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FULL PAPER

Impact of modern radiotherapy techniques on survival outcomes for unselected patients with large volume non-small cell lung cancer

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Objective: Intensity modulated radiotherapy (IMRT) is used, where necessary, for bulky or complex-shaped, locally advanced, non-small cell lung cancer (NSCLC). We evaluate our real-world experience with radical radiotherapy including concurrent chemoradiation (CCRT), and analyse the impact of IMRT on survival outcomes in patients with larger volume disease.

Methods: All patients treated between May 2011 and December 2017 were included. Analyses were conducted for factors affecting survival, including large volume disease that was defined as planning target volume (PTV) > 500 cc.

Results: In 184 patients with large volume disease, the median overall survival was 19.2 months, compared to 22 months seen with the overall cohort of 251 patients who received radical radiotherapy. PTV and using CCRT were significant predictors for survival. IMRT was

used in 93 (50.5%) of 184 patients with large PTV. The patients treated using IMRT had significantly larger disease volume (median PTV = 859 vs 716 cc; p -value = 0.009) and more advanced stage (proportion of Stage IIIB: 56 vs 29%; p -value = 0.003) compared to patients treated with three-dimensional conformal radiotherapy. Yet, the outcomes with IMRT were non-inferior to those treated with 3DCRT. CCRT was used in 103 (56%) patients with large volume disease and resulted in a significantly better median survival of 24.9 months. The proportional benefit from CCRT was also greater than in the overall cohort.

Conclusion: Despite being used for larger volume and more advanced NSCLC, inverse-planned IMRT resulted in non-inferior survival.

Advances in knowledge: IMRT enables the safe use of curative CCRT for large-volume, locally-advanced NSCLC.

INTRODUCTION

A significant proportion of patients with non-metastatic non-small cell lung cancers (NSCLC) present with locally advanced (stages IIIA and IIIB) disease.^{1,2} Radical radiotherapy combined with chemotherapy given concurrently or sequentially remains the standard treatment for most patients with inoperable, locally advanced NSCLC.^{3,4} Planning radical radiotherapy for Stage III and large volume lung cancers can be challenging. With wider availability of inverse planning, intensity modulated radiotherapy (IMRT) is being increasingly used for the treatment of these patients with NSCLC, despite the absence of randomised comparison with three-dimensional conformal radiotherapy (3DCRT) in controlled trials.⁵⁻⁷

When discussing treatment options, the information for patients is often based on the expected outcome from

published trials. It remains to be seen whether the outcomes reported in large randomised controlled trials (RCTs) with strict entry criteria, hold true for unselected, real-world patients with larger radiation target volumes that are routinely treated outside the controlled environment of these clinical trials.⁸⁻¹⁰ The median planning target volume (PTV) reported in a large contemporary trial, the Radiation Therapy Oncology Group-0617 trial (RTOG 0617), was 426 and 486 cc for patients treated using 3DCRT and IMRT, respectively.¹⁰

In our centre, the use of IMRT for lung cancer is guided by tumour and planning factors. We use 3DCRT as the default planning technique, and inverse-planned IMRT using volumetric modulated arc therapy (VMAT) is used where necessary, for adequately covering the PTV whilst satisfactorily meeting the dose constraints for organs at risk.^{7,11} IMRT is not used with the sole purpose of reducing margins.

In the current study, we describe our treatment protocol and analyse our survival outcomes for unselected NSCLC patients treated with radical radiotherapy including concurrent chemoradiotherapy (CCRT) in the real-world setting. In particular, we aim to evaluate the subgroup of patients with large volume disease, explore the impact of using IMRT and the survival benefit from using CCRT on these patients.

METHODS AND MATERIALS

All patients who received radical radiotherapy with curative intent from May 2011 to December 2017, for inoperable locally advanced NSCLC, at our tertiary cancer centre were included in this retrospective analysis. The treatment plan for all of these patients was jointly decided at the lung cancer multidisciplinary team meeting. Prior to treatment, all patients had histological confirmation of NSCLC and staging work-up using a whole body positron emission tomography and MRI of the brain. Curative treatment was considered for all patients with Stage I, II or III disease. Patients with M1a disease who had malignant pleural effusion or pleural disease were excluded from curative treatment and offered palliative systemic treatment or supportive care. Patients with Stage IV disease who had a separate nodule in the contralateral lung (M1a) or had single metastasis or oligometastases and were treated with curative intent were also included. Patients who were deemed inoperable or declined surgery were considered for radical radiotherapy. Patients who received post-operative radiotherapy were not included in this study.

Pulmonary function tests comprising of forced expiratory volume in 1 s (FEV1) and lung diffusion capacity for carbon monoxide were carried out prior to treatment. Radical radiotherapy was only carried out if the pulmonary functions were satisfactory. CCRT was the treatment of choice for all fit patients, while those who were frail or less fit received sequential chemoradiotherapy (SCRT). Patients who were unfit for chemotherapy or had contraindications to chemotherapy received radiotherapy alone (RT).

Our treatment planning policy has been described in detail previously.^{7,11} Briefly, gross tumour volume was delineated on the slow axial scan in order to obtain entire motion envelope corresponding to the internal target volume. This was expanded by an isotropic margin of 5 mm (trimmed from natural anatomical boundaries) to obtain the clinical target volume. A further expansion of 1 cm axially and 1.3 craniocaudally was used, to generate the PTV.^{12,13} Plan evaluation and acceptance criteria included coverage of 95% of the PTV by 95% of the prescribed dose, while ensuring that the maximum point dose to spinal canal did not exceed 48 Gy, and lung V20 was less than 35% (Appendix A, Table 1 in [Supplementary Material 1](#)) Our radiotherapy planning conformed to standard guidelines published by the European Organization for Research and Treatment of Cancer.^{12,13}

CCRT was delivered using conventional radiotherapy at 2 Gy per fraction (usually 60 Gy in 30 fractions), whereas SCRT was often delivered using either accelerated hypofractionated radiation (55 Gy in 20 fractions, at 2.75 Gy per fraction) or conventional

fractionation¹⁴. Most radiotherapy-alone (RT-alone) treatments were either accelerated hypofractionated radiotherapy or continuous hyperfractionated accelerated radiation therapy using 1.5 Gy per fraction, three times daily at least 6 h apart, for 12 consecutive days.^{14–16}

The concurrent chemotherapy regimen comprised of cisplatin 50 mg m⁻² intravenous on days 1 and 8, followed by days 29 and 36, along with Etoposide on days 1–5 and 29–33. Due to logistical reasons, most patients received intravenous Etoposide (50mg m⁻²) along with cisplatin and oral Etoposide 100 mg m⁻² on the subsequent days. Our choice for chemotherapy regime, although different from that used in the RTOG 0617 trial, is an established and acceptable chemotherapy regime in this setting.^{17,18}

For the purpose of this study, we defined large volume disease based on PTV, used for radiotherapy planning. A PTV greater than a cut-off volume of 500 cc was accepted as large volume disease, as this value is clearly greater than the median (450 cc) for the overall cohort reported in the RTOG 0617 trial.^{9,10} In the RTOG 0617 trial, the median PTV was described as 426 and 486cc for patient cohorts treated using 3DCRT and IMRT, respectively.¹⁰

All statistical analysis was carried out using R (v. 3.4.2) using the Rstudio integrated development environment.¹⁹ Descriptive analysis was performed and differences between groups were explored using appropriate non-parametric tests (Kruskal–Wallis test or Wilcoxon Mann–Whitney *U* test for continuous variables and χ^2 test for categorical variables). The first set of descriptive analysis explored the difference between the groups based on the treatment type. Variables analysed included the age, gender, histology, stage, performance status and treatment modality. The overall survival was calculated from the date of diagnosis of the disease to the date of death. The database was closed to analysis on 25/04/18 and patients who were alive at the time of analysis were censored. The overall survival was estimated using the Kaplan–Meier method and compared using the log rank test. Adjusted analysis of the survival was performed using cox proportional hazards model with appropriate diagnostic tests for testing the assumptions of proportionality, linearity and absence of outliers.

RESULTS

Between May 2011 and December 2017, 251 patients received radical radiotherapy with curative intent for NSCLC, at our tertiary cancer centre. Of these, 139 (55.3%) patients underwent CCRT, while the others were treated with SCRT (*n* = 29, 11.6%) or radiation therapy alone (*n* = 83, 33.1%). Demographic parameters and broad treatment parameters for the entire cohort of 251 patients are displayed in [Table 1](#).

Outcomes for the entire cohort

The median follow-up for the entire cohort of 251 patients was 34 months [95% confidence interval (CI): 26.3–41.7 months] and the median overall survival for the cohort was 22 months (95% CI: 19.2–26.1 months). The median PTV for the entire

Table 1. Descriptive table showing the parameters for the entire cohort

Variable	Parameter	CCRT (139)	SCRT (29)	RT (83)	p-value
Age	Median (IQR)	61 (55–66)	64 (56–68)	71 (65–74)	<0.01*
Gender	Male	118 (85%)	26 (90%)	69 (83%)	0.70
Histology	Adenocarcinoma	67 (48%)	10 (34%)	30 (36%)	0.15
	Non-adenocarcinoma	72 (52%)	19 (66%)	53 (64%)	
ECOG PS	0	17 (12%)	1 (3%)	3 (4%)	<0.01*
	1	112 (81%)	19 (66%)	49 (59%)	
	2	10 (7%)	9 (31%)	29 (35%)	
	3	0 (0%)	0 (0%)	2 (2%)	
Stage	I–IIA	13 (9%)	1 (3%)	10 (12%)	0.15
	IIIA	64 (46%)	15 (52%)	40 (48%)	
	IIIB	60 (43%)	10 (34%)	31 (37%)	
	IV	2 (1%)	3 (10%)	2 (2%)	
Radiation modality	3DCRT	76 (55%)	18 (62%)	48 (58%)	0.74
	IMRT	63 (45%)	11 (38%)	35 (42%)	
PTV volume	Median (IQR)	692 (519–899)	597 (439–785)	711 (550–898)	0.27

3DCRT, three-dimensional conformal radiotherapy; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity modulated radiotherapy; IQR, interquartile range; PS, performance status; PTV, planning target volume.

Variables marked with * were significant at p -value < 0.05.

Difference between groups for categorical variables was tested using the Kruskal-Wallis test for continuous and χ^2 test for categorical variables.

cohort was 688.7 cc (interquartile range: 506.3–900.0 cc). PTV and planning data were missing for six patients as their data were not retrievable from the archive. Table 1 describes the baseline variables for this cohort.

For the whole cohort, a cox regression analysis employing variables including age, gender, histological type, performance status, PTV, stage group, and treatment approach used was developed and validated. The summary of the cox regression

model is presented in Table 2. Continuous variables like age and PTV were expanded using restricted cubic splines using three knots to determine if linearity assumptions were fulfilled. While linearity assumptions were fulfilled for age, PTV demonstrated a non-linear relationship and was subsequently modelled using restricted cubic splines. The cox regression demonstrated that PTV and use of CCRT were independent and significant prognostic factors that determined survival, further justifying our choice of subgroups for analysis.

Table 2. Depicts the results of the cox regression model for the entire population

Variable	Comparison	Hazard ratio	Lower 95% CI	Upper 95% CI
Age	58:70	1.20	0.87	1.60
Gender	Female:male	0.78	0.46	1.30
Histology	Adeno:non-adeno	1.00	0.72	1.50
ECOG PS	2–3:0–1	1.20	0.74	1.90
Stage	I–IIA:IIIA	0.90	0.48	1.70
	IIIB:IIIA	1.30	0.89	1.90
	IV:IIIA	1.40	0.48	3.90
Treatment*	RT:CCRT	2.40	1.50	3.80
	SCRT:CCRT	2.40	1.40	4.00
PTV Volume*	510:900	1.80	1.30	2.50
Radiation modality	IMRT:3DCRT	0.90	0.62	1.30

Adeno, adenocarcinoma; CCRT, concurrent chemoradiation; CI, confidence interval; 3DCRT, three-dimensional conformal radiotherapy; ECOG PS, European Cooperative Oncology Group performance status; IMRT, intensity modulated radiotherapy; Non-adeno, Non adenocarcinoma; PTV, planning target volume; RA, radiotherapy alone; SCRT, sequential chemoradiation.

Variables marked with * were significant at p value < 0.05.

Figure 1. Kaplan–Meier curves of overall survival by PTV. Difference between groups tested using the log rank test. PTV, planning target volume.

Outcomes in larger volume patients

Of the entire cohort, 184 patients were found to have large volume disease (PTV >500 cc). Of these patients, 103 had received CCRT, 18 received SCRT and the remaining 63 received radiotherapy alone. The baseline variables for this cohort (Appendix A, Table 2 in [Supplementary Material 1](#)) are largely similar to the parameters shown in [Table 1](#).

Patients undergoing radiation alone were older and had poorer performance status as compared to patients undergoing CCRT or SCRT. The median overall survival for all patients with large volume disease was 19.2 months (95% CI 17.7 to 22.5 months). As can be seen from [Figure 1](#) (and deduced from [Table 2](#)), patients with PTV exceeding 500 cc had significantly poorer overall survival. In this subgroup of patients, the cox proportional

hazards model showed that the use of CCRT was the only significant factor that predicted overall survival (Appendix A, Table 3 in [Supplementary Material 1](#)).

Outcomes in larger volume patients—impact of IMRT

An important aspect of this investigation was to explore the use and impact of IMRT in the population of patients with larger volume PTVs. The results shown in [Table 3](#) demonstrate that the use of IMRT in this population was dictated by the larger PTV and higher stage. IMRT was used for 93 patients with a median PTV of 859 cc (range: 698–1044 cc). This was significantly more than the median PTV of 716 cc (range: 626–907 cc) seen in 91 patients treated using 3DCRT. A significantly higher proportion of patients (56%) treated using IMRT had with Stage IIIB disease, compared with 29% for 3DCRT.

In the cohort of 184 patients with large volume disease, there was no significant difference in survival between IMRT and 3DCRT ([Figure 2](#), Panel A). Patients treated with CCRT using IMRT had a 2 year overall survival of 49.9% (95% CI: 36.8–67.7%), which was comparable to 51.3% (95% CI: 37.5–70.4%) in those treated with CCRT using 3DCRT ([Figure 2](#), Panel B). As previously described, IMRT was used only where dosimetric constraints were not felt to be achievable using 3DCRT. There was no significant difference in the other variables, thereby suggesting that the use of IMRT made CCRT safely deliverable, despite larger volumes and higher stage distribution in this cohort.

Outcomes in larger volume patients—impact of CCRT

The benefit from CCRT in terms of survival was explored in the two defined groups of patients (large volume disease with PTV >

Table 3. The distribution of the baseline disease and treatment related parameters among patients with larger disease volume (PTV >500 cc) divided into those receiving IMRT or 3DCRT

Variable	Parameter	3DCRT (91)	IMRT (93)	p-value
PTV volume	Median (IQR)	716 (626–907)	859 (698–1044)	0.009*
Age	Median (IQR)	64 (59–71)	63 (58–68)	0.39
Gender	Male	79 (87%)	84 (90%)	0.45
ECOG PS	0–1	71 (78%)	75 (81%)	0.33
	2–3	20 (22%)	18 (19%)	
Stage	I–IIA	9 (10%)	6 (6%)	0.003*
	IIIA	54 (59%)	33 (35%)	
	IIIB	26 (29%)	52 (56%)	
	IV	2 (2%)	2 (2%)	
Histology	Adenocarcinoma	33 (36%)	35 (38%)	0.85
Treatment	CCRT	47 (52%)	56 (60%)	0.46
	SCRT	9 (10%)	9 (10%)	
	RT	35 (35%)	28 (30%)	

Adeno, adenocarcinoma; CCRT, concurrent chemoradiation; 3DCRT, three-dimensional conformal radiotherapy; ECOG PS, European Cooperative Oncology Group performance status; IMRT, intensity modulated radiotherapy; Non-adeno, non adenocarcinoma; PTV, planning target volume; RT, radiotherapy alone; SCRT, sequential chemoradiation.

Variables marked with * were significant at p value < 0.05.

Figure 2. Kaplan–Meier plot of overall survival (using IMRT vs 3DCRT) in all patients with PTV >500 cc (Panel A) and those patients with PTV >500 cc who received CCRT (Panel B). *p*-value calculated using the log rank test. 3DCRT, three-dimensional conformal radiotherapy; CCRT, concurrent chemoradiation; IMRT, intensity modulated radiotherapy; PTV, planning target volume.

500 cc and smaller volume disease with PTV ≤ 500 cc). As shown in Figure 3, the 2 year survival in patients undergoing CCRT was 50.39% (95% CI: 40.44 to 62.79%) in patients with large PTV vs 81.19% (95% CI: 67.37 to 97.83%) in those with smaller PTV. This corresponds to a median survival of 24.9 vs 53.8 months in the two groups, respectively.

The absolute improvement in the 2 year overall survival for patients treated with CCRT was 33.08% in patients with large PTV (corresponding to a hazard ratio 0.43) vs 40.39% in patients with smaller PTV (hazard ratio 0.36). However, the proportional increase in the 2 year overall survival from CCRT in patients with large PTV was 191 vs 99% in those with smaller PTV. This means that although the absolute benefit from CCRT was smaller, the proportional improvement in the overall survival was greater in patients with large PTV.

DISCUSSION

The outcomes from the current study confirm that radical radiotherapy treatment (CCRT, SCRT or RT-alone) for inoperable, locoregionally advanced NSCLC is feasible and effective for unselected patients with larger volume disease, in the real-world setting. This single-institution, retrospective series shows the efficacy of a well-defined treatment regimen based on standard

guidelines for large volume disease in our demographic group. This is despite the differences in disease factors (stage distribution, disease bulk represented by PTV) when compared with published clinical trials such as RTOG 0617.^{9,10}

Despite being used to treat patients with significantly worse performance status and larger inoperable tumours, IMRT has been shown to provide equivalent survival to 3DCRT.^{20–22} Large retrospective analyses have reported equivalent or better outcomes with IMRT in Stage III NSCLC as compared to 3DCRT.^{23,24} Published data on Stage III NSCLC from the National Cancer Data Base where IMRT was used for 422 (16.6%) of 2543 patients has shown that the use of IMRT was not related to the tumour stage or size, but had increased over time. IMRT was associated with significantly better overall survival compared with 3DCRT in patients with T_3 and T_4 tumours in both multivariate analysis and propensity-matched cohorts.²³ The results from RTOG 0617 showed that despite having larger tumour volumes, patients treated with IMRT had equivalent outcomes as 3DCRT.¹⁰ The current study confirms these findings in a non-trial setting and demonstrates that these outcomes were maintained in patients with significantly larger PTV and more advanced stage (greater proportion of patients with Stage IIIB NSCLC) than those reported in the RTOG trial.

Figure 3. Kaplan–Meier curves of survival in patients who received CCRT, those with PTV >500 cc (Panel A) and those with PTV ≤ 500 cc (Panel B). *p*-values derived from log rank test. CCRT, concurrent chemoradiation; PTV, planning target volume.

All reported studies comparing IMRT to 3DCRT are retrospective, except the secondary analyses of RTOG 0617.^{10,25} Moreover, even within RTOG 0617, the choice between using IMRT and 3DCRT was not randomised but left to the physician's discretion,⁹ and the IMRT was more likely to be used at a high-volume centre.¹⁰ This was not unexpected as data from the Surveillance, Epidemiology, and End Results registry, linked to Medicare claims had already shown that practice environment including availability and local expertise influenced implementation and use of IMRT for lung cancer, rather than patient and tumour factors.⁶ This is probably because of higher costs incurred per patient when using IMRT for lung cancer, as shown in another report from the Surveillance, Epidemiology, and End Results registry-Medicare.²⁶ IMRT also requires highly trained staff using more advanced planning systems, complex dose calculation algorithms and more advanced radiotherapy delivery systems with robust image-guidance.⁴ However, in our high-volume centre with good IMRT planning experience, IMRT was used when necessary for adequately and safely treating the PTV, whilst satisfying the dose constraints for organs at risk. The use of IMRT was determined by the tumour characteristics and topography (determined by the volume and stage of disease). IMRT was not used for increasing plan conformity or reducing toxicity.

Patients with large volume disease (PTV >700 cc) and poorer performance status have been reported in another retrospective series to show poorer outcomes compared to those reported in RCTs.²⁷ The authors had recognised that lack of access to IMRT at the time had prevented the use of higher doses of radiation and may have influenced the outcomes.²⁷ In a subsequent analysis, the same authors showed that patients with tumours in excess of 700 cc had a median survival of 14.5 months.⁸ In the IMRT cohort of the current study, the PTV size is comparable with a median PTV of 859 cc (range: 698–1044cc). For the sake of comparison, when we redefined the IMRT cohort, to include patients with PTV >700 cc, the median survival was 23.4 months. We believe that this difference is related to the use of IMRT, which not only allowed curative radical radiotherapy, but as a consequence also allowed concurrent chemotherapy for many of these patients.

CCRT for locally advanced NSCLC is established in routine clinical practice and has been shown to improve survival compared with sequential chemoradiation (SCRT), at the cost of increased but manageable acute oesophageal toxicity.^{3,28} Randomised trials that have employed CCRT for NSCLC, have also described the median overall survival for standard CCRT ranging from 20 to 28.7 months.^{9,17,18} However, RCTs in lung cancers have necessarily included fit patients who have met the defined inclusion and exclusion criteria and the application of the results to the general population of patients remains questionable.²⁹ Our outcomes are comparable to those reported in a more recent, multicentre, randomised controlled trial (RTOG 0617).^{9,10}

The limitations of the current study include the biases inherent in any retrospective comparison. The data on toxicity were not collected systematically but only for patients who reported their symptoms, and therefore was not analysed. Although attempt was made to reduce the bias by using propensity score based matching to account for the larger volume tumours in patients treated using IMRT, the significant difference in the stage distribution and PTV was not reduced due to the limited size of the cohort.

CONCLUSION

The delivery of radical radiotherapy including CCRT in large volume, locally advanced NSCLC was made feasible by using IMRT, resulting in similar survival outcomes to those observed for relatively smaller volumes recruited in randomised trials. In the absence of randomised evidence supporting IMRT over 3DCRT for lung cancer, the current retrospective study supports the use of IMRT for NSCLC patients with larger volume disease and more advanced stage (IIIB).

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