International Journal of Radiation Oncology biology • physics

www.redjournal.org

Physics Contribution

Optimizing Collimator Margins for Isotoxically Dose-Escalated Conformal Radiation Therapy of Non-Small Cell Lung Cancer

Samantha Warren, PhD,[*,†] Vanessa Panettieri, PhD,[‡] Niki Panakis, MD,[†] Nicholas Bates, MD,[†] Jason F. Lester, MD,[§] Pooja Jain, MD,[||] David B. Landau, MD,[¶] Alan E. Nahum, PhD,[||] W. Philip M. Mayles, PhD,[||] and John D. Fenwick, PhD[*,†]

Department of Oncology, Gray Institute of Radiation Oncology and Biology, University of Oxford, Oxford; †Oxford Cancer Centre, Oxford University Hospitals, Oxford, UK; ‡William Buckland Radiotherapy Centre, Alfred Hospital, Commercial Road, Melbourne, Australia; §Velindre Cancer Centre, Velindre Road, Whitchurch, Cardiff; ||Clatterbridge Cancer Centre, Clatterbridge Road, Wirral; and ¶Department of Radiotherapy, Guy's and St. Thomas' NHS Foundation Trust, London, UK

Received Mar 27, 2013, and in revised form Dec 18, 2013. Accepted for publication Dec 20, 2013.

Summary

For isotoxic conformal radiation therapy of lung tumors, improved absolute dose coverage of the planning target volume is obtained by use of a 2-mm multileaf collimator margin, despite penumbra broadening in lung. This result applies to a range of tumor sizes and positions, and is robust to respiration-induced tumor movement, provided that patient setup margins included in the planning process are sufficient.

Purpose: Isotoxic dose escalation schedules such as IDEAL-CRT [isotoxic dose escalation and acceleration in lung cancer chemoradiation therapy] (ISRCTN12155469) individualize doses prescribed to lung tumors, generating a fixed modeled risk of radiation pneumonitis. Because the beam penumbra is broadened in lung, the choice of collimator margin is an important element of the optimization of isotoxic conformal radiation therapy for lung cancer.

Methods and Materials: Twelve patients with stage I-III non-small cell lung cancer (NSCLC) were replanned retrospectively using a range of collimator margins. For each plan, the prescribed dose was calculated according to the IDEAL-CRT isotoxic prescription method, and the absolute dose (D_{99}) delivered to 99% of the planning target volume (PTV) was determined.

Results: Reducing the multileaf collimator margin from the widely used 7 mm to a value of 2 mm produced gains of 2.1 to 15.6 Gy in absolute PTV D_{99}, with a mean gain $\pm$ 1 standard error of the mean of 6.2 $\pm$ 1.1 Gy (2-sided $P<.001$).

Conclusions: For NSCLC patients treated with conformal radiation therapy and an isotoxic dose prescription, absolute doses in the PTV may be increased by using smaller collimator margins, reductions in relative coverage being offset by increases in prescribed dose.

Reprint requests to: Samantha Warren, PhD, Department of Oncology, Gray Institute of Radiation Oncology and Biology, University of Oxford, Oxford OX3 7DQ, UK. Tel: (44) 1865857045; E-mail: Samantha.warren@oncology.ox.ac.uk

Supported by the Oxford Cancer Imaging Centre funded by CR-UK and EPSRC (S.W.) and by CR-UK Career Development Fellowship C17203 (J.D.F).

Conflict of interest: none.

Supplementary material for this article can be found online at www.redjournal.org.

http://dx.doi.org/10.1016/j.ijrobp.2013.12.034

Introduction

Outcomes after standard radiation therapy of stage IIB-III non-small cell lung cancer (NSCLC) are poor. However, dose escalation can be achieved with acceptable toxicity, even when radiation therapy is combined with sequential or concurrent chemotherapy, potentially leading to improved local control (1-3). Presently it is unclear whether overall survival is improved by dose escalation delivered by extended length schedules (4, 5), but outcomes do appear to improve when escalation is achieved by use of accelerated, isotoxic protocols. Results from a study of individualized radiation dose escalation in the setting of sequential chemoradiation show an increase in median survival from 17.5 months to 23.6 months in comparison with standard treatment (2), while recent published data show a 2-year survival rate of 67% for concurrent chemoradiation with individualized dose escalation (3). In the United Kingdom, trials of accelerated isotoxic radiation dose escalation of sequential chemoradiation (I-START, ISRCTN74841904) and concurrent chemoradiation isotoxic dose escalation and acceleration in lung cancer chemoradiation therapy (IDEAL-CRT, ISRCTN12155469) have been initiated (6). In these studies, tumor dose is prescribed on the basis of the lung dose distribution, subject to minimum and maximum limits and additional dose−volume constraints for cord, esophagus, and brachial plexus.

The low-density lung tissue surrounding NSCLC tumors reduces the target dose coverage achievable using conventional field edge placement. Matching of the 95% (of prescribed dose) isodose contour to the edge of a planning target volume (PTV) located in lung requires field sizes to be increased by at least 1 cm beyond those used when the PTV is located in unit density tissue (7), but these larger fields raise doses in the surrounding lung tissue, limiting the degree of dose escalation that can be safely achieved. Engelsman et al (8) explored the idea of increasing the probability of lung tumor control by shrinking field sizes so that the 95% isodose shifts inside the PTV, thus reducing target coverage but allowing higher doses to be prescribed. Tests on a simple phantom geometry and a single patient dataset showed that significant improvements in the equivalent uniform dose and minimum dose within the clinical target volume could be obtained by use of this approach, suggesting that tumor control is not always maximized by limiting PTV doses to lie within 95% and 107% of the prescribed dose.

In fact, more heterogeneous PTV dose distributions are used in stereotactic body radiation therapy (SBRT) of small lung lesions. An investigation of optimal collimator (beam) margins for lung SBRT found that the choice of margin (determined from Monte Carlo dose calculations) depended on tumor size and lung density but was in the range of 0 to 5 mm (9).

In this work, we investigated the impact of multileaf collimator (MLC) margin on absolute dose coverage of the PTV achieved by conformal radiation therapy of NSCLC, isotoxically escalated according to the IDEAL-CRT protocol (10). In particular we explored whether a single optimal collimator margin can be identified for a range of tumor sizes and locations.

Methods and Materials

The work was performed in 2 stages. First, we carried out a planning study to determine optimal margins for a range of patients. Second, we used a simplified phantom to evaluate the dosimetric effects of respiratory movement of the dense tumor volume within lung, and of changes in surrounding lung density, to determine the impact these effects may have on the choice of collimator margin.

Patient datasets and contours

Coregistered free-breathing 3-dimensional computed tomography (3D-CT) and 10-phase 4-dimensional CT images of 12 NSCLC patients were used in this retrospective replanning study (Table 1). Scans were acquired during quiet breathing, with a slice thickness of 0.25 cm. All patients had given written consent for their images to be used for research purposes. For each patient, the gross tumor volume (GTV) was delineated on the 4D-CT exhale and inhale phases, and these 2 volumes were combined on the free-breathing scan to create a merged target volume. A microscopic spread margin of 7 mm was then applied to the merged volume to create an internal target volume (ITV), and a further patient setup error margin of 5 mm was added to create the PTV. Thus, the total merged GTV-PTV margin was 12 mm, according to our local protocol, slightly larger than the 10 mm minimum total margin specified in the IDEAL-CRT guidelines. Normal lung was defined as total lung volume minus GTV as observed on the free-breathing CT, to model pneumonitis risk. In practice, not all the patients in Table 1 would be treated according to the IDEAL-CRT protocol, which is focused on patients with stage II-III disease, but they were included in this planning study to demonstrate trends for a wide range of tumor locations and field sizes.

Treatment planning

The 3D conformal radiation therapy (3D-CRT) plans were created on the free-breathing CTs of each patient, using 4 or 5 fields entering patients on the same side as the tumor and spanning an average angular range of 230°. The doses were calculated on a standard 2.5-mm grid (compatible with the 2.5-mm CT slice thickness) by use of the convolution-superposition algorithm (AAA, anisotropic analytical algorithm) and grid-based Boltzmann solver (Acuros, AXB) supplied in release 10.0.28 of Eclipse, version 10 (Varian, Palo Alto, CA). Although AAA is used extensively to plan clinical treatments, moderate differences have been reported between AAA and Monte Carlo dose calculations in normal-density and low-density lung (2%-4% and 12%, respectively), whereas differences between AXB and Monte Carlo doses are small (<2%) for both normal-density and low-density lung (11). We have therefore recalculated treatment plans using the AXB algorithm, with monitor units fixed at the values used in AAA plans, to check dosimetric accuracy in the presence of lung tissue.

Initially, a collimator margin of 7 mm was set from the edge of the PTV to the midpoint of each leaf of the MLC in the beam's eye views of each field, consistent with values used when the tumor is surrounded by unit density material (12). When doses were calculated by use of the AAA algorithm, this margin allowed plans to be generated with an average 92.5% coverage (range, 82.7%-98.9%) of the PTV by 95% of the isocenter dose while limiting maximum PTV doses to less than 107%. Before isotoxic dose escalation, each plan was prescribed an initial dose of 68 Gy in 30 fractions at the isocenter, copied and recalculated for different collimator margins but the same dose prescription.

Table 1 GTV sizes and TNM stages for patients in this retrospective planning study, listed in order of increasing tumor size

Patient	TNM	Stage	Position	Motion (cm)*	GTV (cm^3)	PTV (cm^3)	Lung-GTV(cm^3)	Field size X × Y (cm)†	Mean lung EQD (Gy)‡
1	TxN2M0	III A	Mediastinum	0.7	8.9	102.9	4118	7.7 × 7.0	7.3
2	T1aN0M0	I A	L lingual	0.7	11.5	111.7	4776	7.2 × 7.8	9.4
3	TxN2M0	III A	Mediastinum	0.3	13.5	105.9	2897	8.5 × 6.7	9.8
4	T1bN2M0	III A	R upper	0.3	26.6	208.7	2717	9.2 × 9.2	18.9
5	T2aN1M0	II A	R mid	1.0	29.9	191.7	3033	8.3 × 8.9	16.2
6	T2aN2M0	III A	R upper	0.7	36.4	244.1	4331	10.6 × 8.1	14.5
7	T2aN2M0	III A	L lower	0.6	49.6	258.4	2524	8.4 × 10.9	20.8
8	T2aN0M0	I B	R lower	1.2	69.4	380.7	4933	10.4 × 9.3	17.2
9	T2aN1M0	II A	L upper	0.8	84.0	396.4	4571	11.3 × 9.7	16.8
10	T2bN1M0	II B	R mid	0.4	94.1	330.7	3035	10.4 × 9.4	15.8
11	T4N0M0	III A	R upper	0.1	122.1	524.0	3990	11.4 × 10.4	21.2
12	T3N0M0	II B	R lower	1.4	177.2	736.4	4342	15.4 × 11.4	22.9

Abbreviations: EQD = mean equivalent dose in 2 Gy fractions delivered to the lung; GTV = gross tumor volume; PTV = planning target volume.
* Maximum displacement of the GTV in the cranial–caudal direction observed in different phases of 4-dimensional computed tomography.
† Smallest field size for the 7-mm margin reference plan.
‡ Mean lung dose (Gy) to the lung-GTV volume for a 7-mm margin plan with 68 Gy prescribed to the isocenter.

Isotoxic dose escalation

Isotoxic dose prescription aims to achieve the same modeled risk of radiation pneumonitis for each patient (3, 6, 13), calculated via the mean equivalent dose in 2 Gy fractions delivered to the lung (EQD_2) computed from the (lung-GTV) differential dose–volume histogram (DVH) (14). The patient-specific dose escalation regimen used in the IDEAL-CRT trial has been described previously (13, 15), and is illustrated in Schema E1 (available at www.redjournal.org).

After calculation of an initial plan, the prescribed dose (PD) was escalated to generate a fixed normal lung mean EQD_2 level of 18.2 Gy. This dose was reduced by 10% to allow for any effect of concurrent chemoradiation, and constrained by the requirement that (lung-GTV) V_{20} is less than 35%. Isotoxic prescribed doses were calculated for the each plan, and tumor dose coverage was assessed using the absolute isotoxic PTV D_{99} metric (absolute dose to the hottest 99% of the PTV). Patient-by-patient paired differences between isotoxic PTV D_{99} values obtained for each collimator margin versus a 7-mm margin were quantified (tabulating mean differences ± standard errors of the mean [SEM] for all patients) and their significance was assessed by use of Student *t* test.

In IDEAL-CRT, dose is limited by other normal tissue constraints (cord, $D_{0.1cc}$ <47 Gy; brachial plexus, $D_{30\%}$ <60 Gy, $D_{0.1cc}$ <65 Gy; heart, $D_{100\%}$ <45 Gy, $D_{67\%}$ <53 Gy, $D_{33\%}$ <60 Gy; esophagus, D_{1cc} <65, 68, 71 Gy; 6+6 trial design) and is restricted to the range of 63 to 73 Gy. Because we wished to specifically investigate tradeoffs between PTV coverage and lung dose in this study, the dose constraints on normal tissues (cord, esophagus, brachial plexus) and the IDEAL-CRT upper and lower limits on prescribed dose were not applied initially.

Phantom dataset

The phantom contains a lung insert in which a 40-mm diameter cylindrical tumor-like structure (GTV) can be located at 4 different positions (Fig. 1) to approximate different phases of the breathing cycle. The total range of tumor positions was 25 mm in the cranial–caudal direction and 5 mm anterior–posterior, which represents a larger amplitude of respiratory movement than that seen in patients analyzed in this study (Table 1). The lung material was initially assigned −719 Hounsfield units (HU) (normal-density lung) in all 4 phases, and subsequently −950 HU (low-density lung) to explore the effects of lung density on the dose distribution during respiration. The material used to represent the tumor was assigned 0 HU. We also determined the effect of carrying out calculations on a 1-mm dose grid.

Results

Optimal isotoxic collimator margin

Decreasing the MLC margin reduced the relative PTV dose coverage but also increased the absolute IDEAL-CRT isotoxic prescribed doses (which for the moment we did not limit to 63-73 Gy). The overall result was that as the collimator margin was reduced from 7 mm to 2 mm, absolute isotoxic PTV D_{99} values rose-reductions in relative D_{99} being more than offset by increases in prescribed dose. However, reducing the collimator margin further, below 1 mm, led to a rapid drop-off in the absolute dose coverage of the PTV. Data are shown in Figure 2 for patient 7, whose tumor had a volume in the middle of the range studied here. For this patient, reducing the collimator margin from 7 mm to 2 mm led to an increase in prescribed dose from 60.2 Gy to 70.9 Gy, and a net gain of 4.7 Gy in absolute PTV D_{99} dose.

The variation of absolute PTV D_{99} with collimator margin is shown in Figure 3a for all 12 patients. A margin of 2 mm is optimal, independent of tumor volume, field size or tumor movement; the average optimal margin value worked out at 1.7 mm ± 0.2 mm according to the AAA algorithm and 2.0 mm ± 0.2 mm according to AXB. Figure 3b shows the means (±1 SEM) of patient-by-patient paired differences between absolute D_{99} levels achieved by use of various collimator margins versus a 7-mm margin. Gains in D_{99} ranged between 2.1 and 15.6 Gy, with a mean of 6.2 ± 1.1 Gy SEM. (2-sided P<.001) and

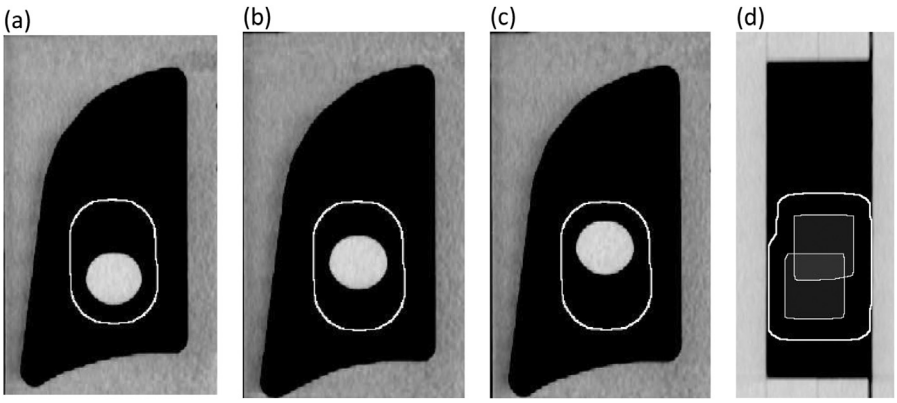

Fig. 1. The gross tumor volume (GTV) is represented by a 40-mm diameter cylinder of unit density, located at 4 different positions, roughly simulating movement during the breathing cycle. (a-c) Coronal views show the GTV at its inferiormost, mid, and superiormost positions. The planning target volume created by merging the GTVs and applying margins is shown as a white line. The GTV can occupy 2 positions at its inferiormost extent, 1 sited 5 mm posterior to the other positions, as shown in magnified sagittal image (d).

a standard deviation of 3.8 Gy. In general, substantially higher PDs could be delivered to patients with smaller tumors (patients 1-3 in Fig. 3a) or with centrally located or upper-lobe tumors (Table 1). However, these patients may in practice be candidates for SBRT, and we therefore reanalyzed the data for patients 4 to 12 only (Fig. 3c). For this subset, a smaller gain in mean dose of 4.4 ± 0.4 Gy (2-sided $P<.001$) was achieved by reducing the collimator margin from 7 mm to 2 mm, but a gain of 2.1 Gy was achieved for even the largest tumor volume (patient 12). In addition, for this patient the PD of 63 Gy delivered using a 7-mm collimator margin was associated with a (lung-GTV) V_{20} of 38.7%, making the patient ineligible for dose escalation, whereas with the use of a 2-mm collimator margin, a PD of 63 Gy was associated with V_{20} of 34.9%, within the normal tissue constraints of the IDEAL-CRT protocol.

Effect of dose calculation algorithm

The influence of the dose calculation algorithm on the optimum collimator margin was studied for all patients. Coverage of the PTV by the 95% isodose contour was substantially higher in plans initially calculated using AAA than in those recalculated using the AXB algorithm (80.8% vs 92.5%). However, the differences between mean lung EQD_2s calculated by the 2 dose calculation algorithms were much smaller, the largest observed difference (AAA-AXB) being −0.3 Gy for patient 12, as were the associated differences in isotoxically prescribed doses, the maximum PD difference (AAA-AXB) of +0.84 Gy also being observed for patient 12. The D_{99} coverage values obtained by use of the AAA algorithm were slightly higher than those obtained using the AXB (on average by 0.7%). However, this improved coverage was seen across the range of collimator margins (Fig. 2, patient 7); therefore, although the AAA algorithm predicted a higher absolute D_{99} for the 2-mm margin than did AXB, the same collimator margin value was optimal for both dose algorithms studied.

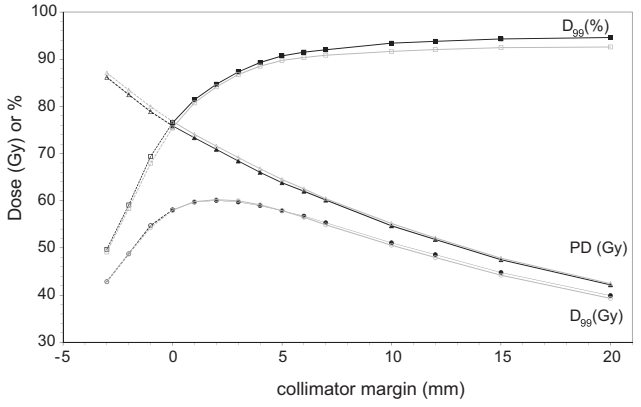

Fig. 2. Variation of absolute planning target volume D_{99} dose with collimator margin plotted for patient 7. Prescribed doses (PD) and relative coverage (D_{99} [%]) are also shown. Black and gray lines represent calculations made using the anisotropic analytical and Acuros algorithms, respectively.

Phantom study of dosimetric changes induced by respiratory motion

Analysis of plans calculated on the static phantom, set up with the GTV located at each of its 4 positions within the lung insert, shows that for the same treatment plan, variations in PTV D_{99} dose induced by changes in tumor location within the PTV were less than 1.5% (Fig. 4). This was true for the 7-mm and 2-mm collimator margins (Table 2, Fig. 3) irrespective of the dose calculation algorithm and grid used. The reduction in PTV D_{99} dose when different densities were assigned to the surrounding lung tissue were also within 1% when 7-mm and 2-mm margin plans were compared, indicating that the optimum margin value of 2 mm is valid for both normal-density and low-density lung (Table E1, available at www.redjournal.org).

Discussion

For the specific isotoxic escalation scheme and the patients studied here, a mean gain in PTV D_{99} of 6.2 Gy (range, 2.1-15.6 Gy) could be achieved by reducing the collimator margin from 7 mm to 2 mm, because the resulting reduction in relative dose coverage of the PTV was more than compensated by an

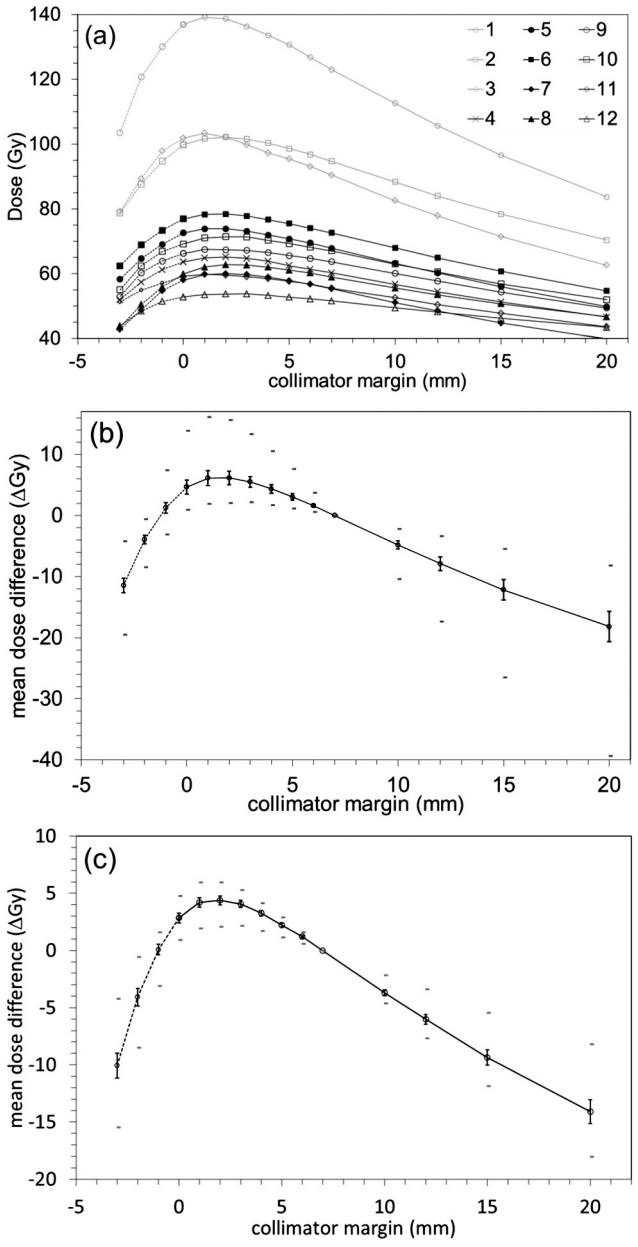

Fig. 3. (a) Variation in isotoxic absolute planning target volume (PTV) D_{99} dose versus collimator margin for all patients (numbered as in Table 1); data for patients 1-3 with smaller PTV are shown as gray lines. (b) Means (and 1 standard equivalent of the mean confidence intervals) of paired differences between D_{99} for each margin and the 7-mm margin reference plan for all 12 patients. Maximum and minimum D_{99} differences for each collimator margin are shown as gray dashes. (c) Mean paired differences, 1 standard equivalent of the mean confidence intervals, and maximum and minimum D_{99} values for patients 4-12.

increase in prescribed dose, although target localization accuracy must be sufficiently accounted for by movement margins when applying tighter collimator margins. We carried out a phantom study to explore the impact of changing lung density and of using a smaller dose calculation grid. In all cases, the same optimum collimator margin of 2 mm achieved the best absolute PTV dose coverage assessed via the D_{99} metric,

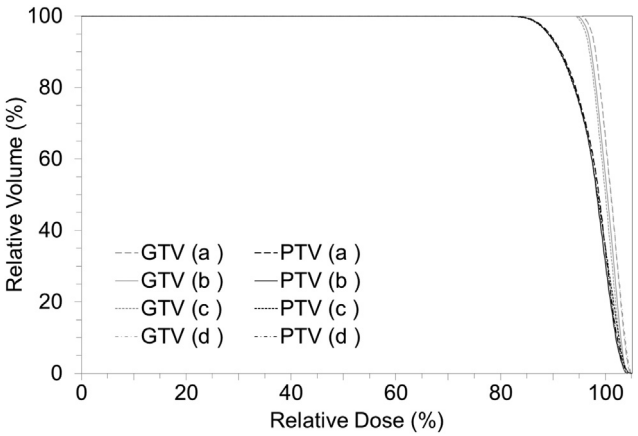

Fig. 4. Gross tumor volume (GTV) and planning target volume (PTV) dose−volume histograms computed for the GTV located in 4 different positions (a-d) within the static phantom shown in Figure 1.

optimally balancing isotoxically prescribed doses against relative PTV coverage.

Changes in dose may result from variations in the distribution of mass density within the PTV caused by tumor movement between different phases of the breathing cycle. A more rapid buildup of dose in the GTV than in the surrounding lung causes the dose to track the tumor, although previous studies based on phantom measurements, 4D-CT images, and dose accumulation techniques have found that this effect is small (16-18). Consequently, PTV coverage calculated on a single CT dataset with a single GTV position may marginally underestimate the real dose accumulated over the respiratory cycle, because dose coverage at the extremes of tumor movement is slightly higher than that calculated for a fixed central position. Our phantom-based calculations confirm that tumor movement does not result in any deterioration in PTV coverage; differences in location of the GTV within the PTV proved to have little impact (<1%) on doses delivered to the PTV, even when a 2-mm margin was used.

Monte Carlo dosimetric analyses of SBRT treatments of lung cancer suggest that optimal collimator margins lie in the range 0 to 5 mm (9, 19). The optimum collimator margin may depend on the algorithm used to compute dose; however, we obtained the same optimal margin using both the AAA and the AXB algorithms, AXB being more accurate, particularly at the lung-tumor interface (11, 20, 21).

One limitation of this study is that in order to focus on the tradeoff between lung dose and tumor coverage, we did not initially consider constraints on doses delivered to other organs at risk. In practice, the steeper dose gradients outside the PTV created by the tight 2-mm collimator margin also usefully reduce doses to other normal structures (eg, cord) lying close to the target volume. The IDEAL-CRT cord dose limit was reached before the isotoxic lung dose limit for 3 of the 12 patients studied when a 7-mm collimator margin was used, precluding dose escalation; however, when a 2-mm margin was used, these patients' prescribed doses could be increased by 6.6 to 14.8 Gy.

Conversely, it is important to note that because doses in plans created by use of wider collimator margins decrease more gently around the PTV, these plans will be less sensitive to any diminution in target coverage that may result from target localization, MLC positioning, or beam modelling uncertainties. Therefore,

Table 2 PTV coverage for the static phantom, achieved using 7-mm and 2-mm collimator margins and tabulated for different GTV positions within the PTV for the AAA and AXB dose algorithms

Simulated position	GTV movement	7-mm margin AAA, D_{99} (%)	2-mm margin AAA, D_{99} (%)	7-mm margin AXB, D_{99} (%)	2-mm margin AXB, D_{99} (%)
Mid	Center	92.7	85.8	91.5	84.9
Exhale	+10 mm cranial	92.4	85.5	91.0	84.6
Inhale and post	−15 mm caudal and −5 mm post	93.1	85.8	90.7	84.0
Inhale	−15 mm caudal	93.2	86.0	91.4	84.8
	Max diff	0.8%	0.5%	0.8%	0.9%
	Abs diff (Gy)	0.54	0.34	0.54	0.61

Abbreviations: AAA = anisotropic analytical algorithm; AXB = Acuros; GTV = gross tumor volume; PTV = planning tumor volume.

smaller collimator margins should be applied only if adequate patient movement and setup margins are included in the planning process.

Conclusions

For isotoxically prescribed conformal treatments of NSCLC, absolute dose coverage of the PTV assessed by the D_{99} metric may be maximized by using of smaller collimator margins than are usually applied in treatment planning for lung cancer. In practice, these narrower collimator margins reduce relative PTV coverage by around 7%, and they should therefore be used only if gains at least this great can be achieved in prescribed dose: for IDEAL-CRT a 7-mm collimator margin should be used to treat patients eligible for the maximum 73-Gy dose because narrower margins reduce the PTV coverage while failing to raise the prescribed dose.

References

1. Wurstbauer K, Weise H, Deutschmann H, et al. Non-small cell lung cancer in stages I-IIIB: Long-term results of definitive radiation otherapy with doses ≥80 Gy in standard fractionation. *Strahlenther Onkol* 2010;186:551-557.
2. van Baardwijk A, Wanders S, Boersma L, et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. *J Clin Oncol* 2010;28:1380-1386.
3. De Ruysscher D, van Baardwijk A, Steevens J, et al. Individualised isotoxic accelerated radiotherapy and chemotherapy are associated with improved long-term survival of patients with stage III NSCLC: A prospective population-based study. *Radiother Oncol* 2012;102:228-233.
4. Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010;28:2475-2480.
5. Cox JD. Are the results of RTOG 0617 mysterious? *Int J Radiat Oncol Biol Phys* 2012;82:1042-1044.
6. Fenwick JD, Nahum AE, Malik ZI, et al. Escalation and intensification of radiotherapy for stage III non-small cell lung cancer: Opportunities for treatment improvement. *Clin Oncol* 2009;21:343-360.
7. Miller RC, Bonner JA, Kline RW. Impact of beam energy and field margin on penumbra at lung tumor-lung parenchyma interfaces. *Int J Radiat Oncol Biol Phys* 1998;41:707-713.
8. Engelsman M, Remeijer P, van Herk M, et al. Field size reduction enables iso-NTCP escalation of tumor control probability for irradiation of lung tumors. *Int J Radiat Oncol Biol Phys* 2001;51:1290-1298.
9. Jin L, Wang L, Li J, et al. Investigation of optimal beam margins for stereotactic radiotherapy of lung-cancer using Monte Carlo dose calculations. *Phys Med Biol* 2007;52:3549-3561.
10. Landau DB. Isotoxic dose escalation and acceleration in lung cancer chemoradiotherapy: A phase I/II trial of concurrent chemoradiation with dose-escalted radiotherapy in patients with stage II or stage III non-small cell lung cancer. 12/03/2013. Available from: http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=6961.
11. Bush K, Gagne IM, Zavgorodni S, et al. Dosimetric validation of Acuros XB with Monte Carlo methods for photon dose calculations. *Med Phys* 2011;38:2208-2221.
12. Mayles WP, Moore AR, Aird EG, et al. Questionnaire based quality assurance for the RT01 trial of dose escalation in conformal radiotherapy for prostate cancer (ISRCTN 47772397). *Radiother Oncol* 2004;73:199-207.
13. Panettieri V, Malik ZI, Eswar CV, et al. Influence of dose calculation algorithms on isotoxic dose-escalation of non-small cell lung cancer radiotherapy. *Radiother Oncol* 2010;97:418-424.
14. Joiner MC, Bentzen SM. Time-dose relationships: The linear-quadratic approach. In: Steel GG, editor. Basic Clinical Radiobiology. London: Arnold; 2002. p. 134-146.
15. De Jaeger K, Hoogeman MS, Engelsman M, et al. Incorporating an improved dose-calculation algorithm in conformal radiotherapy of lung cancer: Re-evaluation of dose in normal lung tissue. *Radiother Oncol* 2003;69:1-10.
16. Admiraal MA, Schuring D, Hurkmans CW. Dose calculations accounting for breathing motion in stereotactic lung radiotherapy based on 4D-CT and the internal target volume. *Radiother Oncol* 2008;86:55-60.
17. Mexner V, Wolthaus JW, van Herk M, et al. Effects of respiration-induced density variations on dose distributions in radiotherapy of lung cancer. *Int J Radiat Oncol Biol Phys* 2009;74:1266-1275.
18. Brugmans MJ, van der Horst A, Lebesque JV, et al. Beam intensity modulation to reduce the field sizes for conformal irradiation of lung tumors: A dosimetric study. *Int J Radiat Oncol Biol Phys* 1999;43:893-904.
19. Cardinale RM, Wu Q, Benedict SH, et al. Determining the optimal block margin on the planning target volume for extracranial stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;45:515-520.
20. Fogliata A, Nicolini G, Clivio A, et al. Critical appraisal of Acuros XB and anisotropic analytic algorithm dose calculation in advanced non-small-cell lung cancer treatments. *Int J Radiat Oncol Biol Phys* 2012;83:1587-1595.
21. Fogliata A, Nicolini G, Clivio A, et al. Dosimetric evaluation of Acuros XB advanced dose calculation algorithm in heterogeneous media. *Radiat Onco* 2011;6:82.