 (25)	0.496	0.062
Infection	2				
No infection		98.4 (62)	85.2 (46)		
Infection G1-3		1.6 (1)	11.1 (6)	8.087	0.026
Stage	1				
IIA		11.1 (7)	3.7 (2)		
IIIA		60.3 (38)	51.9 (28)		
IIIB		27.0 (17)	44.4 (24)		0.084
Dyspnea Baseline	4				
No (G0)		66.7 (42)	46.3 (25)		
Yes (G1-3)		31.7 (20)	48.1 (26)	2.184	0.044
ΔDyspnea Baseline-RT	4				
No change or decrease		60.3 (38)	42.6 (23)		
Increase		38.1 (24)	51.9 (28)	1.928	0.086
Cough Baseline	3				
No (G0)		60.3 (38)	53.7 (29)		
Yes (G1-2)		39.7 (25)	40.7 (22)	1.153	0.709
ΔCough Baseline-RT	3				
No change or decrease		60.3 (38)	33.3 (18)		
Increase		39.7 (25)	61.1 (33)	2.787	0.008
Age [yrs][a]					
Median Range		66.2 [44.7;82.0]	64.6 [44.4;79.1]	0.726[a]	0.167
FEV1 [L]	2				
Median Range		2.3 [1.1;4.7]	2.4 [1.2;4.0]	0.962	0.875
FVC [L]	4				
Median Range		3.5 [1.6;7.2]	3.5 [2.3;6.9]	0.996	0.840
FEV1/FVC	4				
Median Range		66.9 [42.0;146.4]	67.3 [46.1;90.7]	0.988	0.852
GTV Volume[b] **[cm^3]**					
Median Range		31.7 [1.8;406.2]	59.4 [4.3;319.5]	2.091[b]	0.002
MLD					
Median Range		15.9 [8.1;23.1]	17.3 [5.8;24.8]	1.077	0.067
V_{5Gy} [%]					
Median Range		53.7 [23.7;86.7]	53.8 [22.6;91.6]	1.015	0.233
V_{20Gy} [%]					
Median Range		26.9 [15.1;38.3]	30.4 [6.6;40.0]	1.041	0.084
MHD					
Median Range		6.3 [0.6;32.0]	10.5 [1.2;28.8]	1.044	0.147

FEV1: forced expired volume in the first second, FVC: forced vital capacity, GTV: gross tumor volume, MLD: mean lung dose, MHD: mean heart dose, V_{20Gy}: volume of the lung receiving 20 Gy or more, V_{5Gy}: volume of the lung receiving 5 Gy or more.
[a] OR per 10 years.
[b] OR per 100 cm^3.

The incidence of RP is presented in Table 2. In arm A, 41% (24 of 59) of the patients developed RP ≥ G2, compared to the 52% (30 of 58) of patients in arm B (Table 3, p = 0.231). In arm A, one patient experienced G4 RP, while one patient died of G5 RP in arm B. The time-to-event curves for arm A and B are presented in Fig. 1A. The median time from start of RT to onset of RP was 63.5 [28;200] (A) and 65 [19;189] (B) days. The larger number of RP events in the high dose arm was not statistically significant (p = 0.18). Twenty-eight patients were censored for loco-regional recurrence (15 (A) and 12 (B)) or death (1 (B)) during the initial nine months. When stratified by MLD below and above the median MLD instead of the treatment arm, the separation between the time-to-event curves decreased (Fig. 1B). The results of the univariate descriptive analysis for the clinical and dosimetric parameters with respect to RP ≥ G2 are presented in Table 3. GTV size, infection at baseline or during RT, dyspnea at baseline and increase of cough during RT (Δcough) were statistically significant. Smoking, histology, stage, Δdyspnea, MLD, and V20 were borderline significant (p < 0.1). None of the baseline pulmonary function measures nor cough at baseline were associated with RP. In Fig. 2 (A), the maximum RP grades for patients with (≥G1) and without (G0) baseline dyspnea are shown. Fig. 2 (B) shows the RP grades for patients with non-increasing (left) versus increasing (right) cough during RT. The two patients which later developed G4-5 RP experienced neither dyspnea nor cough at baseline or at any time during RT (for dyspnea at baseline and Δcough see red arrows Fig. 2). For more detailed information of specific changes of dyspnea and cough during RT and the corresponding distribution of RP, see Figure S1 (supplementary material).

Investigation of inter-correlations between the eleven preselected variables for multivariable analysis yielded that MLD and MHD were correlated, see Spearman correlation matrix in Figure S2 (supplementary material). Further, female sex was correlated with a higher incidence of infection (p = 0.05) and adenocarcinoma (p = 0.002). In the multivariable logistic regression analysis with regularization, the null model (including no variables, thus equalling the overall probability of RP ≥ G2 in the cohort) was within one standard deviation of the minimum deviance model. The binomial deviance as a function of the logarithm of the tuning parameter λ (the weight given to the regularisation L1 term) as well as a trace plot are shown in Figure S3 (supplementary material). The Cox regression with regularization, including time to event information in the analysis, neither reached a multivariable model, Figure S4 (supplementary material).

4. Discussion

We investigated the extensive records of prospectively scored pulmonary toxicities in the NARLAL trial. The incidence of RP in the NARLAL trial was at the higher end of the scale with 41–52% RP ≥ G2 and 19–26% RP ≥ G3 [4,13,18]. Reasons for this might be relatively high doses to the lung, the close surveillance of this cohort and variations in the interpretation of the grading system used for toxicity reporting. A previously reported high incidence of lethal RP in one of the centers [9] increased the awareness and sensitivity to RP during this time. A variety of studies link the incidence of RP to dosimetric parameters, predominantly MLD [12,13,18]. Since no principle of toxicity equality criteria was applied, the MLD was higher in Arm B. Although we observed more RP events in Arm B (Table 1 and Fig. 1), this was not statistically significant. It is important to note that the NARLAL trial was not designed to prove an increase in pulmonary toxicities, but was made as a "pick the winner" design in terms of local control [14]. Considering the RP QUANTEC lung toxicity model [18], a very moderate increase of probability (~2.6%) would be expected for the difference in MLD observed between the two arms. A much larger patient cohort would thus be required to detect this difference. The first large-scale dose-escalation study (RTOG0617) however showed no statistically significant difference between RP ≥ G3 in the standard 60 Gy arm (7%) and the dose-escalated 74 Gy arm (4%), despite a significantly higher MLD in the high dose arm [2]. In contrast, the results of the PLANET dose-escalation trial reported an increase in severe and lethal pulmonary toxicities [10]. Iso-toxic approaches have therefore frequently been applied in subsequent dose-escalation trials [4,6], where the dose to the lungs (and other relevant OARs) is not or only marginally allowed to increase with dose escalation. The recent addition of immunotherapy (Durvalumab) to the treatment of lung cancer patients is expected to increase the risk of pulmonary toxicities, and its effect on dosimetric and other risk factors still warrants further investigation [19,20].

In the univariate analysis, the volume of the GTV, infection, dyspnea at baseline and increase in cough during RT showed a significant relation to RP. The most commonly acknowledged clinical and treatment-related risk factors for RP are age, pulmonary comorbidities, non-smoking (as smoking seems to protect against RP), chemotherapy, dose to the lungs, and possibly also to the heart

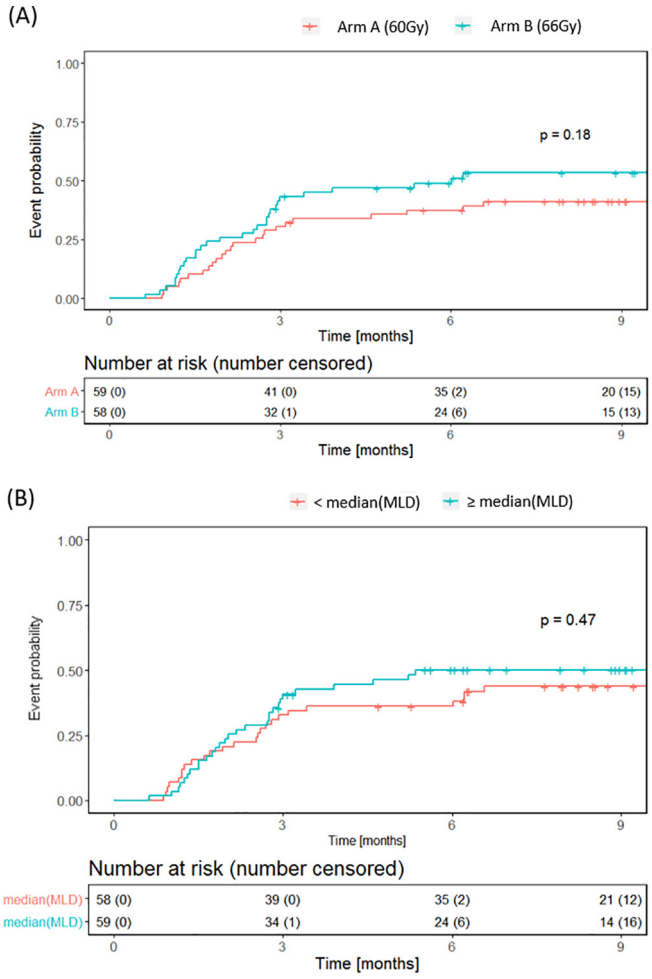

Fig. 1. Time to event analysis of RP ≥ G2 for (A) Arm A (red) and B (blue) and (B) MLD < MLD_{median} (red) and MLD ≥ MLD_{median} (blue), where the MLD_{Median} is 16.5 Gy. Shown are inverse Kaplan Meier curves, and the curves are pairwise compared with a log-rank test. Censored events (relapse or death) is shown as crosses, and the numbers of patients at risk are shown below the curves. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

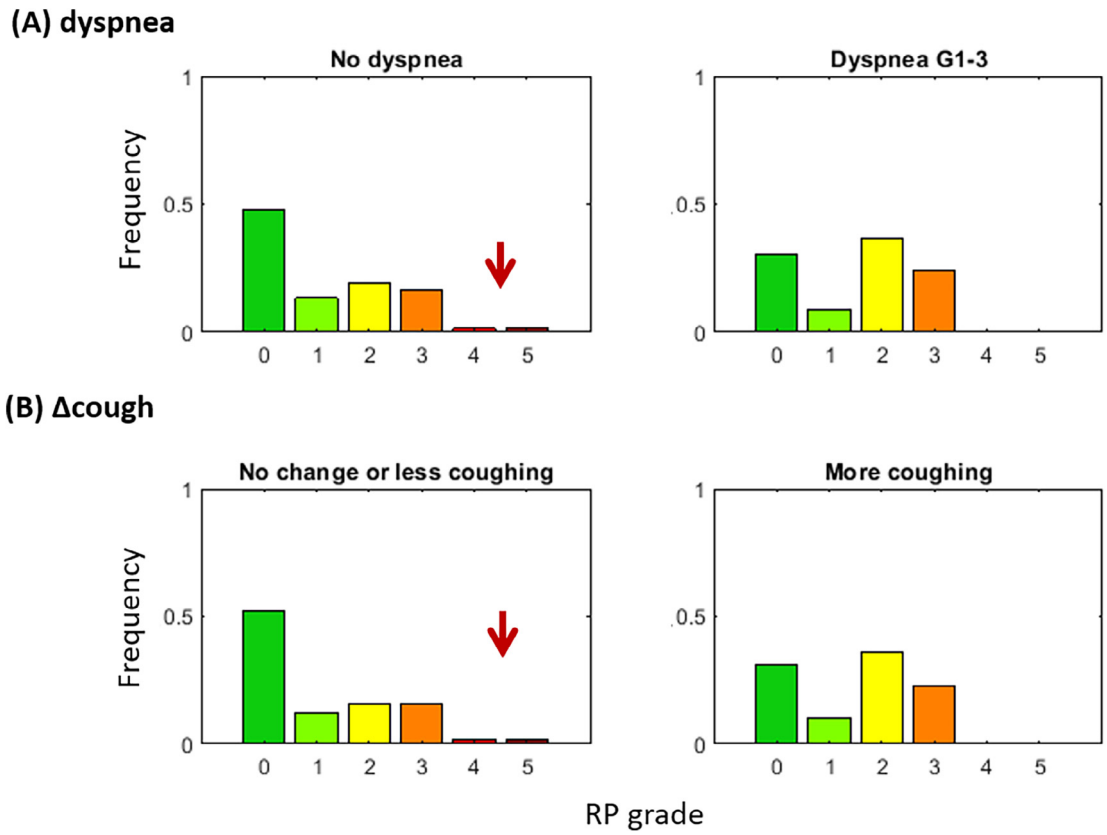

Fig. 2. RP G0-5 for patients with G0 (left) and G1-3 (right) dyspnea at baseline (A) and with no change or decrease (left) and with an increase (right) of cough (B) are shown. The two cases of G4-5 RP are highlighted with red arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[12,13]. Infections have rarely been associated with RP. In our dataset, the only significant association between infection and the other variables was with sex (6 of 7 patients with infection were women). Since sex could not be associated with RP (p = 0.817) in this dataset, this association with infection will be investigated in future studies. The multivariable logistic and Cox regression analysis with regularisation both placed the null model within one standard deviation of the minimum deviance model. Since the purpose of the "one-standard-error rule" is to limit overfitting, the patient cohort was most likely too small in number to produce a statistically sound model for RP. To confirm the validity of the lasso analysis in R, a multivariable logistic regression analysis with regularization was run in Matlab (function: lassoglm), with similar results. Speculations, that the reason for this may have been the ratio between the number of variables and patients (one variable per ten patients) were investigated further by reducing the number of input variables to five (sex, PS, age, MLD, volume of GTV). The results, displayed in Figures S5 and S6 (supplementary materials) show that this did not change the results. A large cohort (350 patients) with prospectively scored dyspnea and cough data is currently collected in the ongoing dose-escalation trial, NARLAL2 [6], where this will be investigated further. For dyspnea and cough, no significant difference between the two arms was observed, neither at baseline nor during RT. Dyspnea and cough are frequently observed in smokers, patients with lung cancer, and other lung (and heart) diseases. While an effective treatment might reduce the symptoms by reducing tumor burden, the symptoms might also increase as a side-effect of the same treatment. The extensive visitation schedule during RT with weekly toxicity recordings allowed us to relate baseline measurements as well as changes during RT in dyspnea and cough to RP. We found that baseline dyspnea (≥G1) and an increase of cough during treatment were statistically significantly related to the development of RP. This supports the findings of Petit et al., who reported that a pre-dyspnea score above one was associated with radiation-induced lung toxicity RILT after RT [21]. A review of the extensive data set [data not shown] was not able to support the findings of Yuan et al., who reported that breathing improved the third week and worsened again during the later course of RT [22]. Review of the specific changes of dyspnea and cough and the corresponding distributions of RP in Figure S1 (supplementary material) suggests that further investigation may be warrented in additional differentiation of Δdyspnea and Δcough. We stress that although there seems to be a tendency towards higher risk of RP for patients with dyspnea and cough before and during RT, it does not follow that patients with no signs of dyspnea and cough do not risk severe or even lethal RP (Fig. 2 + S1).

5. Conclusion

The detailed prospectively scored records of pulmonary toxicities from the NARLAL trial were investigated. The incidence of RP was not significantly higher in the 66 Gy compared to the 60 Gy arm. A higher risk of RP was observed for patients with tumour volume, infection, dyspnea at baseline, and an increase of cough during RT. However, even patients with no sign of dyspnea and cough experienced severe and lethal RP. No statistically sound multivariable model for prediction of RP>=G2 could be established, most likely because the number of patients was too small. This will be investigated further in a larger patient cohort when the successor dose-escalation trial, NARLAL2, is closed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement and Funding

Analysis funded by the Danish Cancer Society, Denmark, (KB-grant R90-A6244) and DCCC Radiotherapy - The Danish National Research Center for Radiotherapy, Danish Cancer Society, Denmark, (grant no. R191-A11526, IP 15).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.11.013.

References

[1] Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase iii chartwel-trial (aro 97–1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (nsclc). Radiother Oncol 2011;100:76–85.
[2] Bradley JD, Paulus R, Komaki R, 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 b 2015;16:187–99.
[3] Bradley JD, Hu C, Komaki RR, et al. Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer. J Clin Oncol, 2020;38(7):706–14.
[4] van Elmpt W, De Ruysscher D, van der Salm A, et al. The pet-boost randomised phase ii dose-escalation trial in non-small cell lung cancer. Radiother Oncol 2012;104:67–71.
[5] Hallquist A, Bergström S, Björkestrand H, et al. Dose escalation to 84 Gy with concurrent chemotherapy in stage III nsclc appears excessively toxic: Results from a prematurely terminated randomized phase II trial. Lung Cancer 2018;122:180–6.
[6] Møller DS, Nielsen TB, Brink C, et al. Heterogeneous fdg-guided dose-escalation for locally advanced nsclc (the narlal2 trial): Design and early dosimetric results of a randomized, multi-centre phase-iii study. Radiother Oncol 2017;124:311–7.
[7] Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage iii nsclc. New England J Med 2018;379:2342–50.
[8] Gray JE, Villegas A, Daniel D, 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.
[9] Khalil AA, Hoffmann L, Moeller DS, Farr KP, Knap MM. New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensitymodulated radiotherapy. Acta Oncol 2015;54:1343–9.
[10] Smith EL, Hann DM, Ahles TA, et al. Dyspnea, anxiety, body consciousness, and quality of life in patients with lung cancer. J Pain Symptom Manag 2001;21(4):323–9.
[11] Deborah JD, Kristjanson L, Sloan JA, et al. Dyspnea in Cancer Patients. J Pain Symptom Manag 2001;21(2):95–102.
[12] Vogelius IR, Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. Acta Oncol 2012;51(8):975–83.
[13] Jain V, Berman AT. Radiation pneumonitis: old problem, new tricks. Cancers 2018;10.
[14] Hansen O, Knap MM, Khalil A, et al. A randomized phase ii trial of concurrent chemoradiation with two doses of radiotherapy, 60gy and 66gy, concomitant with a fixed dose of oral vinorelbine in locally advanced nsclc. Radiother Oncol 2017;123:276–81.
[15] Westberg J, Krogh S, Brink C, Vogelius IR. A dicom based radiotherapy plan database for research collaboration and reporting. J Phys Conf Ser 2014;489:012100.
[16] Brink C, Lorenzen EL, Krogh SL, et al. Dbcg hypo trial validation of radiotherapy parameters from a national data bank versus manual reporting. Acta Oncol 2018;57:107–12.
[17] James G. An Introduction to Statistical Learning with Applications in R. In James G, Witten D, Hastie T, Tibshirani R. (Eds.) New York: Springer Science + Business Media, 2013, p. 213–4.
[18] Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76(3):S70–6.
[19] Saito S, Abe T, Kobayashi N, et al. Incidence and dose-volume relationship of radiation pneumonitis after concurrent chemoradiotherapy followed by durvalumab for locally advanced non-small cell lung cancer. Clin Transl Radiat Oncol 2020;23:85–8.
[20] Shaverdian N, Thor M, Shepherd AF, et al. Radiation pneumonitis in lung cancer patients treated with chemoradiation plus durvalumab. Cancer Med 2020;9(13):4622–31.
[21] Petit SF, van Elmpt WJC, Oberije CJG, et al. [18f]fluorodeoxyglucose uptake patterns in lung before radiotherapy identify areas more susceptible to radiation-induced lung toxicity in non-smallcell lung cancer patients. IJROBP 2011;81:698–705.
[22] Yuan ST, Frey KA, Gross MD, et al. Changes in global function and regional ventilation and perfusion on SPECT during the course of radiotherapy in patients with non-small-cell lung cancer, Int J Radiat Oncol Biol Phys 2012;82(4):631–8.