

ORIGINAL ARTICLE

New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy

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ABSTRACT

Background. Intensity-modulated radiotherapy (IMRT) in locally advanced non-small cell lung cancer (NSCLC) allows treatment of patients with large tumour volumes, but radiation pneumonitis (RP) remains a dose limiting complication. The incidence of severe RP using three-dimensional (3D) conformal radiotherapy, was previously reported to be 17%, with 2% lethal RP. The aim of this study was to monitor the incidence of RP following the introduction of IMRT.

Material and methods. IMRT was delivered using 4–8 beam arrangements and introduced in three phases. In phase I, 12 patients were treated using only one dose constraint (V20), in which the total lung volume receiving 20 Gy was limited to 40%. In phase II, 25 patients were treated with an additional dose constraint of mean lung dose (MLD) ≤ 20 Gy. In phase III, 50 patients were treated with an extra dose constraint (V5) in which the total lung volume receiving a dose of 5 Gy was $\leq 60\%$. RP was prospectively documented. The results of phase I & II (IMRT-1) were compared to those in phase III (IMRT-2).

Results. The median follow-up time was 17 months. The introduction of IMRT was associated with an increase in the incidence of RP in Phase I&II (IMRT-1) to 41%, six of 37 (16%) had grade 5 RP (IMRT-1). Introducing the dose constraint V5, led to a significant reduction in the lung volume receiving doses ≤ 20 Gy from $51 \pm 2\%$ to $41 \pm 1\%$ ($p < 0.0001$). Introducing V5 constraint did not decrease the incidence of severe (grade ≥ 3) RP, but significantly decreased the lethal pneumonitis to 4% (two of 50 patients), $p = 0.05$.

Conclusion. Introducing IMRT resulted in an increase in the incidence of severe and fatal RP, however a new dose constraint to the volume of lung receiving low doses reduced the incidence of lethal pneumonitis.

Treatment outcome of patients with non-small cell lung cancer (NSCLC) has not improved much during the past two decades [1]. This is particularly true for the patients that present with locally advanced disease [2]. Intensity-modulated radiotherapy (IMRT) enabled treatment of patients with large tumour volumes without increasing standard lung dose constraints, such as mean lung dose (MLD) and relative volume of the lung receiving a threshold dose of 20 Gy [3]. An early report on the use of IMRT in treating large tumour volumes in NSCLC by Liao et al. [4] showed that it did not

increase lung complications. Therefore, it was decided to implement IMRT for the treatment of NSCLC patients in Denmark, which has one of Europe's worst survival statistics for this group of patients with a five-year overall survival rate of 9–11% [5]. This poor survival rate has primarily been explained by more advanced disease at the time of diagnosis [6]. Larger tumours are difficult to treat with therapeutic dose using conventional three-dimensional conformal radiotherapy (3D-CRT).

Technological advancements in radiotherapy are seldom introduced through the gold standard phase

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I, II and III clinical trials [7,8]. There is a theoretical possibility therefore, that introducing new techniques may lead to worse results because of either less tumour control or more complications.

While implementing the new IMRT technique at our department, clinical outcome data was prospectively monitored and compared with a historical control group of patients treated with 3D-CRT. The results led to the introduction of a new dose constraint to the volume of the lung receiving ≤ 5 Gy (V5).

This manuscript describes the outcome of the monitoring process, the clinical results that led to the change in the dose constraints and the value of this change in practice.

Material and methods

Patients and treatment

Patients with histologically verified NSCLC receiving curative thoracic radiotherapy at the Department of Oncology in Aarhus University Hospital during the period from January 2011 to June 2012 were included. Data from 87 consecutive patients were analysed. All patients underwent 4D-CT planning to define the target volume. Radiotherapy was aimed at treating the whole primary tumour and the pathological lymph nodes [gross tumour volume (GTV)] as delineated on the mid-ventilation phase of the computed tomography (CT) scan. GTV was expanded to a clinical target volume (CTV) by adding 5 mm margin to GTV. Areas overlapping with large vessels, bones and the opposite lung were subtracted. The internal target volume (ITV) was created by adding 5 mm margin left-right and anterior-posterior, and 5–10 mm superior-inferior. The planning target volume (PTV) that accounts for setup uncertainty was created by adding 5 mm margin to the ITV in left-right and anterior-posterior, while the superior-inferior margin was created by adding 8 mm [9]. The total lung volume was defined as the total lung excluding the GTV. The IMRT planning technique was performed with a median of five beams (range 3–8) and 6 MV energy using Eclipse-TPS and the AAA algorithm (Varian Medical Systems, Palo Alto, CA, USA). Patients received radiotherapy delivered by linear accelerators once daily, five days per week. Chemotherapy used in sequential or concurrent setting consisted of a platin-based agent (cisplatin or carboplatin) in combination with oral navelbine. Patients and tumour characteristics are presented in Table I.

A matching group of 118 patients treated with 3D-CRT in the period between 2007 and 2010 was used as a reference group for the RP incidence [10]. These patients were treated with only one dose constraint V20 in which the relative volume of the

Table I. Patients characteristics.

Patients (n)	IMRT-1 (37)	IMRT-2 (50)
Age (years) median (range)	66 (47–81)	69 (44–84)
Sex		
Male	20	33
Female	17	17
Performance status WHO		
0–1	35	37
2	2	13
Pre-existing COLD		
Yes	13	13
No	24	37
Chemotherapy		
Neo-adjuvant	18	20
Concurrent	16	25
No	3	5
Co-morbidity		
Yes	29	37
No	8	13
FEV1 (L) median (range)	2.2 (1.2–3.6)	1.9 (0.9–4.5)

COLD, chronic obstructive lung disease; FEV1, forced expiratory volume in the first second; IMRT, intensity-modulated radiotherapy.

lung receiving 20 Gy did not exceed 40% (V20 < 40–50%) according to the national guidelines valid at the time. The dosimetric characteristics of this group are presented in Supplementary Table I (available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061216>).

IMRT implementation and dose constraints

The IMRT technique was introduced and monitored in three phases. *Phase I*: From January to March 2011, 12 patients were treated using only (V20 < 40%) dose constraint. *Phase II*: From April to September 2011, the next 25 patients were treated using two dose constraints, V20 < 40% as well as an additional dose constraint to reduce MLD to 20 Gy or less. *Phase III*: From October 2011 to June 2012, an additional new V5 dose constraint was introduced based on Yom et al. [11] planning guidelines in which the total lung volume receiving a dose of 5 Gy should not exceed 60%. Fifty patients were treated in this group with three dose constraints to the lung.

Monitoring and evaluation of radiation pneumonitis

The patients were continuously monitored for side effects and two oncologists reviewed their medical records and treatment plans. RP was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.3 according to which, Grade 3 RP included severe symptoms that interfered with the activities of daily living, Grade 4 RP was life threatening and required treatment with oxygen, while grade 5 RP was fatal.

After completion of treatment, symptom scoring and radiological evaluations of the patients were performed every three months during the first year, then every sixth month until five years, progression or death. If patients reported symptoms they were examined in the clinic outside of this follow-up schedule. None of the patients was lost for follow-up.

Statistical analysis

Patients were divided into two groups: the cohort treated with standard dose constraints V20 or V20 + MLD in phase I and phase II (IMRT-1) were compared to the cohort treated with the addition of the dose constraint V5 (IMRT-2) in phase III. The probability of developing severe RP was analysed by the Kaplan-Meier method as a function of time from the start of radiotherapy. Patients who did not develop RP were censored at the time of their death or at the last available follow-up. Fisher's exact test was used to explore the association between RP and different clinical parameters. Treatment-related and dosimetric variables were tested using the t-test. The log-rank test was used to analyse differences in the risk of RP. A p-value of less than 0.05 was considered statistically significant. SPSS software (version 20) was used for the analyses.

Results

Five of 12 patients (42%) treated using only a V20 dose constraint experienced grade ≥ 3 RP, while two of 12 had grade 5 (17%). That was significantly higher compared to the matching retrospective

control group treated with 3D-CRT in which the incidence of grade ≥ 3 RP was 17% (20/118) and only 2% were fatal. The PTV and dosimetric characteristics were not statistically different between the two groups (Supplementary Table I available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061216>). Twenty-five patients were treated in Phase II with the additional MLD dose constraints MLD ≤ 20 Gy, resulting in a reduction of the incidence of severe RP (grade ≥ 3) to 24% (6/25 patients) but four patients had fatal RP (16%). In phase III 15/50 patients developed grade ≥ 3 RP (30%). The incidence of fatal pneumonitis was 2/50 (4%).

Figure 1 shows the Kaplan-Meier estimate of the probability of grade ≥ 3 RP and grade 5 RP in patients in phase 1 and 2 (IMRT-1, $n = 37$) compared to patients in phase III (IMRT-2, $n = 50$). Introducing the V5 dose constraint in the IMRT-2 group, did not decrease the probability of severe (grade ≥ 3) RP (Figure 1A) compared to the IMRT-1 group, but significantly decreased the probability of lethal pneumonitis from 16% (IMRT-1) to 4% (IMRT-2) ($p = 0.05$) (Figure 1B). All fatal grade 5 RP occurred within the first three months (range 1.4–2.5) after the start of the radiotherapy. All grade ≥ 3 RP developed within the first six months except for three patients developing the event seven, eight and 12 months after the first fraction of radiotherapy.

The median survival of the whole group was 17.5 months (95% CI 13.6–21.3). Patients with no or mild (grade 0–1) RP had a median survival of 23.6 months (95% CI 20.7–26.5), and those with moderate and/or severe (grade 2–3) RP had a median

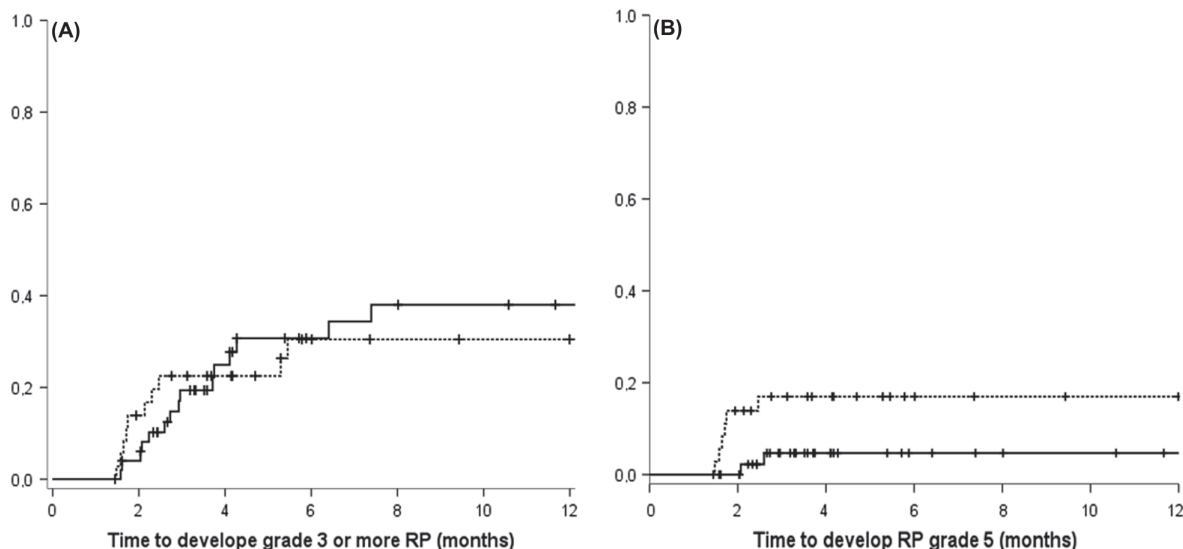


Figure 1. Actuarial analysis of the incidence of radiation pneumonitis (RP) in IMRT-1 with V20 $\leq 40\%$ or V20 $\leq 40\%$ + MLD ≤ 20 Gy (dotted line), in comparison with IMRT-2 (solid line) with V20 $\leq 40\%$ MLD ≤ 20 Gy and V5 $\leq 60\%$. A) For RP grade ≥ 3 (ns). B) Fatal RP grade 5 ($p = 0.05$).

survival time of 16.3 months (12.5–20.1). Most importantly, patients who developed fatal RP had a median survival of only 3.3 months (95% CI 2.7–3.8) from the start of the radiotherapy ($p < 0.0001$).

Figure 2 shows a pooled dose volume histogram (DVH) of the patients in the three implementation phases. DVH curves of phase I and II were similar for the low dose volumes ≤ 20 Gy. Introduction of V5 in phase III significantly reduced the lung volume receiving doses below 20 Gy ($p < 0.0001$). At the same time, the numerical values for V20 were not significantly different between the three phases. The distribution of “lung volumes” irradiated with doses lower than 20 Gy in the three implementation phases is shown in Figure 3. Nearly identical fractions of the lung received less than 20 Gy for phase I and phase II (IMRT-1). However, the volume significantly decreased from $51 \pm 2\%$ (IMRT-1) to $41 \pm 1\%$ (IMRT-2) ($p < 0.0001$), and the MLD decreased from 16.6 ± 0.8 to 14.4 ± 0.6 Gy ($p = 0.02$).

The presence of co-morbidity was associated with severe RP ($p = 0.05$). None of the other clinical factors, such as age, performance status, presence of chronic obstructive lung disease or smoking were associated with the occurrence of RP grade ≥ 3 in the 87 patients treated with IMRT. Apart from one patient aged 62, all patients with fatal RP were older than 70 and had at least one co-morbidity. The dose to the heart represented by heart V20 and heart V50 were not significantly different between groups. However, patients who developed grade 5 RP had larger cardiac volume receiving doses of 50 Gy or more. Their average heart V50 was 25.7% (SEM

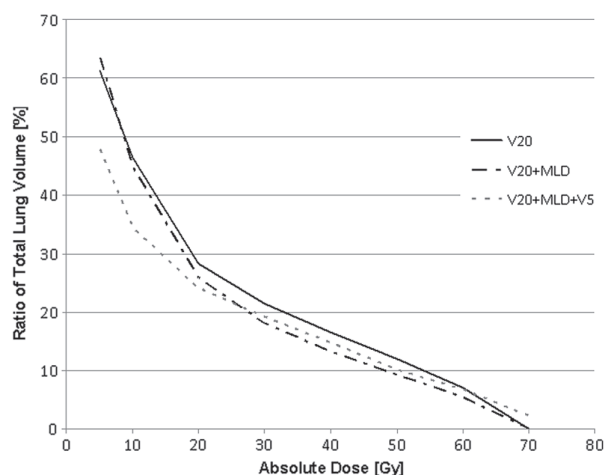


Figure 2. Mean dose volume histogram (DVH) for the lung in the three implementation phases with different dose constraints. Each curve is the average DVH of 12 patients (phase I), 25 patients (phase II) and 50 patients (phase III). The lung volume receiving low doses < 20 Gy, significantly decreased from $51 \pm 2\%$ in phase I and II to $41 \pm 1\%$ in phase III ($p < 0.0001$).

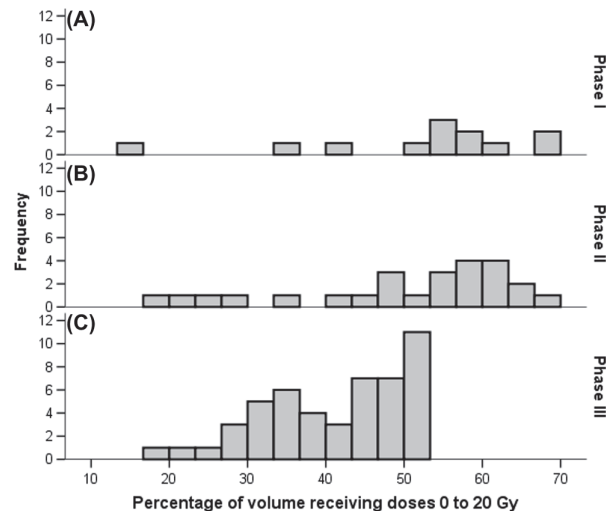


Figure 3. Histogram of percentage of lung volumes receiving low doses ranging from 0 to 20 Gy in patients of the three implementation phases of IMRT. The mean low dose volume in phase I is 52.2% (SEM 4.2), in phase II 50.1% (SEM 2.8) and in phase III 41.1% (SEM 1.3).

9.7), as compared to average V50 of 14.7% (SEM 2.2) in patients who had none, mild or moderate to severe RP.

Figure 4 shows the MLD and V5 for the 87 patients in this study according to the different grades of RP. Noticeably several of the patients with severe RP had V5 values between 50% and 60% and a MLD between 15 and 20 Gy.

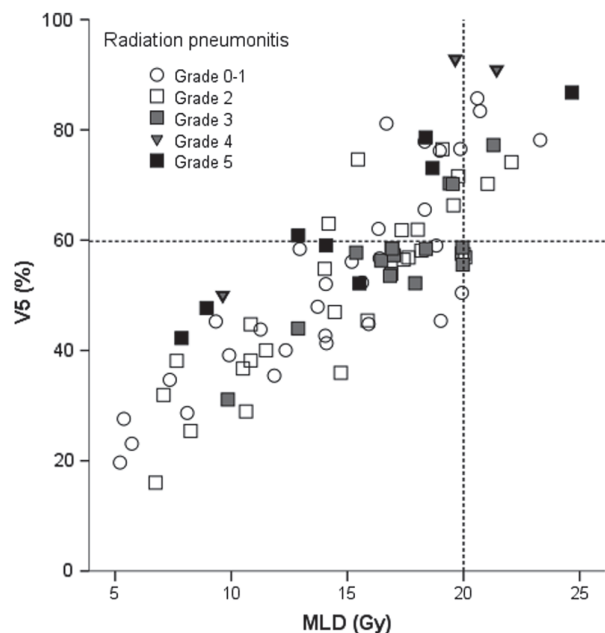


Figure 4. The MLD and V5 in all patients. Each symbol represents one patient. The shape of the symbols indicates the grade of RP. The reference lines are the two new constraints of V5 and MLD.

Discussion

This study reports the experience of introducing a new technique for treating patients with locally advanced NSCLC. The incidence of 16% fatal pneumonitis in the first two phases was alarming and much higher than expected from both the published literature [12,13] and the control group treated with 3D-CRT in the same institution [10]. These patients showed a typical clinical and radiological picture of radiation-induced pneumonitis that did not respond to standard treatment of rigorous antibiotics, respiratory aid and high dose corticosteroids. This confirms that severe RP can be an irreversible condition once started. That is why it is of utmost importance to avoid the occurrence of such complications.

Farr et al. have previously shown that severe RP was a strong independent prognostic factor for survival [10]. Indeed, patients with grade 5 RP in the present study had a median survival of < 3 months, which is much shorter than patients with NSCLC offered palliative treatment (median survival nine months) [14]. This underlines the need for criteria, such as age or presence of co-morbidity, to select patients prone to major complications for a less aggressive treatment. The majority of patients who developed grade 5 toxicity were older than 70 and had at least one co-morbidity. This is in agreement with other reports [15–17].

The fatal RP cases in this study could also be related to the fact that these patients received more dose to the heart, with an average of 25% of the heart volume received doses > 50 Gy, which is relatively high compared to those who developed mild or moderate grades of RP. The recent RTOG 0617 study prematurely stopped for accrual, randomised patients between conventional radiotherapy 60 Gy in 30 fractions versus dose escalation up to 74 Gy in 37 fractions. It showed that patients in the high dose arm had a poorer overall survival compared with patients in the standard dose arm. Deaths related to pulmonary and perhaps cardiac toxicities are the most likely explanations of the poorer survival findings [18].

The evidence to support the use of IMRT in treating lung cancer patients was derived from comparative case series reported by Yom et al. [11]. In their study of the first 68 patients treated with IMRT, they reported – contrary to our findings – a reduction in the incidence of grade ≥ 3 RP from 32% (95% CI 26–40%) using 3D-CRT to 8% (95% CI 4–19%) with IMRT. A possible explanation for this difference is that our IMRT-1 cohort had a median V5 of 70%. In a sub-group analysis, Yom et al. reported that the incidence of 12 months RP was 2% for patients with lung V5 < 70% as compared to a rate of 21% if V5 was > 70%. Updated data from the same institute of

patients treated with lung dose constraints specifying: V5 < 65%, V20 < 40% and MLD 20–22 Gy was published by Jiang [19]. Using these constraints only 13% of the 165 patients treated with IMRT had RP grade ≥ 3 and only 1% was lethal. When we used the constraint V5 < 60% in the IMRT-2 cohort, the incidence of fatal RP was significantly reduced, but the incidence of RP ≥ 3 remained higher than that reported by Yom et al. and unchanged compared to the IMRT-1 group. The explanation of this discrepancy may be that nearly all our patients received induction chemotherapy, while only 29% of patients reported by Yom et al. [11] received induction chemotherapy. Chemotherapy is known to increase the risk of RP [16].

After treating 12 patients with IMRT in our department, we added the MLD of ≤ 20 Gy to the planning constraints. That is a widely accepted simple measure that was first presented by Kwa et al. [20] and later in the Quantitative Analysis of Normal Tissue Effect in the Clinic (QUANTEC) paper [21].

In a planning study by Murshed, it was suggested that IMRT could provide 2 Gy reduction in the MLD and that could reduce the risk of RP by 10% [3]. This presumed risk reduction was not seen in the present data. Though introducing the V5 constraint led to a 2 Gy reduction in the MLD in the IMRT-2 cohort, the incidence of grade ≥ 3 RP was not affected. The association between severe RP and MLD was reported by several authors [13,22]. Claude et al. showed that only MLD, V20 and V30 were predictive of the severe RP [21]. They argued that the complex 3D dose distributions through the lung cannot be reduced to a 2D dose-volume histogram and suggested that a large panel of thresholds from low to high dose could provide advantages, as it would better reflect the dose-volume histogram pattern. The data presented in Figure 4 suggests that the current dose constraints are not sufficient to reduce grade ≥ 3 RP.

Several attempts have been made to extract a single value of merit that could predict RP, such as MLD or volume receiving more than a threshold dose [20,23]. Yorke et al. [24] found that the most significant factors were V5 and V13. Caution should be taken when comparing dosimetric values obtained from older studies using simple dose calculations algorithms as especially the dose to the low dose regions may differ substantially from the more advanced algorithms. The dose obtained from the simple algorithms is lower than the actually delivered dose and thus the former results can only be used as guidance [25].

The introduction of IMRT changed the beam arrangements from 3 to 4 using 3D-CRT to a median of 5 (range 3–8). This resulted in redistribution

of the dose pattern and spread of low doses. In the present study, the introduction of V5 significantly decreased the volume receiving low doses ≤ 20 Gy. In addition, the MLD was significantly reduced. Reporting the dose constraints is a simple measure based on the lung CT scan and does not account for the functional distribution in the lung. Farr et al. recently published data on perfusion single-photon emission computed tomography (SPECT) and found perfusion defect score to be a valuable method for predicting severe RP [26].

Reduction of the MLD could be achieved by reducing the treated volume. Large margins are required to include inter-fractional motion, if patients are set up using external markers or by use of daily bone match [8]. These margins may be reduced by implementation of daily soft tissue matching on the GTV. Moreover, some changes could happen during the course of radiotherapy indicating the need for adaptive radiotherapy in order to maintain target coverage and avoid increased risk of normal tissue complications [27].

Following the introduction of IMRT in our institute, we intensified the efforts to minimise set-up margins and introduced adaptive strategies with further reduction of the MLD (unpublished data).

In conclusion, introducing IMRT combined with chemotherapy for the treatment of NSCLC resulted in higher incidence of RP grade 3 or more in comparison to 3D-CRT. Prospectively monitoring patients and introduction of new dose constraints, especially for volume receiving low doses could reduce the incidence of lethal RP in patients treated with IMRT. Efforts to reduce treatment volumes and more sensitive predictors of RP are strongly needed.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Table I available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061216>