

Toxicity and dosimetric analysis of non-small cell lung cancer patients undergoing radiotherapy with 4DCT and image-guided intensity modulated radiotherapy: a regional centre's experience

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Abstract

Introduction: For patients receiving radiotherapy for locally advanced non-small cell lung cancer (NSCLC), the probability of experiencing severe radiation pneumonitis (RP) appears to rise with an increase in radiation received by the lungs. Intensity modulated radiotherapy (IMRT) provides the ability to reduce planned doses to healthy organs at risk (OAR) and can potentially reduce treatment-related side effects. This study reports toxicity outcomes and provides a dosimetric comparison with three-dimensional conformal radiotherapy (3DCRT). **Methods:** Thirty curative NSCLC patients received radiotherapy using four-dimensional computed tomography and five-field IMRT. All were assessed for early and late toxicity using common terminology criteria for adverse events. All plans were subsequently re-planned using 3DCRT to the same standard as the clinical plans. Dosimetric parameters for lungs, oesophagus, heart and conformity were recorded for comparison between the two techniques. **Results:** IMRT plans achieved improved high-dose conformity and reduced OAR doses including lung volumes irradiated to 5–20 Gy. One case each of oesophagitis and erythema (3%) were the only Grade 3 toxicities. Rates of Grade 2 oesophagitis were 40%. No cases of Grade 3 RP were recorded and Grade 2 RP rates were as low as 3%. **Conclusion:** IMRT provides a dosimetric benefit when compared to 3DCRT. While the clinical benefit appears to increase with increasing target size and increasing complexity, IMRT appears preferential to 3DCRT in the treatment of NSCLC.

Introduction

Patients receiving conventional radiotherapy regimens for locally advanced non-small cell lung cancer (NSCLC) experience 5-year survival rates as low as 15% and severe pulmonary side effects including radiation pneumonitis (RP).¹ A recent meta-analysis of 836 patients (12 institutions) showed symptomatic RP rates of 29.6% (including 1.9% of which was fatal).² Although no

absolute dose thresholds have been identified to prevent a patient developing RP, the probability appears to rise with an increase in radiation received by lung tissue.^{2,3}

Preserving healthy lung tissue for patients undergoing radiotherapy is therefore not only desirable, but increasingly achievable given recent advances in technology. Four-dimensional imaging allows for superior target visualisation and assessment of respiratory motion at both the planning and treatment verification stages

while intensity modulated radiotherapy (IMRT) provides the potential to reduce the dose to surrounding organs at risk (OAR) beyond what is achievable with three-dimensional conformal radiotherapy (3DCRT).

While four-dimensional computed tomography (4DCT) has become increasingly utilised, the implementation of IMRT as the treatment standard for NSCLC remains challenging. This is in part due to an absence of clinical evidence from randomised trials, however a number of centres have undertaken retrospective studies providing reliable information regarding the therapeutic value of IMRT. The MD Anderson Cancer Centre (Texas, USA) published a series of planning studies showing IMRT improves target coverage and conformity⁴ and reduces the amount of high and low dose received by the lungs.⁵ More recent publications report a reduced rate of Grade 3 RP in 68 (8%) IMRT patients when compared with 222 (32%) patients treated with 3DCRT⁶ and that, when combined with 4DCT, IMRT can improve survival rates when compared with CT and 3DCRT.⁷

IMRT has also been reported as beneficial for challenging cases.⁸ Memorial Sloan Kettering Cancer Centre (New York, USA) reported an acceptable 18% Grade 2 RP and 11% Grade 3 RP in 55 cases specifically chosen due to their large target volume or close proximity to an OAR.⁹

Another concern has been the delivery of modulated treatments to a moving target. Although there appears to be the potential for inaccuracies to result from the respiratory-induced target motion, issues such as interplay and gradient effects have been shown to have minimal impact once conventional fractionation is considered.^{10,11}

In 2013, North Coast Cancer Institute (NCCI) implemented 4DCT and IMRT with daily image-guidance radiotherapy (IGRT) for patients undergoing curative treatment for NSCLC. This decision was based on the twin aims of maximising the accuracy of the treatment and ensuring the dose to uninvolved lung tissue, oesophagus and heart were kept as low as possible. We report the toxicity outcomes of the first 30 NSCLC patients treated within this program and provide a dosimetric comparison with 3DCRT plans generated retrospectively for the same cohort of patients. These data will contribute to the evidence base supporting the use of IMRT, 4DCT and IGRT for the treatment of NSCLC.

Methods

Patients and data accrual

North Coast New South Wales Human Research and Ethics Committee granted approval for this review.

Characteristics and treatment details of 30 consecutive NSCLC patients, treated between October 2013 and August 2014 at NCCI, are shown in Table 1. As the primary objectives were the plan comparison and toxicity outcomes, all patients prescribed a curative dose were included.

Simulation

Patients underwent 4DCT (Somatom Sensation Open, Siemens AG, Munich, Germany) stabilised with both arms up in a supine position using an evacuated cushion, wingboard and knee support (Fig. 1). Helical scans of the entire lungs were acquired at 120 kV, 1000 mAs. The respiratory signal provided by a 30-mm abdominal pressure sensor (AZ-733V, Anzai Medical Co., Tokyo, Japan) (Fig. 2) was used to sort the CT data into eight

Table 1. Patient characteristics ($n = 30$).

Patient characteristic	<i>n</i>	%
Age (years)		
Median	63.9	
Range	43–82	
Gender		
Male	21	70
Female	9	30
Histological subtype		
Squamous carcinoma	14	46.6
Adenocarcinoma	12	40.0
Large cell	2	6.7
Unclear	2	6.7
History of smoking	30	100
Stage		
Ia	2	6.7
Ib	1	3.3
IIa	4	13.3
IIb	3	10
IIIa	13	43.3
IIIb	3	10
IV	4	13.3
Location		
Right	14	46.7
Left	16	53.3
Lobe		
Upper	24	80
Lower	3	10
Middle (right)	3	10
Prescription (Gray/fractions)		
60/30 (non-chemo)	2	6.7
60/30 + chemotherapy	21	70
55/20	5	16.7
Other	2	6.7
Planning target volume (cm ³)		
Median	281	
Range	52–758	



Figure 1. Upper body stabilisation equipment including an evacuated cushion localised on a wingboard and Silverman head rest (under cushion).



Figure 2. Patient localised in position. Anterior and lateral alignment tattoo positions are highlighted by lasers and the ANZA respiratory signal sensor can be seen in the anterior position.

bins, including inhale (100%), exhale (0%) and 25%, 50% and 75% of the total displacement of the trace from 0% in both the inhalation and exhalation phases of the breathing cycle. Patients were instructed to breathe with a regular pattern at CT (and treatment) to minimise reconstruction artefacts and to limit any variations of that pattern during their course of treatment. An internal target volume (ITV) was created by expanding the gross disease defined by the maximum-intensity projection of the eight bins (GTV_{mip}) by 6–8 mm, while a further 5-mm expansion was used to create a planning target volume (PTV).¹²

Planning

Patients received concurrent chemoradiation therapy (CCRT) to 60 Gy in 30 fractions ($n = 21$) or radiation only to 55 Gy in 20 fractions ($n = 5$). For reasons of

co-morbidity two patients received 60 Gy without chemotherapy while a further two patients received reduced doses of 50 and 54 Gy in 2 Gy fractions (Table 1). Plans were generated such that 98% of the PTV received coverage with 95% of the prescribed dose (PD). OAR constraints are outlined in Table 2. For the clinical plans, a five-field sliding window technique was developed by a radiation therapist with experience in lung dosimetry in Monaco V3.3 (Elekta Pty Ltd., Maryland Heights, MO, USA) utilising the Monte Carlo algorithm. A 3DCRT plan was retrospectively produced on the same data set within XiO 5.0 (Elekta Pty Ltd.) by the same planner (wherever possible) using a superposition calculation algorithm (Monaco 3DCRT planning unavailable). Planners utilised 3–5 beams with the endpoint being the same minimum target coverage as the clinical IMRT plan. Planners made every effort to conform the dose to the PTV and minimise OAR doses. No time constraints were used and all 3DCRT plans underwent peer review to ensure the same level of quality assurance as given to clinical IMRT plans.

Dose–volume parameters for the PTV and OARs (as outlined in Table 3) were calculated from the dose–volume histogram for each plan. These included ipsilateral lung V20 (percentage volume of the structure receiving 20 Gy) and V30, which have been shown to correlate with the incidence of RP¹³ as well as two measures of high-dose conformity, a conformity index (CI: the ratio of tissue receiving 95% PD to the volume of the PTV)¹⁴ and volume of regret (the volume of tissue outside the PTV that receives at least 95% PD).

Stratification of the results as a product of PTV size and proximity to OARs (heart and oesophagus) was done to better understand clinical scenarios where the greatest advantages may exist for IMRT.

Image guidance

Each patient received daily treatment verification with cone beam computed tomography (CBCT), providing soft tissue visualisation unachievable with planar imaging techniques. Scans were acquired (67 sec, 183 frames, 200° gantry rotation with 120 kV and 10.0 mA per frame) with a nominal dose of 5.3 mGy and reconstructed using XVI software (Elekta Pty Ltd.) with 270 × 264 × 270 voxels and a 1-mm isotropic voxel size. An automated dual registration procedure (using algorithms provided within the software) was performed by first aligning to the vertebrae adjacent to the PTV in order to establish the spinal cord position and second, to the soft tissue within 2 cm of the PTV effectively establishing correct target position. All soft tissue offsets

Table 2. Organ at risk planning constraints (NSCLC).

Organ at risk	Ideal constraint	Major violation
Combined lungs (minus GTVmip)	Mean \leq 15 Gy V20 Gy < 25% (chemo-rad and lower lobe tumours) or V20 Gy < 30% (non-chemo) V5 < 60%	Mean > 20 Gy V20 Gy > 30% (chemo-rad and lower lobe tumours) or V20 Gy > 35% (non-chemo) V5 > 65%
Ipsilateral lung (minus GTVmip)	V20 < 40% and V30 < 30%	V20 > 50% and V30 > 40%
Contralateral lung and pneumonectomy (mesothelioma)	Mean < 8 Gy and V20 Gy < 4%	Mean > 10 Gy and V20 Gy > 10%
Lung lobectomy	Mean \leq 10 Gy and V20 Gy \leq 25%	Mean > 15 Gy and V20 Gy > 30%
Spinal cord	Max dose < 45 Gy hypofractionated < 40 Gy	Max dose > 47 Gy hypofractionated > 42 Gy
Spinal cord + 3 mm	Max dose < 47 Gy hypofractionated < 42 Gy	Max dose > 50 Gy hypofractionated > 44 Gy
Heart	Max dose < 50 Gy < PD when overlap exists and V40 < 30% and Mean < 20 Gy	Max dose > 55 Gy > 105% PD when overlap exists and V40 > 40% and Mean > 26 Gy
Brachial plexus	Max dose < 60 Gy	Max dose > 66 Gy
Oesophagus (cricoid to gastro- oesophageal junction)	Mean < 28 Gy V45 Gy < 35% Max dose < PD	Mean > 34 Gy V45 Gy > 40% Max dose > 110% PD
Central airways	Max dose < PD	Max dose > 110% PD

NSCLC, non-small cell lung cancer; PD, prescribed dose; Gy, Gray; Vx, the percentage volume of a structure receiving xGy; GTV, gross tumour volume.

were corrected prior to treatment as long as cord misalignment was less than 3 mm (greater cord misalignment may be accepted on consultation with the planner and radiation oncologist (RO)). Where target amplitudes exceeded 1 cm (peak–peak) four-dimensional CBCT (4DCBCT) was utilised with the same dual registration technique in order to ensure accurate target alignment. Gross changes within the soft tissue, and significant baseline variations of the tumour were discussed with the treating RO to assess dosimetric and registration implications.

Statistical analysis and outcomes

Data are presented as mean (SD). The paired *t*-test was used to compare plans; a two-tailed $P < 0.05$ was considered statistically significant. Actuarial survival was calculated using the Kaplan–Meier method. Toxicity was graded using CTCAE v4.0 (Common Terminology Criteria for Adverse Events).

Results

Conformity

Both the CI and volume of regret were better within the IMRT plans representing a 51.04% (67.39 cm³) decrease in the average amount of uninvolved tissue receiving doses greater than 95% PD (Table 3). The improvements were greatest in the patients with larger PTVs. The largest improvement in CI was for a case with two targets (226 cm³) where the index reduced from 1.81 (3DCRT) to 1.26 (IMRT). The largest absolute reduction in volume of regret was 279 cm³ for a 650 cm³ PTV (IMRT: 110 cm³ and 3DCRT: 389 cm³).

Combined lungs

Results show lower lung doses within the IMRT group (Table 3). The average V20 reduced by 1.62% while the mean lung dose (MLD) reduced by 0.72 Gy, both showing statistical significance. The amount of low dose received by the lungs was also lower within the IMRT group with a 2.82% average reduction in the volume of lung receiving 5 Gy (although not reaching significance, $P = 0.054$).

Individual lungs

The average reduction in ipsilateral lung doses for the V20, V30 and mean dose were 4.03%, 4.33% and 1.61 Gy, respectively, all of which were statistically significant. Differences in contralateral lung doses were both small and insignificant.

Comparison based on size of PTV

For the 15 smallest PTVs (mean 168 cm³) the differences in combined and ipsilateral lung doses between the IMRT and 3DCRT plans were negligible including identical MLDs (Table 4). For the 15 largest PTVs (mean 501 cm³), a 3.18% and 6.36% reduction in V20 and V5 combined lung doses were obtained within the IMRT group, as well as a 1.42 Gy reduction in average MLD (Table 5). Ipsilateral lung V20 and V30, respectively, saw

Table 3. Dosimetric comparison of mean (SD) doses for IMRT and 3DCRT plans.

Volume	Parameter	IMRT	3DCRT	P-value ¹
PTV	D98 (Gy)	55.37 (2.54)	55.37 (2.54)	NS
	D95 (Gy)	56.69 (2.73)	56.42 (2.49)	0.058
	D50 (Gy)	59.81 (2.93)	59.25 (2.67)	0.021*
	D2 (Gy)	62.26 (3.23)	61.58 (2.85)	0.034*
Lung combined	V20 (%)	17.47 (6.63)	19.09 (8.30)	0.009**
	V10 (%)	27.34 (10.92)	27.40 (12.18)	NS
	V5 (%)	39.64 (15.40)	42.46 (17.85)	0.054
	Mean (Gy)	10.20 (3.64)	10.92 (4.48)	0.002**
Lung ipsilateral	V10 (%)	47.96 (18.61)	49.24 (19.54)	0.059
	V20 (%)	34.84 (13.06)	38.87 (16.44)	0.004**
	V30 (%)	26.84 (10.79)	31.17 (14.76)	0.003**
	Mean (Gy)	17.21 (6.52)	18.82 (7.50)	0.014*
Lung contralateral	V10 (%)	10.62 (8.10)	9.73 (9.43)	NS
	V20 (%)	2.51 (3.21)	2.75 (3.51)	NS
	Mean (Gy)	3.81 (2.06)	4.20 (2.42)	0.052
Spinal cord	Max (Gy)	37.82 (8.02)	34.89 (11.72)	0.050
Heart	Mean (Gy)	7.56 (8.88)	9.02 (10.37)	0.015*
	D2 (Gy)	29.60 (21.13)	34.36 (22.17)	<0.0001**
Oesophagus	Max (Gy)	45.78 (23.12)	47.74 (22.62)	0.051
	Mean (Gy)	14.40 (7.04)	15.22 (7.98)	0.081
	D2 (Gy)	47.44 (16.11)	48.29 (16.45)	NS
	Max (Gy)	51.62 (14.66)	51.91 (14.47)	NS
Conformity	V45 (%)	11.93 (11.43)	15.00 (13.71)	0.021*
	Conformity index	1.21 (0.11)	1.38 (0.18)	<0.0001**
	Regret (cm ³)	64.64 (35.29)	132.03 (87.58)	<0.0001**

Gy, Gray; NS, not significant; Vx, percentage volume of a structure receiving xGy; Dx, dose that covers x per cent of the structure; IMRT, intensity modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; conformity index, ratio of the volume of tissue receiving 95% PD to the volume of the PTV; Regret, the volume of tissue receiving greater than 95% PD; PD, prescribed dose.

¹Paired t-test.

*Significant at 0.05 level (two-tailed).

**Significant at 0.01 level (two-tailed).

6.61% and 7.76% reductions using IMRT while the mean dose dropped on average by 3.23 Gy.

Oesophagus

The V45 was reduced by 3.07% in the IMRT cohort, however the associated reductions in mean dose and D2 (dose received by 2% of the organ) were not significantly different (Table 3).

Heart

Significant reductions in mean dose (1.46 Gy) and D2 (4.76 Gy) were achieved using IMRT compared with 3DCRT (Table 3).

Comparison based on proximity of PTV to the heart and oesophagus

In 67% of patients the PTV was within 5 mm of the heart. For this cohort, the average heart doses for IMRT

were reduced slightly further beyond that of the overall cohort. No meaningful results were available for the corresponding oesophageal cohort as only five patients had a target greater than 5 mm from the oesophagus (Table 6).

Toxicity and survival

Patients were prospectively evaluated and managed for acute and late toxicity (Table 7). Three patients died prior to 3 months from disease-related complications and one case was lost to follow-up (no pulmonary side effects reported at 3 months). Two cases of acute Grade 3 toxicity were reported: one oesophagitis (3.3%) and one skin desquamation (3.3%). Grade 2 oesophagitis rates were 40% with all cases resolved by 3 months. No Grade 3 RP was reported, however two patients developed infective pneumonia and required treatment with antibiotics. Overall survival rates at 18 months were 64% (Stages I–II), 56% (Stage III) and 50% (Stage IV).

Table 4. Conformity and mean (SD) lung doses for small PTVs ($n = 15$; mean 168 cc).

Volume	Parameter	IMRT	3DCRT	<i>P</i> -value ¹
Lung-combined	V20 (%)	14.13 (5.99)	14.21 (6.84)	<0.0001**
	V10 (%)	21.20 (9.62)	20.85 (11.12)	0.002**
	V5 (%)	30.80 (13.71)	30.07 (14.29)	NS
	Mean (Gy)	7.97 (3.21)	7.99 (43.4)	NS
Lung-ipsilateral	V10 (%)	32.62 (15.69)	36.30 (15.59)	NS
	V20 (%)	26.31 (12.04)	27.77 (9.95)	NS
	V30 (%)	20.23 (9.87)	21.11 (9.95)	NS
	Mean (Gy)	13.71 (5.63)	13.72 (5.74)	NS
Conformity index	Conformity index	1.25 (0.08)	1.40 (0.18)	0.011*
	Regret (cm ³)	44.99 (25.99)	73.10 (49.86)	0.016*

PTV, planning target volume; Gy, Gray; NS, not significant; Vx, percentage volume of a structure receiving xGy; Dx, dose that covers x per cent of the structure; IMRT, intensity modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; conformity index, ratio of the volume of tissue receiving 95% PD to the volume of the PTV; Regret, the volume of tissue receiving greater than 95% PD; PD, prescribed dose.

¹Paired *t*-test.

*Significant at 0.05 level (two-tailed).

**Significant at 0.01 level (two-tailed).

Table 5. Conformity and mean (SD) lung doses for large PTVs ($n = 15$; mean 501 cc).

Volume	Parameter	IMRT	3DCRT	<i>P</i> -value ¹
Lung-combined	V20 (%)	20.80 (5.59)	23.98 (6.70)	NS
	V10 (%)	33.48 (8.59)	33.97 (9.55)	NS
	V5 (%)	48.49 (11.66)	54.85 (11.26)	0.08
	Mean (Gy)	12.43 (2.54)	13.85 (3.41)	NS
Lung-ipsilateral	V10 (%)	59.72 (13.22)	63.19 (13.74)	NS
	V20 (%)	43.36 (7.24)	49.97 (11.36)	0.058
	V30 (%)	33.46 (7.06)	41.22 (11.63)	0.026*
	Mean (Gy)	20.70 (5.50)	23.93 (5.26)	0.070
Conformity index	Conformity index	1.17 (0.02)	1.35 (0.19)	<0.0001**
	Regret (cm ³)	84.29 (32.81)	190.97 (77.20)	<0.0001**

Gy, Gray; NS, not significant; Vx, percentage volume of a structure receiving xGy; Dx, dose that covers x per cent of the structure; IMRT, intensity modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; conformity index, ratio of the volume of tissue receiving 95% PD to the volume of the PTV; Regret, the volume of tissue receiving greater than 95% PD; PTV, planning target volume; PD, prescribed dose.

¹Paired *t*-test.

*Significant at 0.05 level (two-tailed).

**Significant at 0.01 level (two-tailed).

Discussion

Intensity modulated radiotherapy has been shown to reduce the dose to healthy lung tissue below what is

Table 6. Mean (SD) OAR doses when PTV comes within 5 mm of the organ.

Organ	Parameter	IMRT	3DCRT	<i>P</i> -value ¹
Heart ($n = 20$)	Mean (Gy)	10.80 (9.31)	12.88 (10.77)	0.019*
	D2 (Gy)	41.11 (15.33)	46.08 (14.96)	0.0002**
	Max (Gy)	59.36 (4.86)	59.71 (2.52)	NS
Oesophagus ($n = 25$)	Mean (Gy)	16.24 (6.01)	17.28 (6.96)	0.052
	D2 (Gy)	53.32 (8.99)	54.57 (8.67)	NS
	Max (Gy)	57.24 (6.46)	57.83 (4.60)	NS
	V45 (%)	14.32 (10.88)	18.00 (13.06)	0.02*

Gy, Gray; NS, not significant; Vx, percentage volume of a structure receiving xGy; Dx, dose that covers x per cent of the structure; IMRT, intensity modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; OAR, organ at risk; PTV, planning target volume.

¹Paired *t*-test.

*Significant at 0.05 level (two-tailed).

**Significant at 0.01 level (two-tailed).

achieved with 3DCRT.^{4,5,8,9} Our assessment of 30 patients treated with five-field IMRT at NCCI confirms this with lower V20 and MLD (both $P < 0.01$), however with the reduction in V5 failing to reach statistical significance ($P = 0.054$). While the reductions may seem modest (1.6% (V20) and 0.7 Gy (MLD)), they often equate to significant amounts of healthy tissue. By stratifying the patients according to target size we may better understand the scenarios where IMRT is increasingly likely to have a clinical advantage. While the statistical power is reduced by halving the patient numbers, the 15 largest PTVs (mean: 501 cc) show a 3.3% and 6.4% reduction in V20 and V5, respectively, and 1.4 Gy reduction in MLD (Table 5). By comparison, the 15 smallest PTVs (mean: 168 cc) show minimal change in dosimetry (Table 4) suggesting that any clinical benefit is likely to be dependent on target size.

Our study also supports a previous work demonstrating improved dose conformity with IMRT.⁴ While it is intuitive that larger tumours would receive greater clinical benefit from improved conformity, we found that the ratio of uninvolved tissue spared high dose increases within the larger PTV cohort with 106.7 cm³ of healthy tissue spared doses in excess of 95% PD using IMRT. While smaller PTVs also show improved conformity (28.1 cm³ of uninvolved tissue spared high doses), it would once again appear that the larger and more complex targets stand to gain the most clinical benefit from IMRT.

Heart toxicity has historically been under-reported. Our results show IMRT can produce lower heart doses but with the variable results (a product of the variation

Table 7. Toxicity outcomes for NSCLC patients treated with IMRT (early $n = 30$, late $n = 26$).

	Grade, n (%)				
	0	1	2	3	4/5
<i>Early toxicity</i>					
<i>Respiratory</i>					
Dyspnoea	7 (23)	17 (57)	6 (20)	0	0
Cough	4 (13)	20 (67)	6 (20)	0	0
Radiation pneumonitis	29 (97)	0	1 (3)	0	0
<i>Oesophagus</i>					
Dysphagia	11 (37)	11 (37)	8 (27)	0	0
Oesophagitis	9 (30)	8 (27)	12 (40)	1 (3)	0
<i>Skin</i>					
Erythema	6 (20)	15 (50)	8 (27)	1 (3)	0
<i>Late toxicity (> 3 months)</i>					
<i>Respiratory</i>					
Dyspnoea	12 (46)	10 (38)	4 (15)	0	0
Cough	12 (46)	14 (54)	0	0	0
Radiation pneumonitis	26 (100)	0	0	0	0
Pneumonia	24 (92)	0	0	2 (8)	0
<i>Oesophagus</i>					
Oesophagitis	23 (88)	3 (12)	0	0	0
<i>Skin</i>					
Erythema	23 (88)	2 (8)	1 (4)	0	0

NSCLC, non-small cell lung cancer; IMRT, intensity modulated radiotherapy.

in target size, target location and prescribed dose) making it difficult to draw conclusions from the patient cohort. It is more meaningful to assess the 20 cases where higher cardiac doses occur due to the organ's proximity to the tumour. While the high standard deviations still indicate patient-to-patient variation, a 5 Gy reduction in the average D2 and 2 Gy reduction in mean dose seem to reflect the greater ability of IMRT to control the dose in regions adjacent the target.

The very high proportion of cases with the oesophagus abutting the PTV meant a similar analysis for this OAR was of little benefit. However, our results show improved oesophageal doses within the IMRT cohort but with questionable clinical and statistical significance. Although seemingly preferable to 3DCRT, oesophageal doses were an area we expected IMRT to show a greater advantage. While we report rates of severe Grade 3 oesophagitis (4.7% of patients receiving CCRT) below the 6% experienced by the Radiation Therapy Oncology Group,¹⁵ less severe oesophagitis can still impact heavily on a patient's quality of life. Further review of the optimisation parameters controlling oesophageal dose may allow for improved results.

Although we report dosimetric benefits in using IMRT for the treatment of NSCLC with respect to lung doses, the improvements are somewhat less than those

previously reported, most notably decreases 8–10% for V20 and 2 Gy for MLD.^{4,5} This is in part not only due to the larger median PTV size within those studies (623 cc and 382 cc), but also potentially due to the methodology of retrospectively planning the IMRT cases. In those studies the IMRT plans were optimised for dose levels (V5–10) not optimised in the clinical 3DCRT cohort that would act to further reduce the MLD and 20 Gy isodose levels within those plans. Conversely, by retrospectively planning the 3DCRT (to which we are unaware of any other such study) we expect a level of false improvement within the 3DCRT plans. Establishing a benchmark IMRT plan potentially prompted the planner to optimise the 3DCRT plans more than would normally be the case in a standard clinical setting. Consequently the dosimetric benefits of IMRT may be greater than what we have demonstrated.

While the relationship between low doses of radiation and the development of RP is not well understood, we consider it prudent to take steps to minimise such dose levels.³ Our study shows improved results with regard to the V5 which may be reflective of a technique employing fewer beams, as has previously been suggested.⁵ Limiting the beam arrangement to five fields allows the planner to optimise the beam angles to reduce the beam pathway through healthy lung tissue which has a minimising effect on low doses.

After 18 months follow-up we report no cases of Grade 3 RP. Assessing Grade 2 RP is more challenging though given the tendency of radiotherapy to exacerbate pre-existing respiratory conditions. While 5 (16.7%) patients had progression from their baseline condition to Grade 2 dyspnoea, this alone is not an indicator of RP. Only one patient received steroids as treatment for respiratory symptoms possibly indicating a Grade 2 RP rate as low as 3%. Further investigations over a larger patient cohort would be required to validate such outcomes.

These toxicity rates are below those reported by Palma *et al.* (Grade 2 and above RP of 29.8% including 1.9% fatality) in what is likely the largest meta-analysis of CCRT patients of its kind.² Our toxicity rates are also favourable in comparison to a recent analysis of 122 CCRT patients treated with 3DCRT alone (Grade 2 and above RP of 54.9% including two fatalities)³ as well as those investigating toxicity outcomes for patients treated with IMRT (Grade 2 of 18% and Grade 3+ of 11%⁹ and Grade 3 RP of 8%⁶). It must be noted, however, that any such comparisons are heavily biased by the high number of treatment and population variables that effect RP rates, including the tendency of those centres to limit the use of IMRT to the more physically challenging cases.

The simulation and IGRT methodologies employed also contribute to toxicity rates given the associated PTV margin requirements ultimately contribute to the size of the target receiving treatment. 4DCT has become increasingly common in thoracic radiotherapy with the primary benefit of accounting for motion in highly mobile targets. Conversely for targets that show little motion 4DCT avoids the use of the generic and excessive margins applicable to conventional methods (greater than 10 mm⁴). In our study 20 (67%) patients had minimal amplitude (<5 mm peak to peak) meaning a decrease in the average PTV size. This has the twin impact of both improving toxicity outcomes, but also minimising the apparent dosimetric benefit (given both appear to correlate with target size).

The frequency and methodology of image guidance also contributes to PTV size. Daily online IGRT protocols have the advantage of correcting for set up errors beyond that of weekly imaging protocols. Similarly registration methods that align to the soft tissue have the benefit of correcting for variations in the baseline tumour position (with respect to bony anatomy) meaning smaller required PTV margins.¹⁶ A recent review of imaging protocols suggests a bony alignment protocol requires a 2-mm increase in PTV margin when compared with soft tissue alignment.¹⁷

While PTV margin calculations are complex and time-consuming our institution utilised a popular formula¹⁸ to review the required PTV margins with respect to methodologies outlined in this report. We modified the formula to account for the ITV method to ensure a uniform margin of 5 mm around the ITV¹² provided adequate coverage for the cohort.

In this study five patients were re-planned based on the soft tissue information afforded by CBCT (tumour regression/progression, weight loss, pneumothorax) indicating a benefit over planar techniques. With respect to soft tissue alignment protocols, care must be taken where multiple targets or significant mediastinal involvement exists, as these portions of the target may move somewhat independently from each other.¹⁷ Furthermore, robust procedures to assess OAR misalignment are required to ensure that structures such as the spinal cord are not compromised with respect to the dose they receive. Our method of dual registration, while specific to a particular vendor, is both a quick and reliable way of ensuring that such structures are not at risk of excessive doses.

While our overall survival rates appear acceptable, it is beyond the scope of this study to investigate potential survival benefits from IMRT as have previously been reported.⁸

Conclusion

The treatment of NSCLC has evolved rapidly over the past 10 years consistent with technological advances. In the absence of any data from clinical trials, decisions to use IMRT have been made on the principle of minimising dose to the surrounding OARs. For patients undergoing conventional dose regimens, this study reports that 4DCT and soft tissue image-guided IMRT can reduce the dose to OARs beyond what is achievable with conventional methods. A reduction in high and low doses received by the OARs will correspond to a decrease in toxicity rates, especially for larger tumours where IMRT demonstrates the greatest clinical benefit. This study adds to the growing evidence base that IMRT can become the standard treatment choice for conventionally fractionated NSCLC radiotherapy.

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Conflict of Interest

The authors declare no conflict of interest.

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