

ORIGINAL ARTICLE

Adaptive radiotherapy for locally advanced non-small cell lung cancer, can we predict when and for whom?

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ABSTRACT

Background. Adaptive radiotherapy (ART) could be a tool to reduce toxicity and to facilitate dose escalation in stage III NSCLC. Our aim was to identify the most appropriate time and potential benefit of ART.

Material and methods. We analyzed volume reduction and dosimetric consequences of 41 patients who were treated with concurrent (cCRT) (n = 21) or sequential (sCRT) chemoradiotherapy to a median dose of 70 Gy, 2 Gy/F. At every treatment fraction a cone-beam CT (CBCT) was performed. The gross tumor volume (GTV-T) was adapted (exclusion of lymph nodes) to create the GTV-T-F1. Every fifth fraction (F5–F30), the GTV-T-F1 was adapted on the CBCT to create a GTV-T-Fx. Dose volume histograms were recalculated for every GTV-T-Fx, enabling to create lookup tables to predict the theoretical dosimetric advantage on common lung dose constraints.

Results. The average GTV reduction was 42.1% (range 4.0–69.3%); 50.1% and 33.7% for the cCRT and sCRT patients, respectively. A linear relationship between GTV-T-F1 volume and absolute volume decrease was found for both groups. The mean V5, V20, V30 and mean lung dose increased by 0.8, 3.1, 5.2 and 3.4%, respectively. A larger increase ($p < 0.05$) was observed for peripheral tumors and cCRT. Lookup tables were generated.

Conclusion. ART offers the most beneficial dosimetric effects when performed around fraction 15, especially for patients with a large initial GTV-T treated by cCRT.

Lung cancer is the most common cause of cancer death worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers of which about 30% are locally advanced (LA) at diagnosis [2]. Although concurrent chemoradiotherapy (cCRT) improves survival compared to sequential one (sCRT), there remains room for improvement in the treatment of LA-NSCLC [3]. Different strategies have been studied, including altered fractionation [4] and dose escalation [5]. However, dose escalation is severely hampered by normal tissue toxicity [5,6] and can lead to deleterious results when used without taking patient-, tumor- and treatment characteristics into account [7,8]. This hurdle can be overcome by patient-individualized treatment approaches such as individualized dose-escalation using fixed dose constraints [9] or adapting the

treatment-fields to the shrinking tumor [10]. However, adaptive radiotherapy (ART) is time consuming and it is not clear which patient is eligible or what the optimal time point for ART should be. Technical advances, such as intensity-modulated radiotherapy (IMRT) and tumor motion strategies, may further improve the therapeutic ratio. To reach full potential, these strategies imply the use of image-guided radiotherapy (IGRT), e.g. by using a cone-beam computed tomography (CBCT) [11,12]. The latter also allows monitoring tumor volume or -position changes over the treatment course [13–16]. In this retrospective study, we quantified tumor volume changes during cCRT and sCRT and analyzed possible predictive factors of volume and dosimetric parameter changes, as well as the potential gain on organs at risk (OAR). Furthermore, we aimed to create a

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predictive tool that should enable to identify who may benefit from ART, and if so, when.

Material and Methods

Patient, tumor and treatment characteristics

Forty-one consecutive patients (33 male; mean age 64, range: 49–81) were irradiated between March 2010 and December 2012, either with cCRT or sCRT. Chemotherapy consisted of three cycles of platinum-based combination therapy. All patients were treated with IMRT using nine non-coplanar intensity-modulated beams conform an in-house developed class solution [17]. A median dose of 70 Gy (range, 62–70 Gy) delivered in 2 Gy daily fractions was prescribed to the PTV. RT started at Day 1 in the concurrent scheme or within 28 days after completing induction chemotherapy. Baseline tumor characteristics are presented in Table I. The location of the primary tumor allows us to differentiate between centrally and peripherally located lesions.

Target delineation and imaging

For every patient a slow planning CT and a 2-deoxy-2-[18] fluoro-D-glucose positron emission tomography (PET) images in treatment position were

acquired without any breathing compensation. The initial gross tumor volume (GTV-T) and the involved lymph nodes (GTV-lnn) were respectively delineated in lung window setting and mediastinal window setting on the treatment planning CT using mutual information of both biologic (3D PET/CT) and anatomic imaging (planning CT) according to international guidelines [18]. No elective irradiation of the lymphatic regions was conducted. Both the GTV-T and GTV-lnn were expanded by 5 mm to create a clinical target volume (CTV-T and CTV-lnn). It was then adapted to exclude bony and vascular normal structures. A sum of both CTVs was performed to create a final CTV. A planning target volume (PTV) was created by an isotropic expansion of the CTV by 5 mm. At every treatment fraction, a kV-CBCT scan was performed with the on-board imager (Varian Clinac Systems, Palo Alto, CA, USA). CT-CBCT co-registrations were performed by a group of trained RTTs, supervised and approved by the radiation oncologist. Six-degree co-registration on bony anatomy match was initiated using the region of interest including the ribs, the involved lung and the part of the mediastinum. If required, manual correction was applied in order to achieve accurate match at the level of the tumor and surrounding lung. The acquired CBCT images and their registration to the planning CT were automatically imported into the Eclipse treatment planning system (TPS) (Varian Medical Systems, Palo Alto, CA, USA). Based on the first CBCT, the initial GTV was adapted to create the GTV-T-F1. Adaptation implied excluding the lymph nodes (CBCT imaging quality does not allow its accurate evaluation) and adjusting the GTV to the tumor volume of the first fraction. This GTV-T-F1 was used as baseline. For every fifth fraction during the remainder of the treatment, the GTV-T-F1 was copied to the corresponding CBCT scan. The GTV-T-Fx was shaped by adapting the GTV-T-F1 to the corresponding tumor volume on the CBCT in lung window setting. GTV-T-Fx adaptation was performed only in regions where previously present macroscopic tumor tissue visually disappeared. To avoid inter-observer variations and to ascertain unbiased comparison of the volume evolution, all delineations were performed by one radiation oncologist (P.B.). Contouring of the OAR (lungs, spinal cord, heart, esophagus) was performed on the treatment planning CT by a dedicated dosimetrist (B.G. or C.D.) and reviewed by a radiation oncologist. The structure “lungminusGTV-T-Fx” was defined by subtracting the GTV-T-Fx from the lungs on the treatment planning CT without altering the initial densities and/or recalculating the dose distribution in order to maintain consistent evaluation throughout the treatment.

Table I. Baseline tumor characteristics.

	All	cCRT	sCRT
Pathology			
adenocarcinoma	28	15	13
squamous	12	5	7
NOS	1	1	0
Location			
peripheral	27	13	14
central	14	7	7
Stage			
IIA	1	1	0
IIIA	24	12	12
IIIB	15	8	7
IV ^a	1	0	1
T Stage			
1	5	3	2
2	17	8	9
3	10	5	5
4	9	5	4
Tumor GTV_T_F1 (cm ³)			
Median (range)	28.6	88.1	21.25
range	(1.9; 531.7)	(6.3; 531.7)	(1.9; 258.1)

^asolitary metastasis; curative approach.

cCRT, concurrent chemoradiotherapy; Central, planning target volume of the primary tumor lies adjacent to or invades the mediastinum; NOS, Not otherwise specified; Peripheral, all non-central tumors; sCRT, sequential chemoradiotherapy; T-stage, TNM classification 2009; Tumor GTV_T_F1 (cm³): Gross tumor volume (GTV) of the primary tumor (T) at fraction 1 (F1).

Analysis of tumor volume and dosimetric parameters

The dose volume parameters of the GTV-T-Fx and lungminusGTV-T-Fx were exported from the Eclipse TPS to Excel v14.0 (Microsoft, Redmond, WA, USA) and SPSS v21 (IBM Corp, Somers, NY, USA). From these files, the volumes of the GTV-T-Fx and the dosimetric parameters V5, V20, V30 and mean lung dose (MLD) of the lungminusGTV-T-Fx were extracted. This allowed analysis of volume and dosimetric parameter changes during CRT and investigation of the impact of the location, histology and CRT sequencing. Due to the absence of pathology specification, one patient was excluded for analysis of the impact of histology on volume and dosimetric parameters (Tables I and II). Due to a strong displacement of the tumor position during treatment and hereby compromising the accurate co-registration another patient was excluded from the study for all dosimetric analyses (Table II). The two-sided t-test for independent samples was used to determine statistical significant differences between two datasets. The Levene's test for equality of variances was used. Linear regression analysis was performed in order to investigate relationship between the initial and the final tumor volumes (GTV-T-F1 vs. GTV-T-F30). Furthermore linear relationship between the GTV-T-F1 and the four corresponding dosimetric parameters (V5, V20, V30, MLD) at each given fraction (5, 10, 15, 20, 25, 30) were analyzed leading to a total of 24 correlations (e.g. one relation is a GTV-T-F1 size vs. lungminusGTV-T-V20 at F25). Values of $p < 0.05$ were considered as statistically significant.

Construction of lookup tables

As the initial GTV-T-F1 size might influence the change of the various dosimetric parameters, the whole population was divided into cohorts of small ($0-50 \text{ cm}^3$ for sCRT and $0-100 \text{ cm}^3$ for the cCRT) and large ($50-300 \text{ cm}^3$ and $100-300 \text{ cm}^3$) GTVs. For each sub-group the median values were used to calculate the change (e.g. 50 for the $0-100 \text{ cm}^3$ group). Using the results of the regression analysis between the GTV-T-F1 and the lungminusGTV-T dosimetric parameters, lookup tables were generated. The expected change could be expressed as the multiplication of the GTV-T-F1 (in cm^3) with the coefficient and adding the intercept. From these equations, we generated two sets of lookup tables: the first part allows a prediction of the percent change of the dosimetric parameters at a certain fraction given the GTV-T-F1 volume. The second part of the lookup table allows an estimation of the possible gain in function of the remaining fractions.

Calculating the effect of remaining fractions

The possible positive changes of tumor shrinkage might suggest later adaptation, but the maximum gain is fading away with each treated fraction ($2.8\% \approx 1/35$ for a 35-fraction treatment) in a cumulative manner urging the need for early modification. This conflicting situation leads to a proper identification of the optimal time for possible adaptation, by searching for the highest values of the combined effect.

Table II. Mean percent changes in initial (F1) and final (F30) parameters with regards to location, histology and chemotherapy sequence.

	Total group	Tumor location			Histology ^a			Chemotherapy mode		
		Central	Peripheral	p-Value	Adeno carcinoma	Squamous cell carcinoma	p-Value	Sequential CRT	Concurrent CRT	p-Value
GTV										
N	41	14	27		28	12		20	21	
Mean volume decrease (%)	42.10	39.57	43.40	0.53	44.65	36.71	0.22	33.66	50.13	<0.01
SD	18.19	17.17	18.88		19.19	15.71		17.57	15.14	
Lung – GTV										
N ^b	40	14	26		28	11		20	20	
Mean increase of V5 (%)	0.78	0.31	1.03	0.04	0.57	1.36	0.26	0.24	1.31	0.01
SD	1.33	0.47	1.57		0.81	2.14		0.31	1.71	
Mean increase of V20 (%)	3.09	1.24	4.08	0.05	2.31	5.32	0.30	0.90	5.27	0.01
SD	5.54	1.52	6.62		3.38	9.00		1.02	7.20	
Mean increase of V30 (%)	5.20	2.05	6.90	0.03	3.85	9.07	0.26	1.61	8.80	0.01
SD	8.92	2.19	10.64		5.73	14.08		1.94	11.51	
Mean increase of MLD (%)	3.42	1.43	4.50	0.03	2.70	5.55	0.28	1.09	5.75	0.01
SD	5.42	1.72	6.39		3.97	8.03		1.42	6.84	

^a1 patient was excluded due to lack of histology specification and ^b1 patient due to strong replacement of the tumor during treatment. MLD, mean lung dose; SD, standard deviation; V5,20,30, percentage of lung receiving 5, 20 and 30 Gy, respectively.

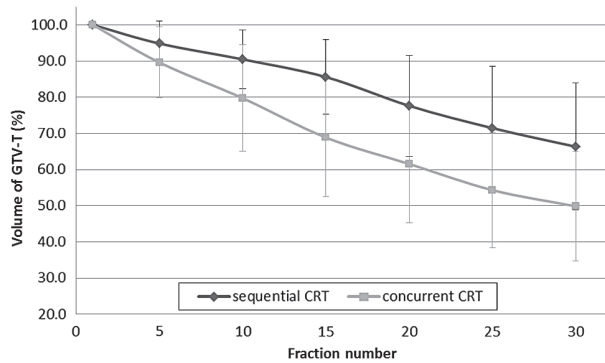


Figure 1. Behavior of the GTV-T volume change during RT for cCRT and sCRT. cCRT, concurrent chemoradiotherapy; sCRT, sequential chemoradiotherapy.

Results

Only for the chemotherapy sequence, a statistically significant difference was found ($p = 0.003$) regarding the volume change over the treatment course (Table II). For cCRT the GTV-T volume decrease slowed down as the number of fractions increased: the mean volume decrease was 31.1% between fraction 1 and 15, and 19.0% between fraction 15 and 30. For sCRT, conversely, the volume decrease of the GTV-T was slower during the initial 15 fractions (Figure 1). Regression analysis confirmed a linear relationship between the GTV-T-F1 and GTV-T-F30 for both groups ($p < 0.01$), predicting an average shrinkage of 29.4% and 40.5% for the sCRT and the cCRT groups, respectively (Figure 2).

For all investigated parameters, the increase in irradiated normal lung parameters was statistically significantly larger for peripheral locations and cCRT

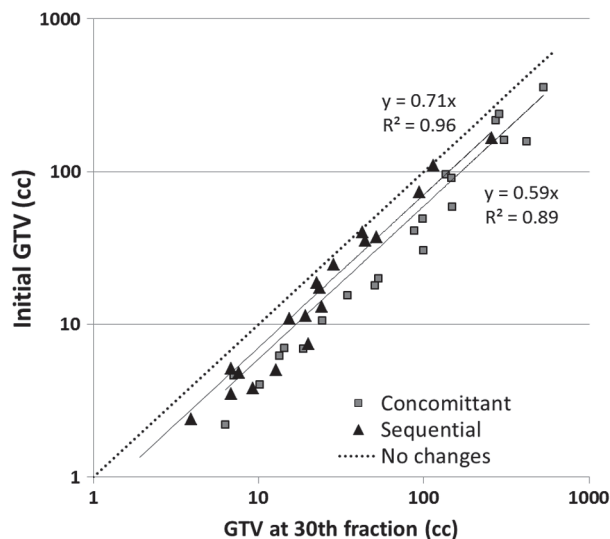


Figure 2. Linear regression analysis. Graphic presentation demonstrating a linear relationship between the GTV-T-F1 and GTV-T-F30 for both groups (presented in a logarithmic scale).

($p < 0.05$). No statistically significant differences were observed based on tumor histology ($p > 0.05$). By rigidly fusing the weekly-adapted volumes to the initial treatment plan, weekly virtual lung DVHs were recalculated showing, an increased mean V20, V30 and MLD of 0.9%, 1.6% and 1.1%, respectively, for the sCRT group and up to 5.3% (V20), 8.8% (V30) and 5.8% (MLD) in the cCRT group for the whole treatment (Table II).

Based on previous findings, distinction was made between cCRT and sCRT. Linear regression analysis of the GTV-T-F1 and lungminusGTV-T dosimetric parameters are summarized in Supplementary Table I (available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061209>) collecting the coefficients and intercepts for the construction of the lookup tables. With time (/fraction number) each parameter showed an increasing change for all the sub-groups (Supplementary Table II, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061209>). For a 35-fraction treatment this reduction effects at 5, 10, 15, 20, 25 and 30 fractions are corresponding to a 86%, 71%, 57%, 43%, 29% and 14%, respectively. Taking the remaining fractions into account we determined the maximum gain for each parameter. For cCRT this momentum is estimated at 15 fractions, for sCRT at 20 fractions (Table III, Supplementary Figure 1, available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061209>). The absolute percent change of the dosimetric parameters was higher for cCRT than for sCRT, in line with the higher GTV-T volume decrease during cCRT. Also, the percent change of the dosimetric parameters was higher if the initial GTV-T volume is bigger.

Discussion

LA-NSCLC remains a therapeutic challenge. Dose-escalation is one of the radiotherapeutic strategies to increase local control and survival. However, we are limited by normal tissue constraints, which may explain the failure of dose escalation in previous studies [7] and impede further dose escalation strategies. Adaptive RT is one of the possible solutions to overcome this hurdle by avoiding an increase in the dose to the OAR due to tumor volume decrease during treatment. However, this patient individualized treatment is time- and resource consuming and not all patients benefit at the same moment, if at all. Lookup tables, enabling us to predict when to adapt the treatment and for which patients, could allow us to avoid unnecessary efforts. Obviously, this is only useful if our results of tumor shrinkage are in accordance with previously published results.

Table III. The maximum possible gain of the dosimetric parameters.

Groups	Reduction effect	Maximum gain (%)			
		Sequential CRT		Concurrent CRT	
		0–50 cm ³	50–300 cm ³	0–100 cm ³	100–300 cm ³
V5					
at fraction 5	0.86	0.02	−0.01 ^a	0.10	0.30
at fraction 10	0.71	0.03	0.04	0.11	0.42
at fraction 15	0.57	0.04	0.07	0.26	0.61
at fraction 20	0.43	0.05	0.10	0.21	0.61
at fraction 25	0.29	0.04	0.09	0.15	0.49
at fraction 30	0.14	0.02	0.09	0.08	0.27
V20					
at fraction 5	0.86	0.07	−0.02 ^a	0.47	1.23
at fraction 10	0.71	0.13	0.14	0.52	1.62
at fraction 15	0.57	0.15	0.26	1.30	2.57
at fraction 20	0.43	0.18	0.36	1.07	2.41
at fraction 25	0.29	0.17	0.33	0.77	1.86
at fraction 30	0.14	0.10	0.30	0.41	1.01
V30					
at fraction 5	0.86	0.13	−0.03 ^a	0.80	2.14
at fraction 10	0.71	0.22	0.29	0.88	2.83
at fraction 15	0.57	0.27	0.52	2.08	4.27
at fraction 20	0.43	0.32	0.69	1.69	4.08
at fraction 25	0.29	0.30	0.62	1.21	3.15
at fraction 30	0.14	0.17	0.57	0.64	1.72
MLD					
at fraction 5	0.86	0.09	−0.02 ^a	0.48	1.40
at fraction 10	0.71	0.15	0.20	0.54	1.93
at fraction 15	0.57	0.18	0.37	1.22	2.74
at fraction 20	0.43	0.21	0.48	0.95	2.68
at fraction 25	0.29	0.20	0.44	0.69	2.12
at fraction 30	0.14	0.11	0.41	0.37	1.16
No. of cases from the original cohort		16	4	13	8

^aGTV might still in a growing phase.**bold** = highest gain.

MLD, mean lung dose; V5,20,30: percentage of lung receiving 5, 20 and 30 Gy, respectively.

Our overall volumetric results, measured on weekly cone-beam CT images, showed an average GTV reduction of 42.1% or 1%/day over 30 fractions and a mean period of 42 days. We observed a significant difference between patients treated with cCRT and sCRT with an average GTV reduction over 30 fractions of 50.1% (1.2%/day) and 33.7% (0.8%/day) respectively. A tumor volume reduction of 1.2% per day is in excellent accordance with previously published results of tumor shrinkage data during cCRT or RT only [10,13]. Our overall volume regression data is also in good agreement with previously published reports using various imaging modalities [10,13,19–22], as is the significant impact on tumor regression in case of cCRT compared to a sequential scheme [23]. The latter may be explained by previous tumor shrinkage during chemotherapy and/or accelerated tumor repopulation [24]. The effect of tumor repopulation is well known in limited disease small cell lung cancer and may also explain why tumor regression slows down in the second half of the cCRT regimen. Indeed, in case of cCRT, we

observed a deceleration of weekly volume reduction after 15 fractions. This observation is in line with the paper by Woodford suggesting that a GTV decrease of more than 30% in the first 20 fractions would be a useful trigger point for adaptive planning [14]. We preferred to individualize this trigger point per patient by generating lookup tables, which shows a theoretical decrease in lung DVH in case effective ART would be performed. Again, this value was significantly higher in patients treated with cCRT. Also the location of the tumor plays a significant role, in favor of the peripherally located tumors. Taking into account that a peripherally located tumor is totally surrounded by lung tissue, this observation is not surprising.

Using both volume and dosimetric data, we constructed lookup tables in order to predict, according to the timing of the RT and volume of the tumor, if and when ART could be useful, in order to decrease the lung dose or to allow for a patient individualized isotoxic dose-escalation. When looking at the optimal moment to perform a single adaptation during RT

we also found a fixed trigger point at 15 fractions and 20 fractions for cCRT and sCRT, respectively. The potential underdosage of microscopic disease after ART is a genuine concern, particularly in case of IMRT planning where steep dose gradients are warranted. Guckenberger et al. addressed this issue and concluded that ART does not compromise dose coverage and tumor control probability of volumes of potential microscopic disease [10].

Limitations of the current study include the small number of patients in each treatment arm and the omission of breathing motion into our calculations. Although Shmidt et al. have shown that the impact of anatomical tumor changes in general resulted in larger dosimetric changes than both respiratory motion and baseline shifts [25], increasing tumor motion with decreasing tumor volume has been described [8]. Another potential shortcoming of our study is that delineation of malignant lymph nodes was not feasible on CBCT and therefore not addressed for. However, their shrinkage may not be ignored when implementing adaptive treatment [26]. Furthermore, our dosimetric parameter calculations are based on rigid fusion and tumor volumes of the consecutive CBCTs during treatment. The latter two shortcomings however imply that the dosimetric benefit might even be higher if effective plan adaptation would be performed.

In conclusion, ART as determined by repeated CBCT imaging might be a feasible strategy to prospectively validate the lookup tables aiming at selecting the optimal candidate and timeframe to benefit from ART to its full potential.

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Supplementary material available online

Supplementary Figure 1 and Tables I, II available online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1061209>