Radiotherapy and Oncology 168 (2022) 234–240

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Survival benefits for non-small cell lung cancer patients treated with adaptive radiotherapy

Ditte Sloth Møller [a,1,*], Christina Maria Lutz [a,1], Azza Ahmed Khalil [a], Markus Alber [b,c], Marianne Ingerslev Holt [d], Maria Kandi [a], Hjørdis Hjalting Schmidt [a], Marie Tvilum [a], Ane Appelt [e,f], Marianne Marquard Knap [a,2], Lone Hoffmann [a,2]

[a] Department of Oncology, Aarhus University Hospital, Denmark; [b] Department of Radiation Oncology, Heidelberg University Hospital; [c] Heidelberg Institute for Radiation Oncology (HIRO), Heidelberg University Hospital, Germany; [d] Department of Clinical Genetics, Sygehus Lillebaelt, Vejle, Denmark; [e] Leeds Institute of Medical Research at St James's, University of Leeds; and [f] Leeds Cancer Centre, St James's University Hospital, Leeds, United Kingdom

ARTICLE INFO

Article history:
Received 7 October 2021
Received in revised form 11 December 2021
Accepted 27 January 2022
Available online 2 February 2022

Keywords:
NSCLC
Adaptive radiotherapy
Pneumonitis
Survival
Image guided radiotherapy

ABSTRACT

Introduction: Tumor match and adaptive radiotherapy based on on-treatment imaging increases the precision of RT. This allows a reduction of treatment volume and, consequently, of the dose to organs at risk. We investigate the clinical benefits of tumor match and adaptive radiotherapy for a cohort of non-small cell lung cancer patients (NSCLC).

Methods: In 2013, tumor match and adaptive radiotherapy based on daily cone-beam CT scans was introduced to ensure adaption of the radiotherapy treatment plan for all patients with significant anatomical changes during radiotherapy. Before 2013, the daily cone-beam CT scans were matched on the vertebra and anatomical changes were not evaluated systematically. To estimate the effect of tumor match and adaptive radiotherapy, 439 consecutive NSCLC patients treated with definitive chemo-radiotherapy (50–66 Gy/25–33 fractions, 2010–2018) were investigated retrospectively. They were split in two groups, pre-ART (before tumor match and adaptive radiotherapy, 184 patients), and ART (after tumor match and adaptive radiotherapy, 255 patients) and compared with respect to clinical, treatment-specific and dosimetric variables (χ^2 tests, Mann Whitney *U* tests), progression, survival and radiation pneumonits (CTCAEv3). Progression-free and overall survival as well as radiation pneumonitis were compared with log-rank tests. Hazard ratios were estimated from Cox proportional hazard regression.

Results: No significant differences in stage ($p = 0.36$), histology ($p = 0.35$), PS ($p = 0.12$) and GTV volumes ($p = 0.24$) were observed. Concomitant chemotherapy was administered more frequently in the ART group (78%) compared to preART (64%), $p < 0.001$. Median[range] PTV volumes decreased from 456 [71;1262] cm^3 (preART) to 270 [31;1166] cm^3 (ART), $p < 0.001$, thereby significantly reducing mean doses to lungs (median, preART 16.4 [1.9;24.7] Gy, ART 12.1 [1.7;19.4] Gy, $p < 0.001$) and heart (median, preART 8.0 [0.1;32.1] Gy, ART 4.4 [0.1;33.9] Gy, $p < 0.001$). The incidence of RP at nine months decreased significantly with ART (50% to 20% for symptomatic RP (≥G2), 21% to 7% for severe RP (≥G3), 6% to 0.4% for lethal RP (G5), all $p < 0.001$). The two-year progression free survival increased from 22% (preART) to 30% (ART), while the overall survival increased from 43% (preART) to 56% (ART). The median overall survival time increased from 20 (preART) to 28 months (ART).

Conclusion: Tumor match and adaptive radiotherapy significantly decreased radiation pneumonitis, while maintaining loco-regional control. Further, we observed a significantly improved progression-free and overall survival.

Locally advanced non-small cell lung cancer (LA-NSCLC) is routinely treated with concurrent chemo-radiotherapy. Despite an intensive treatment strategy with risk of severe toxicity [1–4], two-year progression free survival (PFS) is as low as 20–30%, often due to lack of local tumor control [4–7].

Radiotherapy of LA-NSCLC is challenged by several treatment uncertainties caused by patient setup, breathing motion, and inter-fractional anatomical changes. The latter occur frequently

* Corresponding author at: Aarhus University Hospital, Department of Oncology, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: dittmoel@rm.dk (D.S. Møller).

[1] We would like shared first author between Ditte Sloth Møller and Christina Maria Lutz.

[2] We would like shared last author between Marianne Marquard Knap and Lone Hoffmann.

https://doi.org/10.1016/j.radonc.2022.01.039
0167-8140/

and affect the dose delivered to tumor and normal tissues alike. The most commonly observed anatomical changes are atelectasis, pleural effusion, pneumonia [8], tumor shrinkage [9], tumor deformation, and differential shifts between tumor and lymph nodes [10–11].

On modern treatment machines, the patient anatomy can be monitored daily by cone-beam computed tomography (CBCT). In case of dose deterioration, the treatment plan can be adapted (adaptiveRT). By virtue of CBCT-mediated patient setup according to the tumor location (tumor match) as opposed to bony anatomy and adaptiveRT, geometric uncertainties can be largely eliminated and thus, the total irradiated volume can be reduced [18].

Although adaptiveRT strategies have been proposed for several tumor sites (e.g. prostate, lung, head and neck, cervix) [12–15], they typically require extra resources. Consequently, large-scale data on outcome parameters such as overall survival with long follow-up are sparse, and published results usually pertain to small and selected patient groups [16–17].

The combination of tumor match and adaptiveRT was introduced for all lung cancer patients at Aarhus University Hospital (Denmark) in 2013 [11,18]. This led to a significant reduction in treatment volumes and consequently in doses to organs at risk [18]. Whether these nominal improvements in physical parameters translate into clinical benefits is the subject of this manuscript. We quantify the efficacy of tumor match and adaptiveRT for LA-NSCLC in an unselected cohort of 439 consecutive patients in terms of survival, loco-regional failure, and incidence of radiation pneumonitis.

Material and methods

Patients

In this retrospective study, we included 472 consecutive NSCLC patients treated with curatively intended radiotherapy with 50–66 Gy (25–33 fractions) from February 2010 to January 2018 at Aarhus University Hospital. Stage I-II patients were included if the tumor location was not eligible for SBRT. Stage IV patients with oligo-metastatic disease, where a single brain metastasis was radically removed by surgery or stereotactic radiotherapy, were included. Five patients with previous lung radiotherapy and 26 patients in recruiting trials were excluded. Two patients were lost to follow-up, leaving 439 patients for final analysis. The patients were split into two consecutive groups based on introduction of tumor match and adaptiveRT in April 2013, with 184 patients treated before (preART) and 255 patients treated after (ART).

Chemotherapy

Standard concomitant chemotherapy was administered in three cycles of a platinum derivative (carboplatin AUC5 or cisplatin 75 mg/m^2) combined with vinorelbine (60 mg/m^2 day 1 and day 8 in each cycle). Start of radiotherapy coincided with the second cycle of chemotherapy. Sequential chemotherapy, completed two to five weeks before radiotherapy start, consisted of one to four cycles of carboplatin (AUC5) combined with vinorelbine (60 mg/m^2 day 1 and 8 in the first cycle, 80 mg/m^2 day 1 and 8 in subsequent cycles in absence of hematological grade 3 toxicities).

Imaging and target definition

All patients were staged based on a diagnostic 18 flouro-deoxyglucose positron emission tomography (^{18}F-FDG-PET)-CT and endobronchial ultrasonography (EBUS). The pathology was proven by biopsy of both tumor and malignant lymph nodes. The mid-ventilation phase of a 4D-CT with intravenous contrast was used for target definition and treatment planning. From 2011, an additional PET-CT was acquired with the 4D-CT to complement the diagnostic PET-CT. In preART, the gross tumor volume (GTV) was uniformly expanded by 5 mm and corrected for bones and large vessels to create the clinical target volume (CTV). To account for respiratory motion, the CTV was further expanded by 5 mm (left–right, LR), 5 mm (anterior-posterior, AP), 10 mm (cranio-caudal, CC) to create the internal target volume (ITV). To account for planning and treatment related uncertainties, the ITV was expanded by 5 mm (LR), 5 mm (AP), 8 mm (CC) into a planning target volume (PTV). In ART, the respiratory motion was included by super-positioning the GTV in all phases of the 4D-CT to form an internal GTV (iGTV) [19–20]. The iGTV was expanded isotropically by 5 mm and corrected for bones and large vessels to form the CTV. The CTV was then expanded by 4 mm (LR, AP) and 5 mm (CC) for the primary tumor and 7 mm (LR, AP) and 8 mm (CC) for the lymph nodes to form the PTV.

Radiotherapy

Treatment planning was performed in Eclipse version 8–13 (Varian Medical Systems) using AAA for dose calculation and either conventional 3D-conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). The lung dose constraints were V_{20Gy} < 40% and mean lung dose <20 Gy initially. During 2011, this was changed to V_{20Gy} < 35% and mean lung dose <19 Gy, and V_{5Gy} < 60% was added. While these constraints were fulfilled for the majority of patients, the number of patients violating constraints decreased with ART: V_{5Gy} < 60% (27% preART vs 2% ART), V_{20Gy} < 35% (12% preART vs <1% ART) and Mean lung dose <19 Gy (27% preART vs <1% ART). Patients were positioned via daily CBCT before treatment. In preART, patient position was corrected according to a match of the thoracic vertebrae. In ART, patients were positioned by match to the primary tumor and radiation therapists systematically monitored the daily CBCT scans for anatomical changes online. Changes being persistent for three fractions were evaluated offline for decreased target coverage, in which case a new 4D-CT was acquired and the treatment plan adapted [11].

Retrospective data collection

Retrospective data collection was approved by the Danish Data Protection Agency and the Danish National Board of Health (3-3013-2756/1). Final data collection dates to July 2020, and minimum follow-up time is therefore 30 months. The following patient characteristics were collected: stage (American Joint Committee on Cancer 7th Edition), histology, current smoking status, age, gender, lung function (Forced expiratory volume in 1 second (FEV1)), and performance status (PS, Eastern Cooperative Oncology Group ECOG)). The treatment was characterized in terms of previous surgery, chemotherapy (none, sequential or concomitant), prescribed radiotherapy dose corrected for undelivered dose in case of early treatment termination, mean lung and heart dose (MLD, MHD), GTV volume (for post-operative patients without GTV, CTV volume was used), PTV volume, and radiotherapy technique (IMRT or 3D-CRT). The first failure was recorded as loco-regional or distant. In case of simultaneous loco-regional and distant failures, patients were recorded in both categories. Most recurrences were verified by biopsy, except brain metastases. The recurrence was dated as the first MRI, PET or CT scan where failure was suspected.

Radiation pneumonitis (RP) was scored by a history of radiotherapy, radiographic evidence, and clinical presentation (symptoms of shortness of breath, dry cough, low-grade fever and chest pain) by an experienced oncologist. National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grading system for pneumonitis was used. Onset of

RP could not be determined retrospectively and RP was therefore dated at maximum grade.

Analysis

All analyses were performed in R (version 3.6.1) and p-values above 0.05 were considered significant. Patient and treatment characteristics were compared by χ^2 tests (categorical variables) and Mann-Whitney U tests (continuous variables). All times to events were counted from the radiotherapy start date. Incidences of RP (both symptomatic (grade 2–5) and severe (grade 3–5)), loco-regional failures (LRF) and distant metastasis (DM), death with no evidence of disease (DNED), progression of disease (PD), progression-free survival (PFS) and overall survival (OS) in the two groups were presented by either Kaplan-Meier or one minus Kaplan-Meier curves. In all cases, the two groups were compared with log-rank tests, and hazard ratios (HR) including 95% confidence intervals ([lower CI, upper CI]) between the two groups were calculated from fitted cox proportional hazard functions.

Results

The median time of follow-up in preART was 8.4 years and 5.3 years in ART (reverse Kaplan-Meier estimate). Basic patient and treatment characteristics for both groups are presented in Table 1. Both treatment groups were comparable with respect to all demographic clinical parameters between the two, with the exception of radiotherapy delivery technique (more IMRT in ART) and chemotherapy. The use of concomitant chemotherapy increased over time from 64% of patients (preART) to 78% (ART) while the use of sequential chemotherapy decreased from 28% (preART) to 9% (ART). The introduction of tumor match and adaptiveRT decreased PTV volumes significantly from 456 cm^3 in preART to 270 cm^3 (median) in ART, see Table 1. No significant differences in stage, surgery and GTV volumes were observed.

The substantial reduction in irradiated PTV volume was reflected in radiation doses to the lungs and heart, which were reduced by approximately 4 Gy for both median MLD and MHD (Table 1, see also DVH parameters for lungs and heart listed in Appendix B). Concordantly, the incidence of both symptomatic RP ($p < 0.001$, HR = 0.31 [0.22,0.46]) and severe RP ($p < 0.001$, HR = 0.30 [0.17,0.52]) decreased significantly in ART relative to preART. In preART, 7.1% (13/184) of patients experienced lethal (G5) RP, compared to 0.4% (1/255) of patients in ART ($p < 0.001$, HR = 0.05 [0.01,0.41]). At nine months following completion of radiotherapy, symptomatic RP decreased from 50% (preART) to 20% (ART), while severe RP decreased from 21% (preART) to 7% (ART), see Fig. 1.

Fewer patients experienced progression of disease after RT in the ART group ($p = 0.05$, HR = 0.80 [0.64,1.00], Fig. 2). However, a slightly higher frequency of simultaneous loco-regional and distant recurrences was observed in the ART group. Therefore, no statistically significant differences in loco-regional failures ($p = 0.2$, HR = 0.84 [0.63,1.12]) or distant metastases ($p = 0.8$, HR = 1.03 [0.78,1.36]) were found between the groups, see Fig. 3. Further, a significantly better PFS ($p = 0.01$, HR = 0.76 [0.62,0.94]) was observed, with an increase of PFS at two years from 22% to 30% ($p = 0.01$, Fig. 4). Likewise, OS increased significantly ($p = 0.002$, HR = 0.71 [0.57,0.88]) (Fig. 4). At two years, the OS increased from 43% to 56% ($p = 0.003$) and the median OS time increased from 20 to 28 months. Multivariate cox-regression testing the impact of ART, GTV volume, concomitant chemotherapy and performance status is presented for both OS and PFS in Appendix A. They yield a significant impact of ART and GTV volume ($p < 0.001$) on both OS and PFS, of performance status only on OS ($p = 0.02$ for OS and $p = 0.6$ for PFS). In neither of the models, concomitant chemotherapy was significant ($p = 0.32$ for OS and $p = 0.93$ for PFS). A non-significant reduction of DNED, mainly caused by decreased number of patients suffering from fatal G5 RP, was observed in ART patients ($p = 0.07$, HR = 0.60 [0.34,1.05]) (Fig. 5).

Discussion

The tumor match and adaptiveRT strategy reported here targets uncertainties in daily patient positioning and anatomical changes, both over time and from day-to-day. The use of CBCT-based setup and 4D-CT-based iGTV definition was accompanied by a treatment margin reduction that radically decreased treated volume by on average 40% for similar median tumor sizes. Although this strategy reliably reduces normal tissue dose, it could also result in an increased rate of local failures if the margins were shrunk in excess. Hence, there can be an inherent trade-off in margin reduction between reducing toxicity and increasing the frequency of local failures. In contrast, treatment adaptation to large anatomical changes does not show this trade-off. The daily monitoring component of adaptiveRT has formerly been shown to trigger reactions to anatomical changes in ~27% of patients [18], which would otherwise have gone unnoticed. The overall precision of radiotherapy is lower without adaptiveRT. In a previous analysis, for 12% of patients, atelectasis, pleural effusion or pneumonia resulted in under dosage of the target [8]. AdaptiveRT was found to restore target coverage efficiently [18]. Treatment adaptation improves target and normal tissue dose alike, because dose that misses the target due to anatomical shifts is often deposited in adjacent normal tissue.

The reduction of irradiated target volume is strongly reflected in the physical parameters MLD and MHD. This appears to translate into a lower rate and severity of RP, with a significant reduction in symptomatic radiation pneumonitis from 50% to 20% and virtually eliminating deaths caused by RP. This indicates that tumor match and adaptiveRT is highly effective especially for patients with a high risk of clinical toxicity. Previous studies have reported symptomatic RP incidences of 41–50% [4] and 30% [21] and severe RP incidences of 15% [22]. The current study presents lower incidences in ART with 20% symptomatic and 7% severe RP in a consecutive, unselected patient cohort. The study highlights the importance of minimizing unnecessary dose to the lung. Further reduction may decrease RP incidences even further, which can be achieved by for example knowledge based planning [23] and Deep Inspiration Breath Hold [24,25]. Notice that the scoring of RP depends on the choice of treatment when symptoms arise [26], adding some uncertainty to comparisons. On top of the direct patient benefit of a lower risk of RP, more patients may become eligible for adjuvant immunotherapy since RP can be a contraindication [7]. Please note, that adjuvant immunotherapy was not administered to patients in this study, as it was first approved in Denmark in 2019. Thus, the effect of adjuvant immunotherapy could not be evaluated in this study.

Our current data show a smaller part of patients with progression of disease in the ART group and equivalent loco-regional control. This suggests that the applied margins for treatment-related uncertainties combined with the adaptation strategy are sufficient and that higher treatment precision may even increase control.

The observed increase in PFS and OS is likely a composite of several factors, consisting of fewer patients with progression of disease and lower incidence and severity of RP. Median OS times increased from 20 to 28 months. This measurable effect is all the more relevant because it is accompanied by a de-intensification of treatment by virtue of the smaller target volumes. The survival benefit of adaptiveRT is present despite a somewhat poorer pre-

Table 1
Patient and treatment characteristics for ART and preART. Characteristics were compared with χ^2 tests for categorical variables and Mann-Whitney *U* tests for continuous variables. COPD: chronic obstructive pulmonary disease, RT: radiotherapy, GTV: gross tumor volume, PTV: planning target volume. Stage IV patients are treated for oligo metastatic disease with surgery or stereotactic radiotherapy.

	Missing	preART (*n* = 184)	ART (*n* = 255)	*p*-values
Patient characteristics				
Current Smoker	0			0.900
No		123 (67%)	168(66%)	
Yes		61 (33%)	86 (34%)	
COPD	6			0.421
No		108 (60%)	142 (56%)	
Yes		72 (40%)	111 (44%)	
Sex	0			0.128
Men		113 (61%)	138 (54%)	
Women		71 (39%)	117 (46%)	
Performance Status (ECOG)	0			0.119
0		76 (46%)	86 (34%)	
1		89 (53%)	137 (54%)	
2		2 (1%)	32 (13%)	
Age	0			0.156
Median [range]		66.0 [35.0;83.0]	68.0 [41.0;88.0]	
Histology	0			0.354
Adenocarcinoma		89 (48%)	141 (55%)	
Squamos cell carcinoma		84 (46%)	100 (39%)	
NSCLC unspecified		11 (6%)	14 (5%)	
Stage				0.361
I		2 (1%)	7 (2%)	
II		26 (14%)	43 (17%)	
IIIA		70 (38%)	109 (43%)	
IIIB		69 (38%)	80 (31%)	
IV		14 (8%)	14 (5%)	
R1		3 (2%)	2 (1%)	
GTV Volume	0			0.244
Median [range]		58.8 [1.1;405.2]	49.9 [3.3;371.5]	
Treatment characteristics				
Surgery before RT	0			0.772
No		145 (79%)	198 (78%)	
Yes		39 (21%)	57 (22%)	
Chemotherapy	0			<0.001
Concomitant		117 (64 %)	198 (78%)	
Sequential		52 (28%)	23 (9%)	
No		15 (8%)	34 (13%)	
Prescribed Dose	1			0.580
Below 60 Gy		3 (2%)	6 (2%)	
60 Gy		50 (27%)	55 (22%)	
64 Gy		0 (0%)	1 (0%)	
66 Gy		131 (71%)	192 (76%)	
RT Plan	0			<0.001
3D-CRT		28 (15%)	0 (0%)	
IMRT		156 (85%)	255 (100%)	
Mean Lung Dose	0			<0.001
Median [range]		16.4 [1.9;24.7]	12.1 [1.7;19.4]	
Mean Heart Dose	0			<0.001
Median [range]		8.0 [0.1;32.1]	4.4 [0.1;33.9]	
PTV Volume	2			<0.001
Median [range]		455.8 [70.6;1262.1]	269.9 [30.6;1166.0]	

treatment patient performance status in ART (13% vs 1% PS 2). In fact, the OS of 56% in ART at two years is comparable to the OS in the RTOG 0617 phase III trial (57.6%) [2], but patients in RTOG 0617 were highly selected (all patients received concomitant chemotherapy, and only PS 0–1) compared to the unselected population in our ART cohort.

There are several other possible contributing factors to the progression free and overall survival benefit. Besides the large change in radiotherapy treatment margins and precision that accompanied tumor match and adaptiveRT, we saw only few other differences in the treatment of the two groups. One of these, concomitant chemotherapy, has been shown to improve OS slightly for LA-NSCLC compared to sequential chemotherapy [22]. We estimate the contribution in this study to be minimal, as the use of concomitant chemotherapy increases only slightly in ART (64–78%). Furthermore, in the multivariate analysis presented in Appendix A, we find no impact of chemotherapy on the presented results. Another factor may be immunotherapy. As mentioned above, adjuvant immunotherapy was not administered at all to the patients in this study, and does therefore not play a role. Immunotherapy for recurrences, on the other hand, was introduced in 2017, but was only administered to very few patients in this cohort. Finally, the use of IMRT was the only remaining treatment factor to change between the two groups. In the preART group, 15% of patients were treated with 3D-CT, while all other patients were treated with IMRT. On closer evaluation, we found similar PTV coverage for patients treated with 3D-CT and IMRT. It is therefore highly unlikely that the plan optimization strategy has an impact on failure rates and survival.

Differences in staging and follow-up are other possible explanations. Staging was very similar in the two groups, and officially, the follow-up schedule was the same for all patients. Despite this,

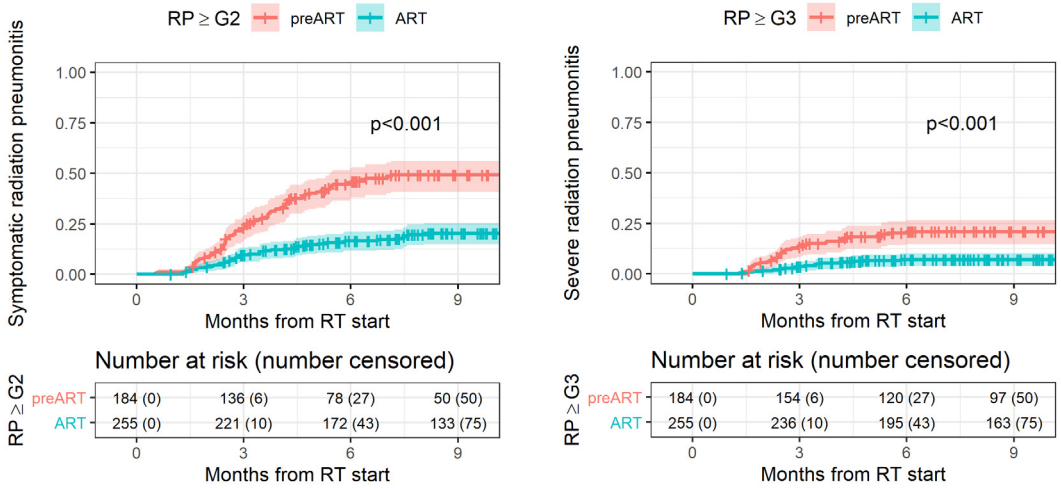

Fig. 1. One minus Kaplan-Meier curves of symptomatic (left) and severe (right) radiation pneumonitis in ART and preART group. Patients are censored in case of death, disease recurrence or loss to follow-up.

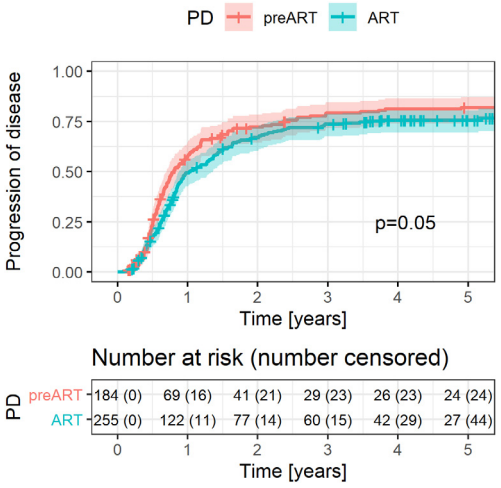

Fig. 2. One minus Kaplan-Meier curves showing any type of failure (loco-regional failure or distant metastasis). Patients were censored in case of death with no evidence of disease and loss to follow-up/data cutoff.

more simultaneous recurrences in the ART group indicate a more thorough follow-up in case of recurrence in later years. Thus, even though we see a significant decrease in patients with progression of disease, we cannot with all certainty conclude that this development originates in better local control.

The significant reduction in heart and lung doses may also contribute to a reduction in other, unattributed toxicity-related deaths in a population with frequent heart and lung co-morbidities. This is supported by results from the RTOG 0617 trial, where a higher heart dose was associated with worse survival [2]. Furthermore, studies on animal models point at an increasing risk of toxicity with a combination of high lung and heart dose [27].

A limitation of the present study is its retrospective nature over a protracted period. It is in the nature of technological advances in radiotherapy, such as the availability of CBCT for daily real-time imaging, that when they provide substantial nominal dosimetric benefits, a randomized trial becomes difficult to conduct due to perceived lack of equipoise. In our study, a reduction of the median MLD by 25% was expected by planning studies performed prior to the introduction of adaptiveRT. This was arguably the largest reduction in normal tissue dose on account of treatment technique

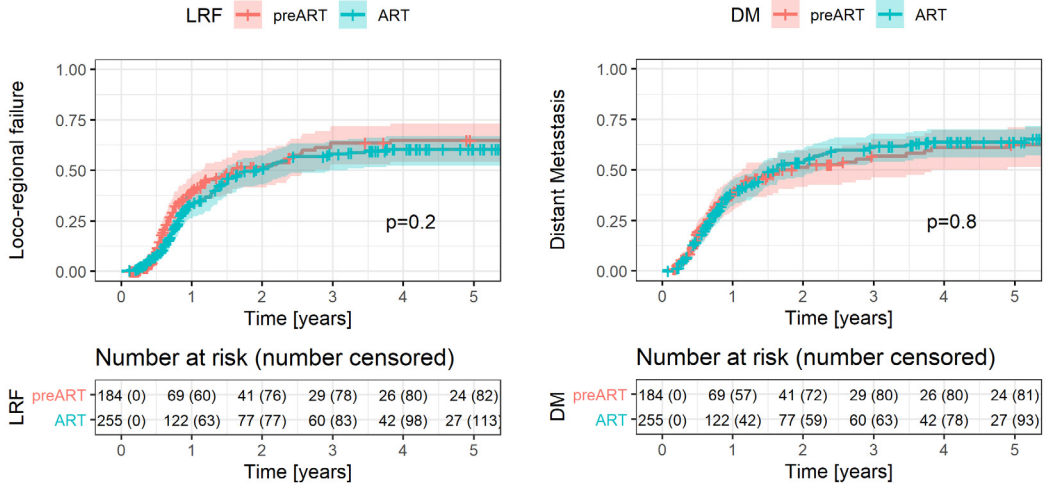

Fig. 3. One minus Kaplan-Meier curves of loco-regional failure (left) and distant metastasis (right). Simultaneous loco-regional and distant failures were included as failures in both analyses. Patients were censored in case of death without recurrence, loss to follow-up/data cutoff and if first failure site was distant metastasis only or loco-regional failure only.

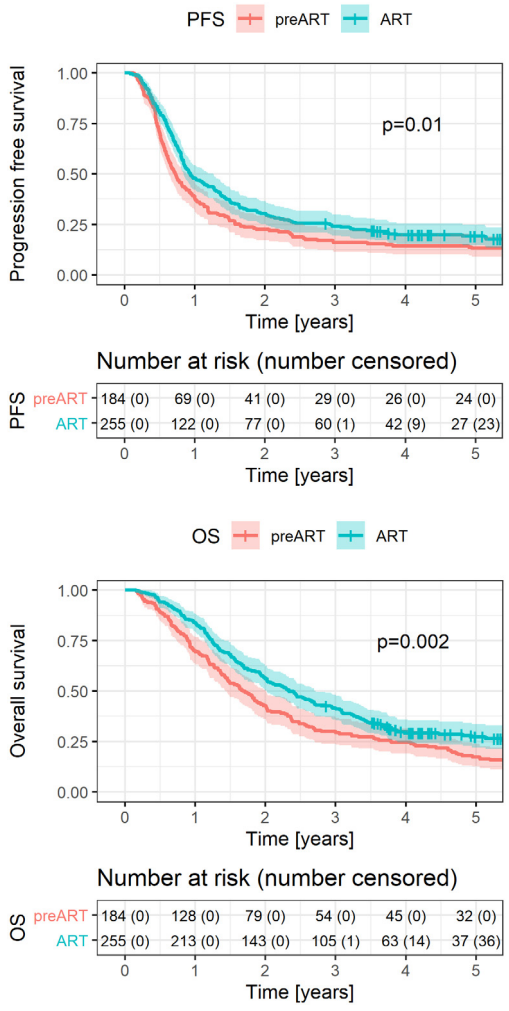

Fig. 4. Kaplan-Meier curves of progression free survival (upper) and overall survival (lower). Patients were censored if lost to follow-up/data cutoff.

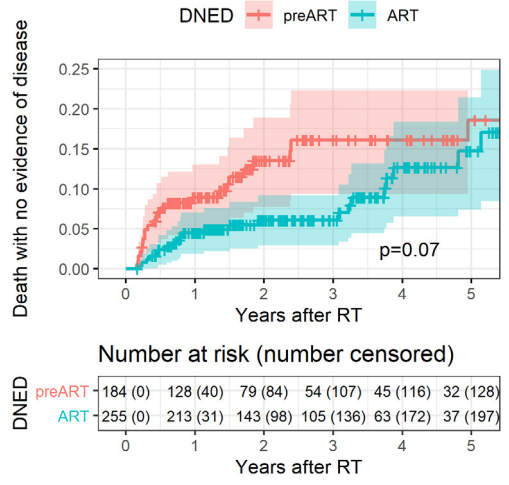

Fig. 5. One minus Kaplan-Meier curves of death with no evidence of disease. Patients were censored in case of recurrence and loss to follow-up/data cutoff.

seen in two decades. Therefore, only a non-randomized, retrospective study could definitively elucidate the clinical benefit of adaptiveRT in a large patient cohort.

In conclusion, daily tumor position verification by cone-beam CT and adaptive radiotherapy for NSCLC reduced the irradiated volumes of lungs and heart while maintaining loco-regional control. A drastic reduction in pulmonary toxicity was observed, with a simultaneous improvement of both progression-free and overall survival.

Funding statement

Ditte Sloth Møller, Lone Hofmann and Marie Tvilum were supported by DCCC Radiotherapy – The Danish National Research Center for Radiotherapy, Danish Cancer Society (grant no. R191-A11526) and Danish Comprehensive Cancer Center. Ditte Sloth Møller, Christina Maria Lutz, Marianne Knap and Marie Tvilum were supported by Danish Cancer Society (grant no. R209-A13036). Christina Maria Lutz was supported by Danish Cancer Society (grant no. R90-A6244). Ane Appelt was supported by Cancer research UK (grant no. C19942/A28832) and Yorkshire Cancer Research (grant no. L389AA).

Conflict of interest statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.01.039.

References

[1] 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 intensity-modulated radiotherapy. Acta Oncol 2015;54:1343–9.
[2] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. LancetOncol 2015;16:187–99.
[3] van Diessen J, De Ruysscher D, Sonke J-J, Damen E, Sikorska K, Reymen B, et al. The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial). Radiother Oncol. 2019;131:166–73.
[4] Hansen O, Knap MM, Khalil A, Nyhus CH, McCulloch T, Holm B, et al. A randomized phase II trial of concurrent chemoradiation with two doses of radiotherapy, 60 Gy and 66 Gy, concomitant with a fixed dose of oral vinorelbine in locally advanced NSCLC. Radiother Oncol 2017;123:276–81.
[5] De Ruysscher D, van Baardwijk A, Wanders R, Hendriks LE, Reymen B, van Empt W, et al. Individualized accelerated isotoxic concurrent chemoradiotherapy for stage III non-small cell lung cancer: 5-Year results of a prospective study. Radiother Oncol 2019;135:141–6.
[6] Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, 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. JCO 2020;38:706–14.
[7] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379:2342–50.
[8] Møller DS, Khalil AA, Knap MM, Hoffmann L. Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. Radiother Oncol 2014;110:517–22.
[9] Knap MM, Hoffmann L, Nordsmark M, Vestergaard A. Daily cone-beam computed tomography used to determine tumour shrinkage and localisation in lung cancer patients. Acta Oncol 2010;49:1077–84.
[10] Schaake EE, Rossi MMG, Buikhuisen WA, Burgers JA, Smit AAJ, Belderbos JSA, et al. Differential motion between mediastinal lymph nodes and primary tumor in radically irradiated lung cancer patients. Int J Radiat Oncol Biol Phys 2014;90:959–66.
[11] Hoffmann L, Holt MI, Knap MM, Khalil AA, Møller DS. Anatomical landmarks accurately determine interfractional lymph node shifts during radiotherapy of lung cancer patients. Radiother Oncol 2015;116:64–9.
[12] Sonke J-J, Aznar M, Rasch C. Adaptive radiotherapy for anatomical changes. Semin Radiat Oncol 2019;29:245–57.

[13] Morgan HE, Sher DJ. Adaptive radiotherapy for head and neck cancer. Cancers Head Neck 2020;5. https://doi.org/10.1186/s41199-019-0046-z.
[14] Tan LT, Tanderup K, Hoskin P, Cooper R, Pötter R. Image-guided adaptive brachytherapy for cervix cancer — A story of successful collaboration within the GEC-ESTRO GYN network and the EMBRACE studies. Clin Oncol 2018;30:397–9.
[15] Kavanaugh J, Hugo G, Robinson CG, Roach MC. Anatomical adaptation—early clinical evidence of benefit and future needs in lung cancer. Semin Radiat Oncol 2019;29:274–83.
[16] Heijkoop ST, Langerak TR, Quint S, Bondar L, Mens JWM, Heijmen BJM, et al. Clinical implementation of an online adaptive plan-of-the-day protocol for nonrigid motion management in locally advanced cervical cancer IMRT. Int J Radiat Oncol Biol Phys 2014;90:673–9.
[17] Castelli J, Simon A, Lafond C, Perichon N, Rigaud B, Chajon E, et al. Adaptive radiotherapy for head and neck cancer. Acta Oncol 2018;57:1284–92.
[18] Møller DS, Holt MI, Alber M, Tvilum M, Khalil AA, Knap MM, et al. Adaptive radiotherapy for advanced lung cancer ensures target coverage and decreases lung dose. Radiother Oncol. 2016;121:32–8.
[19] Wolthaus JWH, Sonke J-J, van Herk M, Belderbos JSA, Rossi MMG, Lebesque JV, et al. Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Int J Radiat Oncol Biol Phys 2008;70:1229–38.
[20] Møller DS, Nielsen TB, Brink C, Hoffmann L, Lutz CM, Drøgemüller Lund M, 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.
[21] Palma DA, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 2013;85:444–50.
[22] Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III Trial RTOG 9410. JNCI J Natl Cancer Inst 2011;103:1452–60.
[23] Hoffmann L, Knap MM, Alber M, Møller DS. Optimal beam angle selection and knowledge-based planning significantly reduces radiotherapy dose to organs at risk for lung cancer patients. Acta Oncol 2021;60:293–9.
[24] Persson GF, Scherman Rydhög J, Josipovic M, Maraldo MV, Nygård L, Costa J, et al. Deep inspiration breath-hold volumetric modulated arc radiotherapy decreases dose to mediastinal structures in locally advanced lung cancer. Acta Oncol 2016;55:1053–6.
[25] Giraud P, Morvan E, Claude L, Mornex F, Le Pechoux C, Bachaud J-M, et al. Respiratory gating techniques for optimization of lung cancer radiotherapy. J Thorac Oncol 2011;6:2058–68.
[26] Marks LB, Bentzen SM, Deasy JO, Kong F-M, Bradley JD, Vogelius IS, et al. Radiation dose–volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76:S70–6.
[27] Ghobadi G, van der Veen S, Bartelds B, de Boer RA, Dickinson MG, de Jong JR, et al. Physiological interaction of heart and lung in thoracic irradiation. Int J Radiat Oncol Biol Phys 2012;84:e639–46.