Intensity modulated radiotherapy for inoperable, locally-advanced non-small cell lung cancer: Development and clinical outcomes at a cancer centre in Eastern India

By

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Contents

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Declaration of collaborative work

I declare that the thesis has been composed by **myself** with appropriate support from my academic supervisors and that the work has not be submitted for any other degree or professional qualification.

I confirm that the work submitted is my own, except the published articles included in Appendices, that were jointly-authored with colleagues. I am the lead (first) author for all of the six submitted articles, and corresponding author for 5 of these 6 articles.

I played the key role in developing the research questions, study concept and design, research methodology, including type of data to be collected, analysis and interpretation. Co-authors have provided help with data acquisition, analysis and statistical support and improvement of manuscript. I have been responsible for writing the first draft and approving the final version of the manuscript for each of the submitted articles.

I have explicit permission from most of my co-authors for using these six articles for my thesis, and a statement of no objection signed by these co-authors was submitted to the University of Warwick, while applying for this research degree (PhD by published works).

List of Abbreviations

3D-CRT	Three-dimensional conformal radiotherapy
4DCT	Four-dimensional computed tomography
CBCT	Cone beam computed tomography
CCRT	Concurrent chemoradiation
CHART	Continuous hyperfractionated accelerated radiotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBUS	Endoscopic bronchial ultrasound
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
Gy	Gray
IFRT	Involved-field radiotherapy
IMRT	Intensity modulated radiation therapy
LA-NSCLC	Locally-advanced non-small cell lung cancer
LPFS	Local PFS
MLC	Multi-leaf collimators
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
NRCT	Non-randomized clinical trials
NSCLC	Non-small cell lung cancer
OAR	Organ(s) at risk
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSPT	Passive scattering proton therapy
PTV	Planning target volume
RCT	Randomized controlled trials
RoB2	Risk of Bias 2
RP	Radiation pneumonitis
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiotherapy
SCRT	Sequential chemoradiation
SIB	Simultaneous integrated boost
TBNA	Trans-bronchial fine-needle aspiration
VMAT	Volumetric modulated arc radiotherapy

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Abstract

Background

The submitted publications outline the sequential steps taken for clinical implementation of intensity modulated radiotherapy (IMRT) for lung cancer at a cancer centre in Eastern India. A literature review combined with a detailed risk assessment for IMRT in lung cancer guided the careful implementation for cases where three-dimensional conformal radiotherapy (3D-CRT) did not generate a safe radiotherapy (RT) plan with acceptable tumour coverage. With growing experience, IMRT was expanded to patients receiving concurrent chemoradiation (CCRT) and accelerated RT, including continuous hyperfractionated accelerated radiotherapy (CHART) as well as moderately hypofractionated accelerated radiotherapy. Survival outcomes from radical radiotherapy and chemoradiation (both sequential and concurrent) were audited and found to be comparable to contemporary published literature. In patients with large volume (>500ml) disease, IMRT resulted in non-inferior outcomes despite treating larger volumes and more advanced stage disease. A predictive model that estimates the probability that IMRT would be necessary to produce an acceptable and safe RT plan, was developed from the planning data of 202 patients.

Methods

An external prospective study was designed to validate this data-driven, decision aid in cohort of patients from multiple hospitals. Apart from assessing the accuracy of the developed predictive model, we are hoping to quantify the planning time saved by opting for IMRT without attempting a 3D-CRT plan. Updated systematic review of prospective studies was carried out to assess the efficacy and safety of IMRT for locally-advanced NSCLC.

Results and conclusion

No direct impact of IMRT or volumetric modulated arc therapy (VMAT) was seen on local control and survival for these patients, on updated systematic review. IMRT and VMAT was shown to be feasible and safe in the treated patient population. IMRT makes curative treatment possible for large-volume or complex-shaped, locally-advanced NSCLC, resulting non-inferior survival outcomes.

Chapter 1

Introduction and outline of the thesis

Introduction

Incidence of locally-advanced NSCLC

Lung cancer is one of the most common cancers in the UK. Between 2016 and 2018 there were over 48,000 new cases every year [1]. About 90% of these patients have non-small cell lung cancer (NSCLC) [2]. NSCLC is the leading cause of cancer-related deaths in the UK (21% of all cancer-related deaths in 2017) and world-wide [1,3,4]. A significant proportion (43%) of patients with non-metastatic NSCLC present with locally-advanced (stages IIIA and IIIB) disease [1–4]. The 5-year survival of lung cancer is 34% for stage-II and 12.6% for stage-III disease [4].

Staging investigations

Staging investigations include whole-body positron emission tomography (PET), magnetic resonance imaging (MRI) of the brain after the initial contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis [5]. Staging endoscopic bronchial ultrasound (EBUS) with guided trans-bronchial fine-needle aspiration (TBNA) is carried out in selected cases [5]. These staging investigations, particularly PET-CT and EBUS, have resulted in shifting the margins between stage II and III (stage migration).

Treatment of locally-advanced NSCLC

Radical radiotherapy (RT) with concurrent chemotherapy is described as concurrent chemo-radiotherapy (CCRT) remains the standard treatment of care for most patients with inoperable, locally advanced NSCLC (LA-NSCLC) [6–8]. Chemotherapy followed by RT is described as sequential chemo-radiotherapy (SCRT) is used where concurrent treatment is deemed inappropriate because of tumour size or extent or patient fitness [9]. If systemic

therapy is contra-indicated because of comorbidity or performance status, radical RT, preferably accelerated RT, using continuous hyperfractionated accelerated radiotherapy (CHART) or moderately hypofractionated RT is used [5,10–12].

Conventionally fractionated RT amounts to 60 Gy in 30 fractions over 6 weeks [13]. The radiation is delivered once a day with 2 Gy per fraction, five days a week. Hypofractionated radiation is delivery of more than 10 Gy per week, and typically comprises of 55 Gy in 20 fractions over 4 weeks, amounting to 13.75 Gy per week [11]. Chemotherapy has been used concurrently with both of these dose-fractionation regimes [13,14] and is the standard of care in fit patients [6].

Surgical resection is carried out in about 46.7% of patients with stage-II and 11% of patients with stage-III NSCLC [1]. A randomised controlled trial has shown that addition of surgery does not add any advantage to chemo-radiotherapy in stage-III NSCLC [15].

IMRT and lung cancer

Dose-limiting organs at risk (OAR) for radical lung RT are normal lung, spinal cord and oesophagus [14,16]. Dose constraints to these OARs can be difficult to satisfy with three-dimensional conformal radiotherapy (3D-CRT) due to a large disease volume, complex tumour shapes and challenging tumour positions, potentially leading to unacceptably high doses of radiation to these OARs [17–20]. Intensity modulated radiation therapy (IMRT) aims to deliver highly spatially precise radiation dose distributions to the planning target volume (PTV) with a steep dose fall-off near the normal critical structures in the vicinity of the target. IMRT involves highly conformal RT combined with modulation of fluence along the beam profile, created by an inverse planning process that uses computerised optimisation, and delivered using a computer-controlled linear accelerator [17,18].

Volumetric modulated arc radiotherapy (VMAT) is a dynamic, rotational IMRT that can be delivered using conventional linear accelerators with conventional multi-leaf collimators (MLC) [21]. VMAT involves delivering the dose to the target volume in a full 358-degree gantry rotation with varying gantry speed, with continuous variation in the MLC positions and the fluence-output (dose rate) [17,21]. IMRT and VMAT have been made possible by improved computing power of planning systems, good planning software and computer-controlled treatment units.

The technological advances of IMRT and VMAT have made it possible to use radical radiotherapy with curative intent for patients with large-volume or complex-shaped LA-NSCLC, resulting in long-term local control and improved overall survival. This has been made possible by increasing computing power of planning systems, good planning software and computer-controlled treatment units [17,18]. Clinical implementation of the technique has been challenging due to the additional experience, training and resources necessary for these complex treatments and quality assurance activity that need to be carried out [17,18].

Other contemporary advances in radiotherapy

Several changes in management of NSCLC came into effect around the same time as IMRT was introduced, many of which could influence outcomes from RT for NSCLC, described as follows:

- More modern diagnostic and staging investigations, such as the routine use of PET, was thought to potentially cause stage-migration in some patients [22–24]. This is particularly true if a normal looking lymph node is avid on PET or abnormal on EBUS and yields malignant cells on EBUS-TBNA. Besides, PET can also help differentiate tumour from distal lung collapse, thereby helping to reduce toxicity.
- Secondly, advances in radiotherapy planning included dose algorithms for heterogeneity correction (type-B algorithms), and the use of 4DCT (respiration-correlated scans) for planning [22]. Type-B algorithms allow

correction for tissue heterogeneity, thereby resulting in computation of more accurate doses to different structures in a radiotherapy plan [25,26]. Four-dimensional CT (4DCT) scans have been reported to reliably capture intra-fractional tumor motion. Outlining the tumour on 4DCT allows for better tumour coverage throughout the breathing cycle [27,28].

- Advances in verification imaging using daily online cone beam computed tomography (CBCT) imaging reportedly increased treatment delivery accuracy [23,24]. Volumetric image verification techniques allow for soft tissue matching as well as bone matching, thereby increasing the ease and accuracy of verification [31]. Respiration correlated CBCT acquired on the treatment unit enables assessment of tumour motion and coverage simultaneously, before treatment delivery [32].
- Fourthly, advances in systemic therapy either as induction (sequential) chemotherapy prior to radiotherapy or upon relapse has shown promising outcomes, thereby confounding the survival data. Early identification and better management of toxicity from treatment may also have an effect on outcome [22].

Increased contouring and planning time is required for the additional complexity of IMRT/VMAT planning by highly skilled and trained workforce [7,17]. Dedicated rigorous machine quality assurance and patient-specific quality assurance programs are necessary, including verification of monitor units [7,17], adding to extra resources required for offering this treatment to patients.

Commissioning extra resources for a new treatment technique typically requires reliable and robust evidence showing improvement in survival outcomes, toxicity or patient experience. However, there is no prospective randomised evidence directly comparing the outcomes from the IMRT/VMAT techniques for lung cancer with those from 3D-CRT. Despite the absence of

evidence from prospective randomised trials, IMRT and VMAT for lung cancer have gradually evolved and increased over time, supported by data from planning studies and retrospective series. As several advances in staging investigations and radiotherapy were implemented simultaneously, the real benefit from an individual component (such as IMRT or VMAT for NSCLC lung) is difficult to quantify.

This could make commissioning of extra resources for IMRT/VMAT difficult to justify for lung cancer, in a resource-constrained setting. As lung cancer was one of the last cancers to be treated with IMRT, the trained workforce, the additional software and the hardware requirements (apart from 4D scanning) were already in place in most radiotherapy departments.

Changing outcomes in patients with LA-NSCLC

The median overall survival from concurrent chemoradiation for locally-advanced NSCLC was between 16.3 and 17 months in clinical trials before IMRT [6,9], whereas the median survival with standard-dose RT in a more recent phase-III trial where IMRT was used for about 47% of 544 randomised patients was 28.7 months [13]. In a subsequent planned analysis, the outcome with IMRT was non-inferior despite having larger tumours and more stage IIIB patients [33]. Subsequently, a single-institution retrospective study on 100 patients from the UK reported the median survival from hypofractionated RT with concurrent chemotherapy as 43.4 months [26].

Some of these improvements in outcome could at least in part be attributed to other contemporary advances in radiotherapy, described above. The real change in outlook for patients with LA-NSCLC was reported from the PACIFIC trial with a significantly longer progression-free survival, at 16.8 months versus 5.6 months (hazard ratio for disease progression or death, 0.52; 95% confidence interval, CI, 0.42 to 0.65; P<0.001)[27]. In an update, the reported median overall survival in patients who received durvalumab was not reached, whereas it was reported in the placebo arm as 28.7 months [36]. The

durvalumab arm was significantly better with a 24-month overall survival rate of 66.3% (95% CI, 61.7 to 70.4), as compared with the placebo arm at 55.6% (95% CI, 48.9 to 61.8) [36].

LA-NSCLC – The Indian context

India is a large country, organised into 28 states and several centrally administered union territories, and is not covered by a centralised cancer registry. Most of the discrete 42 Indian cancer registries have been reported from urban areas, with relatively little coverage of rural areas [37,38]. This leads to problems of: low coverage, urban dominance, lack of quality assurance for data and lack of follow-up and survival data [39]. There is a relative scarcity of published Indian data on the socio-demographic dimensions of lung cancer [38]. According to published reports covering discrete populations, most of the patients with NSCLC present with metastatic (stage IV) disease (up to 48.5%) and locally-advanced (stage III) disease (42-48.5%) [40,41].

Access to critical cancer treatment is low, including availability of radiotherapy machines, delays in treatment, and there is geographic inequity in the distribution of such resources [42,43]. Inappropriate use of systemic therapy or palliative radiotherapy or both are recognised as important reasons for low volume of curative-intent treatment in patients with stages I to IIIB disease [44]. Relatively few series had been reported from India on radical radiotherapy or chemo-radiation prior to our experience, with median survival ranging from 12 to 14 months [44,45]. A recent review looked at all of the series published to date and found that the survival reported in our series compared favourably with contemporary published literature [44].

Overview of this thesis

This thesis focuses on one aspect of the service development improving radiotherapy planning and delivery, through implementation of technically

advanced radiotherapy (particularly, inverse-planned IMRT and VMAT) for lung cancer at a relatively new tertiary care cancer centre in Eastern India between 2013 and 2018. This has been followed through with how the IMRT and VMAT techniques evolved and were integrated with service development and clinical approaches.

The outline of the thesis is presented in the next chapter (Chapter 2). The context and significance of the different published papers and how the papers link with the broad aim of this thesis are also described in this chapter. Chapter 3 comprises the updated systematic review of prospective studies, looking at how IMRT affects survival outcome and toxicity. Chapter 4 proposes a prospective study to externally validate the decision tool that was developed (Appendix 5) in order to predict the likelihood of requiring IMRT for patients with LA-NSCLC [46]. Chapter 5 is the concluding chapter of this thesis.

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Chapter 2

Context and significance of the submitted papers

Introduction

After the completion of my higher specialist training, I took up the post of Clinical Research Fellow at the Christie NHS Foundation Trust. During this post, I received valuable experience and training with Professor Faivre-Finn, who was leading the team that was at the forefront of developing IMRT for lung cancer within the UK [1,2]. In the subsequent years, as more data became available, IMRT became more routine in the lung cancer setting [3–6].

After working as a consultant clinical oncologist within the NHS for a few years, I took up the opportunity and challenge of working abroad to help set-up and improve the lung cancer services at a tertiary care cancer centre at Kolkata, in Eastern India. I was the lead oncologist (and for most part, the only consultant radiation oncologist) treating lung cancers at this institute. Supported by an excellent medical physics team, I had played a leading role in developing the practice of radical radiotherapy, including IMRT and VMAT, for locally-advanced NSCLC.

As the lead (first) author for all of the submitted articles, I played the key role in developing the research questions, study concept and design, research methodology, including type of data to be collected, analysis and interpretation. Co-authors have provided help with data acquisition, analysis and statistical support, improvement of manuscript and have provided input at various stages of this work. I have also been responsible for writing the first draft and approving the final version of the manuscript for each of the submitted articles.

This thesis is aimed at describing the development and evolution of technically advanced radiotherapy, particularly IMRT and VMAT, for locally-advanced NSCLC at a new tertiary care cancer centre at Kolkata, in Eastern India.

Appendix 1: Pitfalls and Challenges to Consider before Setting up a Lung Cancer Intensity-modulated Radiotherapy Service: A Review of the Reported Clinical Experience. Clinical Oncology 2016; 28: 185-197. (Journal Impact factor: 4.126; SCOPUS: percentile 83%; Rank 48/288 within Radiology, Nuclear Medicine and Imaging)

In my first published article submitted for this thesis (Appendix 1), the technical challenges and solutions for safely implementing an IMRT service for NSCLC were analysed in an overview and the early clinical experience from 5 leading hospitals around the world was synthesized in a narrative review (8 citations on Google Scholar) [7]. This article lays down the technical details of this radiotherapy planning and delivery technique, and forms the basis of my subsequent work using IMRT and VMAT for NSCLC.

Significance: This study described the challenges, problems and solutions for using IMRT in lung cancer. Planning studies and retrospective studies were also analysed and synthesized in a non-systematic review, to inform practice at a time when no prospective or randomised clinical data was available in this setting.

Relevance to the current thesis: This review was carried out some years ago when published clinical evidence for actual use of IMRT for locally-advanced NSCLC was sparse and most of the reported literature was retrospective. As this review was out of date and non-systematic, an up-to-date systematic review of the prospective studies on IMRT or VMAT for NSCLC has been carried out (chapter 3), to be included in this thesis.

Appendix 2: Actual gains in dosimetry and treatment delivery efficiency from volumetric modulated arc radiotherapy for inoperable, locally advanced lung cancer over five-field forward-planned intensity-modulated radiotherapy.

Indian Journal of Cancer 2017; 54: 155-60. (Journal Impact factor: 1.224; SCOPUS: percentile 25%; Rank 254/340 within Oncology)

My second publication (4 citations on Google Scholar), submitted for this thesis, was a retrospective analysis of our real-world experience with initial planning and treatment experience with patients with inoperable, locally-advanced NSCLC [8]. These patients were initially planned using multi-segment 3D-CRT (five-field, forward-planned IMRT), which was routine for NSCLC with large tumour volumes or complex shapes, before deciding that VMAT plans were necessary, from 2012 to 2014. We also described our planning methods and analysed the actual dosimetric gain (improvement in tumour coverage while meeting the dose constraints for the normal organs) and the impact on treatment efficiency (shorter treatment delivery time) from VMAT compared to five-field complex 3D-CRT. Aimed at Indian colleagues, this was published in the Indian Journal of Cancer, the official publication of the Indian Cancer Society (indexed on pubmed / MEDLINE).

Significance: This article was aimed at colleagues working in radiation oncology and radiotherapy physics in the Indian setting. This paper was aimed at encouraging wider uptake of VMAT for treatment of locally-advanced NSCLC by demonstrating the gains in dosimetry and efficiency of treatment delivery, with the expectation that more patients with non-metastatic NSCLC would be treated with curative intent using radical doses of radiotherapy.

Appendix 3: Continuous hyperfractionated accelerated radiotherapy using modern radiotherapy techniques for non-small cell lung cancer patients unsuitable for chemoradiation. Indian Journal of Cancer 2017; 54: 120-6. (Journal Impact factor: 1.224; SCOPUS: percentile 25%; Rank 254/340 within Oncology)

In my third article (1 citation on Google Scholar), we present our experience of treating patients from India and the neighbouring countries with locally-advanced NSCLC using continuous hyperfractionated accelerated radiotherapy (CHART) (N=37), from January 2014 to December 2015. This

included a subgroup of patients (N=14) where volumetric modulated arc therapy (VMAT) was necessary in order to safely deliver radical RT [9]. We present the details of tumour and dosimetry parameters, early outcome data, and the feasibility and safety of using CHART in this patient population. Aimed at radiation oncologists from India, this was also published in the Indian Journal of Cancer.

Significance: This article described the experience of CHART in the Indian setting where this dose-fractionation had never been used for lung cancer before. By using VMAT where necessary, CHART was extended to patients who would previously not have been candidates for radical RT. Furthermore, it is well known that radiotherapy services are grossly inadequate in large areas of the developing world and patients often travel great distances to access treatment. For these patients who travel far for cancer treatment, CHART has an added advantage of completing the entire treatment within 12 consecutive days, thereby reducing the logistic and financial burden of cancer.

Appendix 4: Radical radiotherapy or chemoradiotherapy for inoperable, locally advanced, non-small cell lung cancer: Analysis of patient profile, treatment approaches, and outcomes for 213 patients at a tertiary cancer centre. Indian J Cancer 2018; 55: 125-33. (Journal Impact factor: 1.224; SCOPUS: percentile 25%; Rank 254/340 within Oncology).

My fourth article (3 citations on Google Scholar) presents the retrospective analysis of a single-institution experience of treating NSCLC patients using RT with curative intent, using either radiotherapy alone or chemoradiation (sequential or concurrent) [10]. Analyses were carried out for demographics, treatment characteristics and factors affecting overall survival. This was the largest single-centre series from India, with 9% stage II patients and over 88% patients with stage-III NSCLC. The median overall survival was 20 months (N=213) for the entire series and 28 months for the concurrent chemoradiotherapy cohort (N=120), comparable to the contemporary published literature.

Significance: This paper was also aimed at the medical oncologists and radiation oncologists working in the Indian setting in order to encourage wider use of radical radiotherapy and radical chemoradiotherapy with curative intent for lung cancer. The outcomes reported in this paper were favourable compared with other similar series, as reported in a more recent review of lung cancer treatment from the Indian setting [11]. It demonstrated that evidence-based multi-modality treatments in appropriately selected patients with inoperable NSCLC could help reduce variations in approach and help achieve outcomes that are comparable with published literature from the developed world.

Appendix 5: Development and validation of a decision support tool to select IMRT as radiotherapy treatment planning modality for patients with locoregionally advanced non-small cell lung cancers (NSCLC). British Journal of Radiology 2019; 91: 20180431. (Journal Impact factor: 2.196; SCOPUS: percentile 72%; Rank 81/288 within Radiology, Nuclear Medicine and Imaging).

British Journal Radiology is the international research journal of the British Institute of Radiology and is the oldest scientific journal in the field of radiology and related sciences, dating back to 1896.

In my fifth article (1 citation) for this thesis, we describe a predictive model that was developed based on radiotherapy planning records of consecutive patients with NSCLC treated with curative intent radiotherapy from July 2013 to December 2017. This model was then internally validated using a discrete cohort of patients treated in 2018. The model estimates the probability a patient with locally-advanced NSCLC would require the use of IMRT techniques [12]. Based on a data of 202 patients, 93 of which received IMRT, we developed a data-driven decision aid which can reproducibly determine the best planning technique for locally-advanced NSCLC. The developed model was presented as a nomogram. We believe that using this model, the dosimetrist can save a median planning time of about 168 minutes per case, by not requiring attempting 3D-CRT, when use of IMRT is likely to be required.

Significance: A nomogram such as this is relevant in resource-constrained smaller cancer centres around the developing world, where physicists and dosimetrists work with fewer IMRT and VMAT licences, whilst planning and treating a large number of patients with radiotherapy. It was also shown that RT planners or dosimetrists could save about 168 minutes per case by using this decision tool and going straight for IMRT planning.

Relevance to the current thesis: This decision tool (nomogram) was validated using a discrete patient cohort from the same hospital as it was developed. This would be described as internal validation, and questions could be raised about bias pertaining to planning and treatment decisions within the centre impacting the nomogram. It was therefore proposed that a study be designed in order to test and externally validate this decision tool using patient scans and planning information from another hospital. A study designed for external validation of this decision tool has been described in chapter 5 of this thesis. If successful, this external validation should demonstrate that this nomogram is reliable and could be generalised to most patients across other hospitals.

Appendix 6: Impact of modern radiotherapy techniques on survival outcomes for unselected patients with large volume non-small cell lung cancer. British Journal of Radiology 2019; 92: 20180928. (Journal Impact factor: 2.196; SCOPUS: percentile 72%; Rank 81/288 within Radiology, Nuclear Medicine and Imaging).

My sixth and final publication (8 citations on Google Scholar), submitted for my dissertation, was also published in the British Journal of Radiology (BJR). After papers originating from the RTOG 0617 trial were published, suggesting that the IMRT group had larger planning treatment volumes compared with 3D-CRT (median, 486 v 427 mL; P = .005) [13], we decided to analyse the impact of IMRT on survival outcomes on larger volume tumours, in patients treated between from 2011 to 2017 at our cancer centre. We defined large volume disease as planning target volume (PTV) > 500 mL, and identified 184 patients (out of 251 patients) as having large volume disease. Out of this cohort, 93

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 91 patients treated with 3D-CRT. Yet, the survival outcomes with IMRT were non-inferior to those treated with 3D-CRT, with a 2 year overall survival of 49.9% versus 51.3%, respectively (p-value = 0.63) [14].

Significance: This paper demonstrated how the use of VMAT enabled the treatment of larger tumours in more advanced stage, with non-inferior outcomes, compared to smaller tumours that were treated using 3D-CRT. Furthermore, this paper showed that despite treating larger tumours, the outcomes for patients treated at our hospital in Eastern India was comparable with outcomes reported in multi-centre, randomised trials and from outcomes reported within the NHS, and compared favourably with other Indian centres [11,15].

Conclusion

This chapter summarises the context and significance of the submitted published works to my journey with IMRT and VMAT for locally-advanced NSCLC, at a tertiary cancer centre in Eastern India. The proposed articles (Appendices 1–6) fit together in a common theme, describing the chronological steps in the development and evolution of this technique at this institution, through the following steps:

1. Literature review prior to setting up IMRT and VMAT for lung cancer.
2. Initial experience of using VMAT for patients where complex multi-segment 3D-CRT had failed to achieve all of the planning objectives.
3. Combining VMAT with continuous hyperfractionated, accelerated radiotherapy (CHART) where necessary, for lung cancer.
4. Auditing and presenting the outcomes (toxicity and survival) from radical chemo-radiotherapy and radical radiotherapy which included patients treated with VMAT.

5. Development of a data-driven decision aid (nomogram) which may help planners go straight for IMRT technique without attempting 3D-CRT.
6. Analysis of the impact of IMRT on survival outcomes in patients with larger volume disease in our patient cohort, and how that compared with the published large, multi-centre, randomised controlled trial (RTOG 0617 trial).

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Chapter 3

Efficacy and safety of intensity modulated radiotherapy (IMRT) as curative treatment for inoperable, locally-advanced non-small cell lung cancer: A systematic review

Abstract

Intensity-modulated radiotherapy (IMRT) is widely used for the treatment of non-small cell lung cancer (NSCLC), despite the paucity of prospective, randomised evidence to support its use. Planning studies and retrospective series have shown to reduce doses to normal tissue and organs. Accessibility of technology and dosimetric advantages result in attempts at treatment intensification by dose escalation or combining new systemic therapy or regimes. Caution should be exercised particularly for patients with large planning target volume (PTV), major vascular abutment or presence of significant haemoptysis before treatment, as there is a paucity of prospective data regarding the efficacy and safety of IMRT in lung cancer when compared with three-dimensional conformal radiotherapy and IMRT data from other cancer sites should not be extrapolated. IMRT has been associate with lower rates of severe pneumonitis and cardiac doses are smaller. This systematic review suggests that when used cautiously at standard dose-fractionation, IMRT is effective and safe for inoperable, locally-advanced NSCLC (LA-NSCLC), based on prospective interventional and observational studies.

PROSPERO 2021 CRD42021239551

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021239551

BACKGROUND

A significant proportion of patients with non-metastatic non-small cell lung cancers (NSCLC) present with locally-advanced (stages IIIA and IIIB) disease [1–3]. Curative-intent radiotherapy combined with chemotherapy given concurrently or sequentially remains the standard treatment for most patients with inoperable, locally advanced NSCLC [4–6]. If systemic therapy is not used because of age, comorbidity or performance status, radical radiotherapy (RT) preferably accelerated RT using CHART has been recommended by the National Institute for Health and Care Excellence (NICE) [7]. Planning radical radiotherapy for Stage III and large volume lung cancers can be challenging, using three-dimensional conformal radiotherapy (3D-CRT) [8,9]. This is particularly difficult for tumours with complex shapes or close to critical organs [10].

IMRT is a form of advanced high-precision RT using a computer-controlled linear accelerator, which delivers highly conformal radiation doses to the planning target volume (PTV), allowing a steep dose fall-off near the normal critical structures in the vicinity of the target [10–13]. Planning studies and retrospective series have shown a decrease in known predictors of lung toxicity (V20 and mean lung dose) and the maximum spinal cord dose with IMRT [14–17].

With wider availability of inverse planning, intensity modulated radiotherapy (IMRT) had been adopted into clinic practice for lung cancer, initially to satisfy the dose constraints for organs at risk (OAR). Volumetric modulated arc therapy (VMAT) – a form of dynamic IMRT where the dose to the target volume is delivered in a continuous gantry rotation with varying gantry speed [18] – is a faster way of delivering IMRT and is being increasingly used for treatment of

lung cancer. This is happening despite the paucity of prospective data regarding the efficacy and safety of IMRT for these patients and the absence of randomised comparison with 3D-CRT in controlled trials [9,10,19,20]. Potential dosimetric advantages, accessibility of technology, a need to meet normal organ dose constraints or a desire to escalate dose are some of the factors recognised as supporting the use of IMRT. Therefore, most of the published data on IMRT or VMAT is retrospective, either single-institution or large population-based series [10,20].

We present a systematic review of published prospective interventional or observational studies, including non-randomised and randomised trials, in order to assess whether IMRT for inoperable, locally-advanced NSCLC, is effective and safe.

OBJECTIVES

To carry out a systematic review of the efficacy and safety of IMRT for inoperable, locally advanced (stage II-III) NSCLC, by using pre-defined outcome measures for survival and toxicity.

METHODS

The protocol for this systematic review was recorded at inception on the 4th of March 2021, in PROSPERO (an international prospective register of systematic reviews), and indexed as CRD42021239551.

Types of studies

Prospective interventional or observational cohort studies describing the actual clinical use of static or dynamic IMRT, including VMAT or tomotherapy for treatment of patients with inoperable, locally-advanced or stage II-III NSCLC have been included. These are prospective single-centre or multi-centre cohort studies, non-randomized clinical trials (NRCT) or randomized controlled trials (RCT). Included studies have been published in a peer reviewed journal.

Retrospective studies have been excluded from this systematic review. Studies published only as an abstract or as a conference proceeding are excluded. Comments, views, editorials or correspondence have been excluded unless describing a prospective study with clinical outcome.

Criteria for including studies for this review

Inclusion criteria: Prospective interventional or observational cohort studies pertaining to the actual clinical use of IMRT or VMAT for treatment of patients with inoperable, locally-advanced or stage II-III NSCLC.

Exclusion criteria: The following studies were excluded from this review.

- Studies on patients who do not have stage II or III NSCLC.
- Studies with outcome data (survival and toxicity data) missing.
- Non IMRT or VMAT treatments, as well as publications with no real focus on IMRT for lung cancer.
- Studies including patients with small cell lung cancers, mesothelioma, metastatic cancers, other cancers, as well as studies with mixed diagnoses.
- Publications based on or including stereotactic ablative body radiotherapy (SABR), stereotactic body radiotherapy (SBRT), brachytherapy or palliative RT, and studies with mixed treatment modalities.
- Studies or publications based on proton therapy, where patients treated using IMRT or VMAT photons have not been reported as a clearly defined subgroup.
- Publications including patients who have undergone prior lung surgery, or studies which describe pre-operative or post-operative RT treatment.

Participants/population

Patients with unresectable or inoperable, locally-advanced (stage II - III) NSCLC, who are treated with curative or radical RT, using IMRT. They may receive sequential or concurrent chemoradiotherapy or radiotherapy-alone.

Intervention

IMRT which is a highly conformal radiotherapy that combines several intensity-modulated beams or arcs to provide highly conformal dose distributions. Variants include static and rotational IMRT, such as VMAT or tomotherapy.

Use of IMRT has also subsequently allowed treatment intensification, by using dose-escalation, hypofractionation or simultaneous integrated boost (SIB). Publications that include these forms of treatment intensification were also be included.

Comparator or control

Not applicable.

Studies were not be excluded based on the presence of absence of a control or comparison group.

Types of outcome measures

Primary outcome

Median overall survival. Defined as the time in months from study enrolment or observation to death from any cause.

Secondary outcomes

1. 1-year, 2-year, 3-year and 5-year survival.

2. Progression-free survival (PFS).

3. Toxicity data (grade 3 or higher based on CTC or RTOG criteria; acute oesophageal or lung toxicity).

Search methods for identification of studies

Search (not limited by date range - since inception until October 2020) on MEDLINE and EMBASE for any published study in peer reviewed journals. The search strategy has been designed to return citations referring to lung cancer and intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). Once the search and screening processes has been completed, the reference lists of the included studies will be reviewed for any relevant citations missed by the original search. If a substantial number of additional citations are found, then a supplementary search will be performed using keywords designed around the citations missed by the original search.

The full search strategy is attached as a supplementary material.

Data collection and analysis

Selection of studies

The PRISMA flow diagram (Figure 3.1) summarises the process of selecting the studies, through the steps identification, screening and inclusion of studies. Preliminary search was started on 8th of October 2020.

The search strategy was re-run on the 9th of May 2021, limited to the last 1 year in order to include more recent publications up-to the final analyses, and further studies were assessed and retrieved for inclusion. Language has been restricted to English.

Data extraction and management

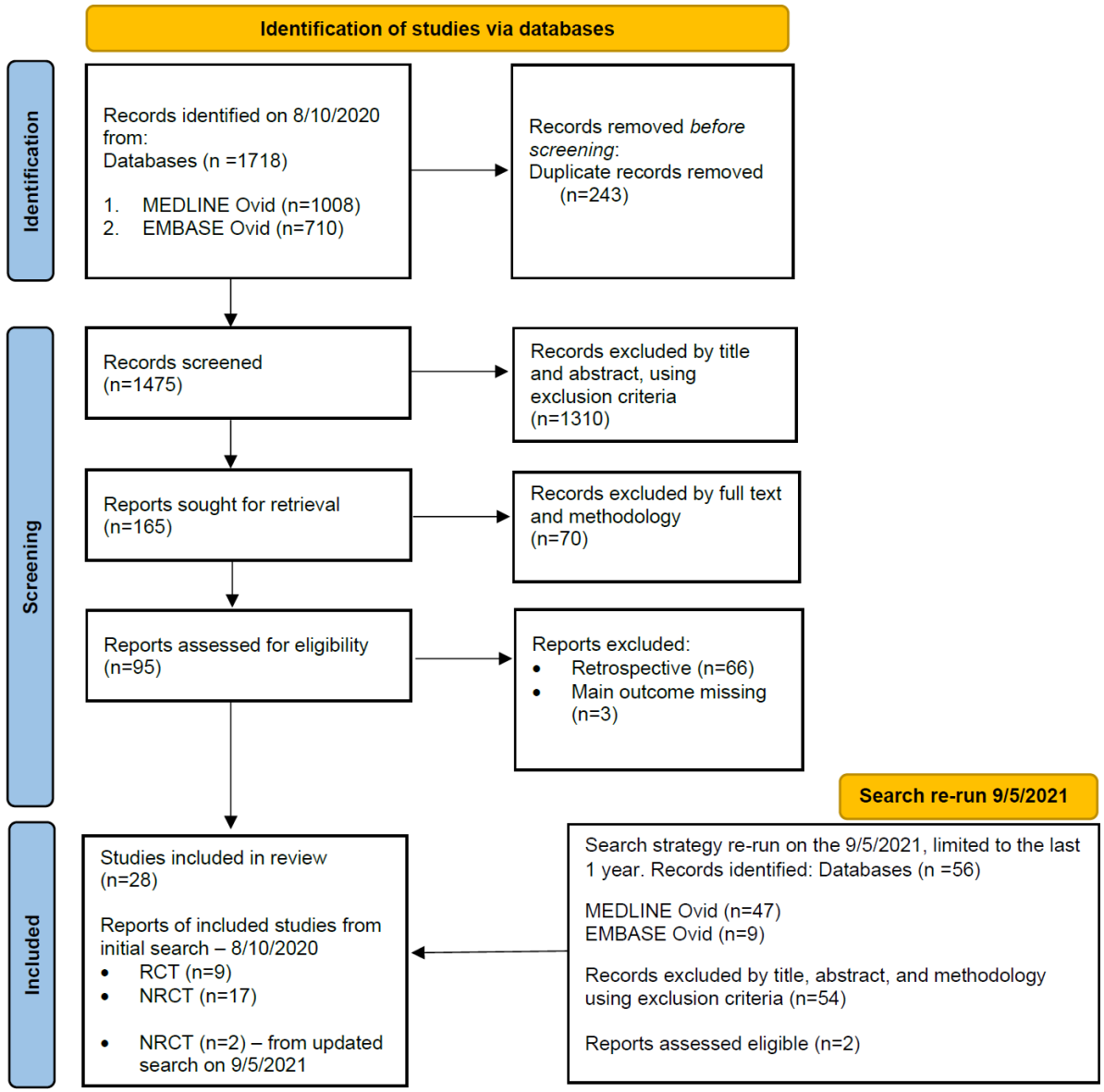
Generated citations were imported stored within an open-source, reference management software package called Zotero (Corporation for Digital Scholarship, Vienna, Virginia, USA). Duplicate citations were removed using an automated algorithm, as well as manually by the first author. The remaining citations were screened by a single author, first by title, and then by abstract,

to exclude citations clearly not relevant to the inclusion criteria. The remaining citations have then been reviewed as full texts by the first author, and assessed for inclusion by subsequent discussion. Any disagreements were resolved by consensus or by referral to a third reviewer, where necessary. The reasons for the exclusion of any papers at the full text review stage have been recorded and presented as part of the systematic review.

The full text papers of all required citations were available via the subscriptions of our institution, or subscriptions supported by NHS England.

Figure 3.1: PRISMA flow diagram

Figure 1: PRISMA flow diagram for systematic review of efficacy and safety of IMRT as curative treatment for inoperable, locally-advanced NSCLC



Assessment of risk of bias in included studies

Quality assessment was performed for each included paper guided by the NIH quality assessment tool for observational or interventional cohort studies and randomized trials. For non-randomized studies, we have used the Newcastle-Ottawa Scale (NOS) which contains eight items, categorised into three groups: Selection, Comparability and Outcome.

Publications reporting randomized controlled trials have been assessed using Risk of Bias 2 (RoB2) [21] tool on Review Manager software version 5.4.1 (available from the Cochrane website). Discrepancies were resolved by involving the other members of the team in the discussion. Quality assessment will be completed by two authors for each paper and used to inform an overall assessment of the risk of bias as being either good, fair or poor. Any disagreements arising between the two assessors have been resolved by discussion among the review authors.

No specific quality threshold has been used to exclude papers from any subsequent analysis, and an evaluation of any identified sources of bias, together with an assessment of study quality, has been discussed within the context of the results and presented in a narrative synthesis of the review.

Strategy for data synthesis

The extracted data has been presented primarily in tabular form with separate tables summarizing the studies looking at curative-intent IMRT/VMAT for inoperable, stage II-III NSCLC. These tables include data on the aims, study designs, the studied patient population, the actual interventions, outcomes and conclusions as assessed within the included studies. Outcomes (survival and toxicity) for each relevant analysis has also been displayed in tabular form. Data pertaining to clinical practice (target volumes, dose-fractionation and combination with chemotherapy) is also displayed. A narrative synthesis discussing the results from the included studies, combined with a discussion

of study quality and potential explanations for any differences in the results between papers, is presented alongside each table.

After assessment of the included studies for heterogeneity, including statistical heterogeneity, heterogeneity of methodology and other assessments, it was agreed that meta-analysis of the results is not appropriate. This decision was made after discussions among the authors, one of who is a medical statistician, and who also advised on methodology.

RESULTS

Results of the search

The PRISMA flow diagram (displayed in Figure 3.1) summarises the entire process of selecting the studies, through the steps identification, screening and inclusion of studies. Preliminary search started on 8th of October 2020, and resulted in a total of 1718 publications, that were imported and saved into Zotero (Figure 3.1). Duplicate records amounting to 243 were removed before screening the search results. The resulting 1475 records were screened by title and abstract, using the inclusion and exclusion criteria, and 1310 records were excluded. The remaining 165 records were retrieved and 70 records were excluded by methodology and full-text. After assessing 95 publications, 66 were excluded because of retrospective nature of the studies and 3 were excluded because median overall survival was not reported. The remaining 26 articles were selected for the systematic review.

The search strategy was re-run on the 9th of May 2021, limited to the last 1 year in order to include more recent publications up-to the final analyses, and further studies were assessed and retrieved for inclusion. A further 2 articles were identified and added at this stage, leading to a total of 28 articles for this systematic review.

Included studies

The 28 studies that were obtained from the systematic search were assessed and categorized into the following 3 broad groups:

1. Randomised controlled trials (RCT) for treatment of patients with inoperable, LA-NSCLC, where IMRT or VMAT has been used. This includes studies on proton therapy, where patients treated using IMRT or VMAT photons have been reported as a clearly defined subgroup. Nine articles resulting from four clinical trials fall within this category, displayed in Table 3.2 [8,22–29].
2. Prospective, non-randomised studies focused on radiotherapy-based intervention for the defined patient group. There are 14 articles/studies in this category and they are typically single-arm phase-I, Phase-II or cohort study (see Tables 3A and 3B [30–44]).
3. Prospective, non-randomised studies, where although IMRT has been used for inoperable LA-NSCLC, the primary focus of the study is systemic therapy (typically dose-finding study or feasibility/toxicity of the combination or patient reported outcomes). There are 5 articles/studies in this category (see Table 4 [45–49]).

Risk of bias in included studies

The 19 prospective, non-randomised studies from groups 2 and 3 have been assessed using the Newcastle Ottawa Scale by at least 2 authors (RKS & JR), and the results are shown in Table 3.1. As this scale was designed for cohort and case-control studies, comparability could not be scored and was not deemed applicable for single-arm studies, with no defined control arm. Therefore, all of the studies (except 1 study, below) scored 6 out of the maximum possible score of 9. However, the study by Khalil AA, et al., from 2015, was a cohort study where patients were divided into two groups: the cohort treated with standard dose constraints were compared to the cohort treated with an additional dose constraint [34]. Therefore, this study had a higher score of 8 points on the NOS.

The RoB2 tool was used for the 4 randomised trials included in this review, and is displayed in Figure 3.2. Overall, risk of bias in the 4 trials selected was

moderate. Selection bias was well addressed as most trials described a satisfactory sequence generation and allocation concealment processes except the NARLAL study (NCT-00887783) [23]. Blinding of the patients or the outcome assessments (to mitigate performance bias and detection bias) was not possible in any of the included trials because of the nature of the interventions within the studies. Three of the 4 RCTs included in this review had all patients treated within the allocated arm and the reporting was complete [23–25]. In these trials, the outcomes were analysed on intention-to-treat basis. The trial where the biases appeared to be significant (NCT-00915005) provided data and reasons on the losses and exclusions of participants as well as the reasons for exclusion (described below) [27]. The level of missing data is low with regard to the total number of randomised participants, limiting the extent to which attrition bias limits our confidence in the results.

RTOG-0617 had the lowest risk of biases [25,26], because of the following reasons:

- Randomisation was done with permuted block randomisation methods, stratified by radiotherapy technique, Zubrod performance status, use of PET during staging, and histology.
- Allocation sequences were generated algorithmically at the RTOG statistics and data management centre, and access to these sequences by participating centres and statistics and data management was prohibited. National Cancer Institute's Oncology Patient Enrollment Network (OPEN) enrolment system was used.
- Detailed trial profile displayed as consort diagram, within the article detailing allocation, analysis and treatment for all patients.
- Results are reported on a modified intent-to-treat basis with all patients included in the assigned group, irrespective of treatment received, but excluding those patients who were found not to meet the pre-defined eligibility criteria.

However, another study (NCT-00915005) comparing passive scattering proton therapy (PSPT) and IMRT, appeared to have significant problems with bias (including selection bias, attrition bias and reporting bias) [27], listed as follows:

- After obtaining consent from 272 patients, 47 patients were excluded before the RT planning process began because of various reasons such as insurance denial, patient wishes, surgery, withdrew consent, etc.
- Forty-four patients were not randomly assigned because of their radiotherapy plans. They were treated with the modality that produced the acceptable dose distribution.
- Of the 181 patients who were randomly assigned, only 149 were treated according to allocation. Thirty-two patients were not treated according to protocol allocation either because of insurance denial after allocation or patient preference.
- The analyses were based on these 149 patients and not on intention to treat (173 patients).

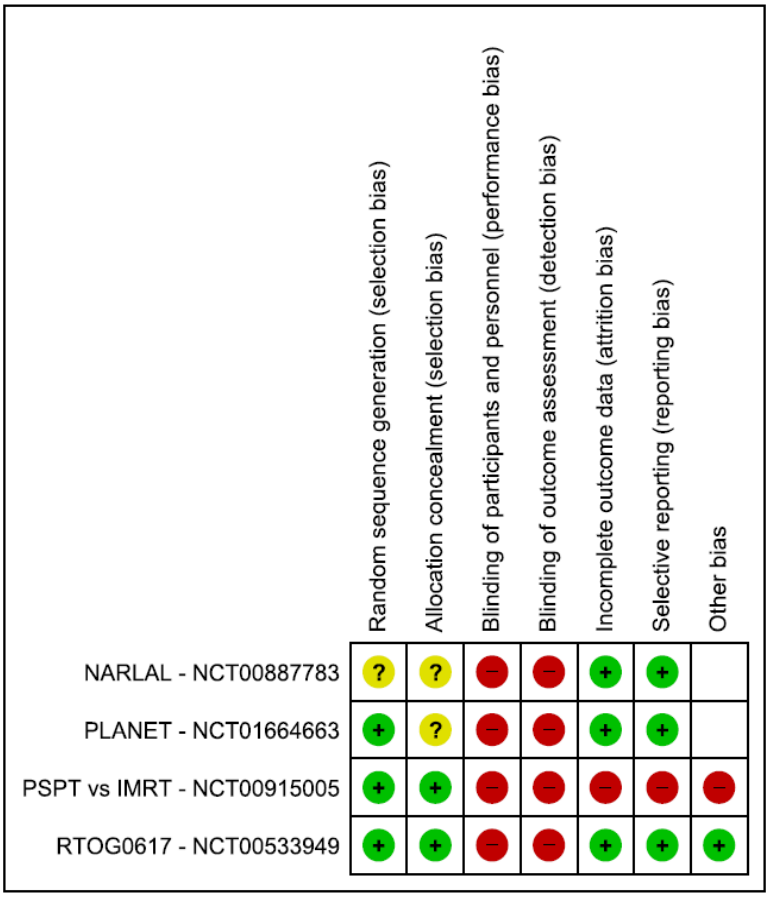
Table 3.1: Scores for the included non-randomised studies according to Newcastle-Ottawa Scale (NOS).

Reference	Selection (Out of 4*)	Comparability (Out of 2*)	Outcome (Out of 3*)	Total NOS (Out of 9)
Adkison JB, et al (2008)	***	NA	***	6
Yu, HM, et al (2008)	***	NA	***	6
Bral S, et al (2010)	***	NA	***	6
Jensen AD, et al (2011)	***	NA	***	6
Bearz A, et al (2013)	***	NA	***	6
Cannon DM, et al (2013)	***	NA	***	6
Khalil AA, et al (2015)	****	*	***	8
Komaki R, et al (2015)	***	NA	***	6
Zhang W, et al (2015)	***	NA	***	6
Lu Y, et al (2016)	***	NA	***	6
Martinussen HMA, et al (2016)	***	NA	***	6
Kim JO, et al (2017)	***	NA	***	6
Wanet M, et al (2017)	***	NA	***	6
Jeter MD, et al (2018)	***	NA	***	6
Ohri N, et al (2018)	***	NA	***	6
De Ruysscher D, et al (2019)	***	NA	***	6
Nguyen PAH, et al (2019)	***	NA	***	6
Glinski K, et al (2020)	***	NA	***	6
Li J, et al (2020)	***	NA	***	6
Haslett K, et al (2021)	***	NA	***	6

*** indicates one point.**

As this scale was designed for cohort and case-control studies, comparability cannot be scored for single-arm studies with no control arm. Therefore, most trials were marked with NA (not applicable).

Figure 3.2: Risk of Bias summary



Effects of interventions

RCT

Nine articles from 4 RCT included in this systematic review, are displayed in Table 3.2. Contemporary staging using PET-CT was routinely used in these trials. Concurrent chemoradiation using a platinum-doublet regime was used in both arms in all of the included trials. Median survival ranged from 23.3 months to 29.5 months in the 3 trials that completed accrual, with the standard dose arms or IMRT arms shown to be either better or not significantly worse/different [23,26,27]. The 1-year survival for standard dose arms or IMRT arms in the included trials ranged from 72–83% [23,24,26,27].

The PLANET trial reported by Hallqvist et al., was prematurely terminated after 36 patients because dose-escalated concurrent chemoradiation up to 84Gy to primary tumour and nodal disease was deemed as hazardous, with a high risk of excessive toxicity despite adjusting for esophageal-associated deaths [24]. In this study, the median survival in the standard arm receiving 68Gy in 34 fractions was 45 months [24].

Chun et al (2017) reported the planned secondary analysis on 482 patients from the largest RCT included in this review (RTOG-0617), and compared outcomes from 3D-CRT and IMRT [8]. Stratification based on RT technique ensured that the use of IMRT and 3D-CRT were similar in the 60Gy and 74Gy dose arms [8,25]. Target volume and tumour stage were not used for stratification. Patients treated with IMRT were found to have lower rates of severe pneumonitis than patients treated with 3D-CRT, despite these patients having larger and more advanced tumours. Although the lung V5 was significantly larger in patients treated with IMRT, it was not associated with any kind of (≥ grade 3) toxicity [8]. Besides, IMRT was able to significantly lower radiation doses to the heart (V20, V40, and V60) ($P < .05$), despite the volume of heart inside the PTV not being different. The heart doses were highly associated with OS on multivariate analysis. The rates of grade 3 oesophagitis and dysphagia, weight loss, and cardiovascular toxicity in both groups (IMRT and 3D-CRT) were not different ($P > .05$). It was therefore suggested that IMRT should be routinely used for locally advanced NSCLC [8]. The NARLAL study comparing 66Gy with 60Gy in 2Gy-fractions showed similar local control and overall survival in both arms, and was well tolerated [23].

Another RCT (NCT-00915005) was carried out to compare outcomes of passive scattering proton therapy (PSPT) versus IMRT, both with concurrent chemotherapy, for inoperable NSCLC [27,29]. Although it was hypothesized that PSPT exposes less lung tissue to radiation than IMRT, no benefit was reported with PSPT for the primary endpoints of radiation pneumonitis (grade 3 or more), presumably because PSPT was not associated with improved lung dose-volume indices [27]. No differences in patterns of local, marginal, or regional failure were shown from the use of IMRT or PSPT, indicating that the

planning techniques used for PSPT were effective for producing locoregional control [27,29]. Response to concurrent chemoradiation by larger tumours predicted favourable survival.

Acute dysphagia or oesophagitis (≥ grade 3) was reported in 7–10% (standard dose arms) and 12–21% (high dose arms) patients within the included studies [23–25,27]. Acute radiation pneumonitis (≥ grade 3) was reported in 7–19% (standard dose arms) and 4–24% (high dose arms) patients. Within the secondary analysis comparing outcomes from 3D-CRT and IMRT, there was no significant difference in acute oesophageal toxicity [8]. However, acute radiation pneumonitis (≥ grade 3) was reported in 7.9% of patients treated with 3D-CRT, compared with fewer (3.5%) patients who received IMRT, despite having larger volume disease and more advanced stage [8]. In the IMRT arm of another study (NCT-00915005), acute lung toxicity (≥ grade 3) was reported as 6.5% (6/92 patients) [27].

NRCT – Studies with focus on radiotherapy

The prospective, non-randomised studies focussing on radiotherapy have been summarised in tables 3.3A and 3.3B. These 14 studies were found to vary in treatment approaches and research questions. Sample size for these studies vary from 12 to 185. These are mostly single-centre, single arm, phase I, II or I/II studies. Apart from one study (Zhang and colleagues) which was limited to patients with stage II NSCLC, all other studies included patients with stage III, or II-III NSCLC. Based on the treatment approach, they are broadly categorised into the following 3 groups:

- **Dose escalation/intensification using acceleration and hypofractionation:** Seven studies looked at dose escalation or intensification using acceleration and hypofractionation [30,31,37,41–44]. The dose escalation was safely achieved and well tolerated in 4 of the studies. However, Cannon and colleagues reported dose-limiting toxicity that was dominated by late radiation toxicity involving central and perihilar structures [31]. Glinski et al., reported that patients with large PTV and major vascular abutment or presence of significant haemoptysis before

treatment are to be excluded from accelerated hypofractionated RT, due to increased risk of toxic death [42]. The largest phase-II study on 185 patients, by De Ruysscher D, et al., showed that individualized, accelerated, isotoxic dose escalation radiotherapy (INDAR) using IMRT concurrently with chemotherapy did not lead to improved overall survival in unselected patients with stage III NSCLC [41].

- **Dose escalation using hypofractionation with simultaneous integrated boost (SIB):** This approach was used in 3 studies [35,38,39]. Favourable long-term survivals, LC and minimal toxicities supported Hypo-SIB-IMRT to be considered for stage II NSCLC patients. Wanet et al., suggested that PET-guided dose escalation using IMRT was feasible, enabling good local control and acceptable toxicity rates. Caution was advised for dose-escalation in centrally located tumours with mediastinal invasion, in order to avoid severe late toxicity [38]. Results from a study reported by Jeter and colleagues, suggested that an SIBV dose of 72Gy (CGE) was the MTD to be given with image-guided IMRT or IMPT, for a subsequent planned randomized phase II study [39]. The median survival in this groups appears to be very high at 38.6 months, 46.5 months and not reached in the studies by Jeter et al. (n=15), Zhang et al. (n=28), and Wanet et al. (n=13), respectively [35,38,39].

- **Implementation of IMRT:** The remaining 5 studies looked at various aspects of IMRT implementation and use [32–34,36,40]. One study looked at the feasibility of a class solution protocol for moderately hypofractionated tomotherapy in patients with LA-NSCLC [33]. Toxicity was acceptable and in line with other reports on radiation pneumonitis (RP) [32]. FDG-PET-CT based selective nodal irradiation with IMRT results in a low failure rate of 2.2% in uninvolved nodes, which is safe and comparable to that after 3D-CRT [36]. Dose-painted IMRT based on pre-treatment PET metrics with concurrent chemotherapy was shown to yield high rates of metabolic response and local disease control for locally advanced NSCLC [40].

The median survival ranged from 16 to 46.5 months and was reported as not reached for 2 studies, 1-year survival ranged from 58.3% to 97.7% and 2-year

survival ranged from 27% to 85%. Median progression-free survival (PFS) ranged from 7 months to 33 months (LPFS). Reported rates of acute dysphagia or oesophagitis (≥ grade 3) were 0–23.1%, and acute radiation pneumonitis were 0-30%.

NRCT – Studies with focus on systemic therapy

These studies were aimed at asking questions that were focussed on systemic therapy, and were typically dose-finding studies or assessing feasibility/toxicity of the combination [45–49]. One study (by Nguyen and colleagues) was focused on patient reported outcomes [49]. Although IMRT or VMAT had been used in these more contemporary studies, they did not seem to add to the available evidence on either safety, feasibility or toxicity from these radiation techniques. Median survival ranged from 19.6 to 36.5 months and 1-year survival ranged from 58.3–84.6%. Median PFS ranged from 8.5 months to 20 months. Acute oesophageal toxicity (≥ grade 3) was reported at 3–25% and acute lung toxicity (≥ grade 3) was reported at 3.3–6.7%.

DISCUSSION

Summary of main results

Three of the randomised trials included in this systematic review, that completed accrual, showed a median survival of 23.3–29.5 months in the standard dose arms or IMRT arms. The 1-year survival was either found to be better (in PLANET and RTOG0617 trials) [24,26] or no worse (in NARLAL trial) [23] for the standard dose arms, ranging from 72–83% [references for 4 RCTs]. The high dose arms were either shown to be not significantly better [23] or had worse overall survival likely associated with toxicity-related deaths [24,25].

The exact reasons for the detriment from high dose radiotherapy within the RTOG0617 is not entirely clear, but possible explanations offered were extended treatment duration, higher doses of radiation to the heart, compliance in the high dose group and uncertain cause of death [25]. Specific heart toxicity outcomes in this trial were not tracked.

The percentage of heart volume receiving at least 5 Gy (V5) and 30 Gy (V30) were found to be important predictors of overall survival on both univariate and multivariate analyses and were recognised as predictors of patient death. The trial protocol suggested non-binding dose-volume guidelines for the heart, however variability in heart contouring was noted within the submitted plans [25].

IMRT was associated with lower rates of severe (≥ grade 3) pneumonitis, despite these patients having larger and more advanced tumours [8]. In another randomised study (NCT-00915005), the rate of (≥ grade 3) acute lung toxicity after IMRT was 6.5%, and no significant benefit was seen with PSPT, which the authors presumed could be associated to lack of improvement in lung dose-volume indices [27].

For all of the non-randomised prospective trials, the median survival ranged from 16 to 46.5 months and was reported as not reached for 2 studies, 1-year survival ranged from 58.3% to 97.7% and 2-year survival ranged from 27% to 85%. Median PFS ranged from 7 months to 33 months (LPFS). Reported rates of acute dysphagia or oesophagitis (≥ grade 3) were 0–25%, and acute radiation pneumonitis (≥ grade 3) were 0-30%.

Although the lung V5 was significantly larger in patients treated with IMRT, the reported rate of severe pneumonitis was lower in this group, therefore it could be argued that lung V5 is not associated with any kind of (≥ grade 3) toxicity, compared to 3D-CRT [8]. Similarly, Khalil and colleagues, showed that introducing IMRT combined with chemotherapy for NSCLC resulted in higher incidence of severe (≥grade 3) or fatal RP, compared to 3D-CRT [34]. Introduction of new dose constraints, especially V5, in addition to V20 and MLD, did not decrease the incidence of severe (≥ grade 3) RP, but could reduce the incidence of lethal RP in patients treated with IMRT [34].

Overall completeness and applicability of evidence

This systematic review covers data from 798 patients treated within 4 randomised controlled trials, and 1093 patients treated within non-randomised

prospective studies. Strict inclusion criteria have been used to study the impact of using IMRT/VMAT for patients with inoperable, stage II-III, locally advanced NSCLC, and in so doing we have excluded studies that included other cancers, stages of NSCLC and radiotherapy or treatment approaches that do not fit the defined inclusion-exclusion criteria. The purpose in undertaking this review was to determine whether using IMRT / VMAT techniques for planning and delivery of radical radiation can be shown to impact survival or toxicity outcomes in prospective studies. The conclusions however are limited by the trial data available and by the treatments used within those trials.

Although use of IMRT has been reported in all of the included studies, there is no RCT that was designed to assess outcomes from IMRT (or VMAT) in a head-to-head comparison with 3D-CRT, for LA-NSCLC. The only real data on the impact of IMRT on survival and toxicity comes from indirect comparison between 3D-CRT and IMRT, in the planned secondary analysis of data from the RTOG 0617 trial [8]. Meta-analysis could not be carried out because of heterogeneity in the research questions and treatment approaches within different trials. The dose of radiotherapy and dose-fractionation was found to vary significantly. The majority of trials where concurrent chemotherapy was used reported platinum-based doublet chemotherapy although there was considerable clinical heterogeneity in terms of frequency of administration (3-weekly vs weekly) and total dose. Some trials used single agent platinum, and some chose carboplatin, instead of cisplatin.

The reported rate of acute dysphagia or oesophagitis (≥ grade 3) was comparable in NRCT and RCT groups; 0–25% for all patients in the NRCT group and 7–21% for all patients (including high dose arms) within the RCT group. Similarly, reported rates of acute radiation pneumonitis (≥ grade 3) was comparable in both groups; 0-30% for NRCT group and 4–24% for all patients in the RCT group. This is not surprising as the NRCT group included patients who received higher doses of radiation comparable to the high dose arms within the RCT group. In fact, data to justify RCT is often derived from early phase, dose-escalation trials that are non-randomised. Small number of patients suffered grade 5 toxicity (death from radiation pneumonitis, fatal

haemoptysis or oesophageal perforation) that has been reported in the included studies and displayed in the tables 3.2, 3.3B and 3.4.

Potential biases in the review process

Some biases persist and affect the review process, despite the best efforts of the reviewers. The authors have attempted to prevent or minimise some of these biases, and have listed other biases that are inevitable because of the nature of our review.

- **Biases in review design** has been reduced by, the authors formulating a research question, defining the key characteristics of the review through PICO, and defining clearly the inclusion and exclusion criteria. Some biases may result from our exclusion criteria, whereby abstracts, conference proceedings, unpublished studies, retrospective studies were excluded.

- **Biases in locating studies** present in the current review includes limiting the search to English language. Furthermore, the search was limited to MEDLINE and EMBASE which would bring up the vast majority of (but not all) clinical trials. Publication bias is present in most reviews, as data from statistically significant studies are more likely to be published. The authors have not looked for eligible studies into multiple commercial or grey literature sources, dissertations or theses.

- **Biases in selecting studies** is present in the current review as the first author was responsible for screening studies and extracting outcome data. Regular team meetings were held to discuss difficult concepts.

- **Bias in synthesising studies** was mitigated by prospectively registering the protocol for this systematic review with the International prospective register of systematic reviews (PROSPERO 2021 CRD42021239551). This should help maintain the quality of the review, promote transparency and replicability, and avoid duplication of effort. At least 2 reviewers carried out the assessment for appraising the quality and risk of bias for the studies. It is difficult to completely get rid of selective outcome reporting, based on

statistical significance. Outcome reporting is always susceptible to clinical relevance and statistical significance.

Agreements and disagreements with other studies or reviews

Outcomes from CCRT before the IMRT era: Before IMRT or VMAT was routinely used for patients with lung cancer, Auperin published a meta-analysis comparing concurrent chemoradiation (CCRT) with sequential chemoradiotherapy (SCRT), based on individual patient data from 1205 patients treated within 6 randomised controlled trials [4]. CCRT resulted in improvement in absolute survival of 5.7% at years, from 18.1% with SCRT to 23.8% with CCRT. CCRT resulted in increase in acute (≥ grade 3) oesophageal toxicity compared with SCRT, from 4% to 18%. There was no significant difference reported in acute pulmonary toxicity [4].

The accrual period for all of these historic trials was from 1988 to 2003, and therefore most trials used a two-dimensional radiotherapy technique, with at least 1 trial using 3D-CRT [4,50]. The doses of radiation varied from 48.5Gy to 66Gy. Besides, the staging work-up was not up to contemporary standards, and PET-CT and brain imaging was not used [4]. However, this meta-analysis established CCRT as the gold standard treatment for selected, fit patients with minimal comorbidities, and benchmarked survival and toxicity data for LA-NSCLC, from the pre-IMRT era. In another meta-analysis of 6 RCT from 2010, the median survival reported for CCRT across all studies was 16–17 months, with that for SCRT was 13–15 months [51].

Current systematic review: In the current systematic review, 3 RCTs that completed accrual, showed a median survival of 23.3–29.5 months in the standard dose arms or IMRT arms [23,26,27]. One RCT was prematurely terminated, and showed a median survival of 45 months in the standard dose arm, and is therefore considered an outlier [24]. For the 19 non-randomised prospective trials included within this review, the median survival ranged from 16 to 46.5 months, and was reported as not reached for 2 studies. Acute (≥ grade 3) oesophageal toxicity was reported in 7–10% patients from the

standard dose arms within the RCT group and in up to 25% of all patients within NRCT.

Although the median survival appeared better in the current review, it is difficult to quantify the real benefit from IMRT, as there are no published RCT directly comparing this technique with 3D-CRT for NSCLC [10,52]. The rates of severe (≥ grade 3) oesophageal toxicity in the current review was slightly higher (up to 25%) than those from CCRT (up to 18%) in the benchmarked, pre-IMRT meta-analysis [4]. This is unsurprising, as IMRT does enable radical radiotherapy in more patients with larger tumours and higher stage disease [8]. IMRT is now widely used in routine practice in many centres around the world [10]. Indirect comparison of outcomes from IMRT with RCTs and meta-analyses from the pre-IMRT era is difficult because of several developments being implemented in parallel [10,52].

In recent years, staging for lung cancer have improved in accuracy with wider adoption of routine PET-CT staging, brain imaging and pathological staging for nodal disease. The delivery of radical radiotherapy has also improved substantially with better definition of treatment volumes, continually evolving techniques for motion management (using respiratory-correlated four-dimensional CT) and image-guided radiotherapy. It can be impossible to ascertain by how much each of these techniques alone may improve survival, and what the added benefit of IMRT/VMAT would be [10,52,53]. Addition of maintenance immunotherapy using Durvalumab has caused significant impact on survival [54] in stage III NSCLC. After a median follow-up of 34 months, the median overall survival was 47.5 months in the durvalumab arm, compared with 29.1 months in the placebo arm [55]. Besides, the systemic therapy on disease progression has also undergone big changes, affecting overall survival for these patients [56–58].

None of the included studies (RCT or NRCT) were designed to look at the impact of IMRT for NSCLC, compared with 3D-CRT, as a primary outcome. Dosimetric advantages, accessibility of technology, a desire to escalate dose or a need to meet normal organ dose constraints have been recognised as factors supporting the use of IMRT [10,59]. IMRT was often used to improve

target volume coverage, reduce dose to normal organs or escalate dose to tumour. The non-randomised studies are a heterogeneous collection of trials with a variety of research questions, a range of doses and fraction sizes, different treatment approaches and several studies had small sample sizes. Therefore, it is difficult to draw any clear conclusions from these studies.

Therefore, the planned secondary analysis from the RTOG 0617 remains the most acceptable comparison between IMRT and 3D-CRT for inoperable, LA-NSCLC, available from contemporary literature [8]. In this study, patients treated using IMRT suffered lower rates of severe (≥ grade 3) pneumonitis than 3D-CRT (7.9% v 3.5%, P = .039), despite having larger and more advanced stage tumours.

AUTHORS' CONCLUSIONS

Implications for practice

IMRT was associated with lower rates of severe pneumonitis and cardiac doses in the RTOG 0617 trial, and this supports routine use of IMRT for locally advanced NSCLC [8]. As a result of RTOG0617 trial, contouring the heart is routinely carried out for all patients receiving radiotherapy for LA-NSCLC. The dose of radiation to the heart is carefully observed and the percentage of heart volume receiving at least 5 Gy (V5) and 30Gy (V30) is routinely computed and documented [25].

Dose escalation studies within the RCT and NRCT groups reported increased toxicity and toxicity-related deaths, therefore caution needs to be exercised while designing future studies for patients with large PTV and major vascular abutment or presence of significant haemoptysis before treatment [31,34,42].

Although sample sizes are quite small in NRCT group of trials where dose escalation using hypofractionation was attempted using SIB, the median survival appears to be relatively higher at 38.6months, 46.5 months and not reached, in the studies by Jeter et al. (n=15), Zhang et al. (n=28), and Wanet et al. (n=13), respectively [35,38,39].

Implications for research

IMRT, per se, appears unlikely to result in improved outcomes, however it could lead to safer approaches with treatment intensification, by allowing better sparing of outlined vital structures. Studies need to be designed for systematically assessing and exploring approaches towards reducing toxicity, as several studies in this review had reported some treatment related deaths. Furthermore, there appears to be a need for setting-up studies aiming to investigate imaging and circulating biomarkers and correlating them with clinical toxicity.

It is believed that, when trying to limit radiation exposure to normal lung, the heart volume possibly received greater doses of radiation therapy in the RTOG0617 trial [25]. Future lung cancer trials through RTOG would include heart dose-volume limitations. The established dose constraints and probability for complications for normal lung were developed from studies published over 15-20 years ago, when radiotherapy was simple and less conformal. Scientific studies need to be repeated in the context of modern radiotherapy techniques so that optimal and mandatory dose-volume constraints for normal lung and heart sub-structures can be computed, in order to develop better understanding of how to optimally balance radiation dose between the heart and lungs.

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Table 3.2: Randomised Controlled Trials on IMRT or VMAT for inoperable, LA NSCLC

Trial (ref)	Patients	Treatments/Study design	N	Outcome	Results (OS/PFS)	Results (toxicity)	Conclusion
RTOG 0617, NCT-00533949 Bradley JD (2020), et al. Bradley JD (2015), et al. Chun SG (2017), et al.	Unresectable, stage III, NSCLC	Intervention: Higher dose of RT (74Gy) concurrently with chemotherapy and addition of cetuximab Control: standard dose (60Gy) of RT concurrently with chemotherapy Mutli-centre, Phase-III Two-by-two factorial Permuted block randomisation methods, stratified by RT technique	496	OS, PFS, LRTC, Toxicity Sub-group analysis (intervention vs 3D-CRT): 2-year rates of OS, PFS, LF, and DM	Median FU: 22.9 months **Median OS (months)** 28·7 (SD) vs 20.3 (HD) **1-yr survival rate** 80% (SD) vs 69.8% (HD) 2-yr survival rate 57.6% (SD) vs 44.6% (HD) 49.4% (3D-CRT) vs 53.2% (IMRT) **(NS)** 5-yr survival rate 32.1% (SD) vs 23% (HD) **Median PFS (months)** 12 (SD) vs 9.6 (HD)	**Acute dysphagia or oesophagitis ≥ grade 3** SD- 7% (16/217) vs HD- 21% (43/207) 3D-CRT- 15.4% (39/254) vs IMRT- 13.2% (30/228) **(NS)** **Acute lung toxicity (RP)** **≥ grade 3** SD- 7% (15/217) vs HD- 4% (9/207) 3D-CRT- 7.9% (20/254) vs IMRT- 3.5% (8/228)	• A 60-Gy radiation dose with concurrent chemotherapy should remain the standard of care for stage III NSCLC, with the OS rate being among the highest reported in the literature. Cetuximab had no effect on OS. • Patients treated with IMRT had lower rates of severe pneumonitis than patients treated with 3D-CRT in this trial despite these patients having larger and more advanced tumours. IMRT should be routinely used for locally advanced NSCLC
PLANET trial, NCT-01664663 Hallqvist A (2018), et al.	unresectable, stage III, NSCLC	Intervention: Dose-escalated RT (up to 84Gy in 2Gy fractions) starting at cycle-2 of 3 cycles platinum-doublet chemotherapy Control: Standard dose RT (68Gy in 2Gy fractions) starting at cycle-2 of 3 cycles platinum-doublet chemotherapy	36 (prematurely terminated)	OS, PFS	Median FU: 49 months **Median OS (months)** 45 (SD) vs 17 (HD) **1-yr survival rate** 72% (SD) vs 56% (HD)		Dose-escalated CCRT up to 84 Gy to primary tumour and nodal disease is hazardous, with a high risk of excessive toxicity despite adjusting for esophageal-associated deaths, the escalated group did worse, and overall caution is advised. Doses to the esophagus of >70–74 Gy with CCT with proper staging was safe and promising.

		Phase-II, block randomization			3-yr survival rate 56% (SD) vs 33% (HD) **Median PFS (months)** 28 (SD) vs 11 (HD)		
NARLAL, NCT-00887783 Hansen O (2017), et al. Pan Yi (2016), et al.	Histologically or cytologically proven, NSCLC, stage IIB–IIIB	Intervention: Randomised after 2 cycles of carbo/vin; 66 Gy/33F in 6½ weeks, concurrently with oral vinorelbine, after 2 cycles of carbo/vin chemotherapy Control: randomised after 2 cycles of carbo/vin; 60 Gy/30F in 6 weeks, concurrently with oral vinorelbine, after 2 cycles of carbo/vin chemotherapy Multi-centre, Phase-II	117	Local progression free interval (LPFI), progression free interval (PFI), OS	Median FU: 32.6 months **Median OS (months)** 23.3 (SD) vs 23.7 (HD) **1-yr survival rate** 83% (SD) vs 81% (HD) 3-yr survival rate 56% (SD) vs 33% (HD) **Median PFS (months)** 8.8 (SD) vs 8.4 (HD)- PFI	**Acute dysphagia or oesophagitis ≥ grade 3** SD- 10% (6/59) vs HD- 12% (7/58) **Oesophageal stricture or ulceration ≥ grade 3** SD- 5% (3/59) vs HD- 7% (4/58) **Acute lung toxicity (RP)** **≥ grade 3** SD- 19% (11/59) vs HD- 24% (14/58) 1 patient grade 4 (SD) and 1 patient grade 5 (HD)	• Both 60 and 66Gy administered concomitant with oral vinorelbine showed similar local control and overall survival, and was well tolerated. The ‘‘pick the winner design” chose 66Gy as the winning arm. However, CCT had to include cisplatin in future trials • Larger V40 and longer L40 were most effective dosimetric predictors of grade 2 or greater acute esophagitis. The upper part of esophagus was also a significant risk factor.
NCT-00915005 Liao Z (2018), et al. Tucker SL (2019), et al.	NSCLC, stage II to IIIB disease, stage IV with a single brain metastasis, or recurrent tumour	Intervention: PSPT (with CCT) prescribed at the dose both IMRT and PSPT plans met dose constraint standards Control: IMRT (with CCT) prescribed at the dose both IMRT and PSPT plans met dose constraint standards	149 149 patients were treated according to random assignment of 181 patients; Analysis not based on	Radiation Pneumonitis, grade 3 CTCAE (v 3.0) or greater; Local failure [Liao et al.] RP – grade 2 CTCAE (v 3.0) or greater; Time to RP from start of	Median FU (months): 24.1 (IMRT) vs 25.7 (PSPT) **Median OS (months)** 29.5 (IMRT) vs 26.1 (PSPT) **1-yr survival rate**	**Acute lung toxicity (RP)** **≥ grade 3** 6 patients (IMRT) vs 6 patients (PSPT) 2 patient grade 5 (IMRT)	• No benefit was noted with PSPT for the primary endpoints of radiation pneumonitis (grade 3 or greater) or local failure (LF), presumably because PSPT was not associated with improved lung dose-volume indices. PSPT significantly reduced heart exposure in terms of both radiation dose and heart volume, and its influence on cardiac toxicity and overall survival is under active investigation. Improvements in both end points were observed over the course of the trial.

Yang P (2019), et al.	after surgical resection treatable with CCRT	Multi-centre, Phase III, parallel assignment Bayesian Adaptive Randomization	intention to treat (173 patients) 203 patients with available DVH data/225 enrolled patients [Tucker et al.]	RT, with disease recurrence or death considered censoring events [Tucker et al.] Local failure (LF), marginal failure (MF) & regional failure (RF) [Yang et al.]	76% overall	20 (9.9%) patients overall	• The analyses indicated that RP risk is best quantified using RMSD. The RMSD to lung predicts risk equally well for IMRT and PSPT (or 3D-CRT, as shown earlier). An important consequence is that delivery of higher doses to smaller volumes (vs lower doses to larger lung volumes) may increase RP risk. • No differences in patterns of local, marginal, or regional failure were found between patients treated with IMRT or PSPT, indicating that the planning techniques used for PSPT were effective for producing locoregional control. Response to CCRT by larger tumours predicted favourable survival.

3D-CRT: three-dimensional conformal radiotherapy, IMRT: intensity modulated radiotherapy, CCRT: concurrent chemoradiation, OS: overall survival, RCT: Randomised Controlled Trial, RT: radiotherapy, LRTC: local regional tumour control, CCT: concomitant chemotherapy, PSPT: passive scattering proton therapy, CTCAE: Common Terminology Criteria for Adverse Events, RP: radiation pneumonitis, FU: follow-up, OS: overall survival, PFS: progression-free survival, PFI: progression-free interval, LF: Local failure, LPFS: local progression-free survival, TTP: time to progression, IMPT: intensity modulated proton therapy, LC: local control

Table 3.3A: Prospective, non-randomised studies on IMRT or VMAT for inoperable, LA NSCLC – focused on radiation-related questions

Reference	Aim/Objective	Study design	Sample size	Patients/Participants	Intervention	Outcome/Endpoint	Conclusion
Adkison JB, et al (2008)	Dose escalation study using image-guided IMRT via HT (while limiting the dose to OAR), delivered in a 5-week hypofractionated schedule to minimize the effect of accelerated repopulation	Single centre, Single arm, Phase-1 dose escalation	46	Stage I-IV histologically confirmed NSCLC with no prior thoracic radiation therapy or malignant pleural effusion	Radiotherapy (HT) limited to the primary site and involved or suspicious nodes. Five dose bins, with dose per fraction ranging from 2.28 to 3.22 Gy resulting in 57 to 80.5 Gy in 25 fractions	To determine the MTD	Dose escalation was safely achieved with lower-than-expected rates of pneumonitis and esophagitis using hypofractionated image-guided IMRT. The MTD was yet to be reached
Yu, HM, et al (2008)	To investigate the efficacy and safety of involved-field radiotherapy (IFRT) for patients 70 years old or more with early-stage NSCLC	multi-centre (4 centres), Single arm	79 treated (80 enrolled)	Early stage (I/II), histological confirmed, NSCLC, medically inoperable or declined surgery	66.6 Gy in 37 fractions (1.8 Gy/fraction) to involved-field (the primary tumour and clinically enlarged lymph nodes) using IMRT with six equidistant coplanar 6-MV beams	Safety and efficacy - ENF, local control, LF, LPFS, time to progression (TTP), and OS	IFRT using IMRT is an acceptable technique for inoperable NSCLC in elderly patients, and it did not cause a significant amount of failure in lymph node regions not included in the tumour volume and improved outcomes in elderly patients.
Bral S, et al (2010)	To prospectively assess the feasibility, toxicity, and local control of a class solution protocol of moderately hypofractionated tomotherapy in Stage III, inoperable, locally advanced NSCLC patients	Single centre, Single arm, Phase-1/2, feasibility and toxicity	40	Stage III, inoperable LA-NSCLC with cytological or histological diagnosis	Treatment according to a uniform class solution (70.5 Gy in 30 fractions) with fixed constraints and priorities using HT	Feasibility and Toxicity. Pulmonary function tests were performed at the start and repeated at 3 months after treatment	The current class solution using moderately hypofractionated HT in patients with LA-NSCLC is feasible. Toxicity was acceptable and in line with other reports on IMRT.
Cannon DM, et al (2013)	To explore RT dose intensification strategies, including hypofractionation, which allows for RT acceleration that could potentially improve outcomes.	Single centre, Single arm, Phase-1	79	histologically or cytologically proven primary NSCLC, where full-dose radiation therapy was recommended	Escalation of dose per fraction according to patients' stratified risk for radiation pneumonitis, with total RT doses ranging from 57 to 85.5 Gy in 25 daily fractions over 5 weeks using IMRT, without concurrent chemotherapy.	To define MTD with dose-escalated hypofractionation. MTD was defined as the maximum dose with ≤ 20% risk of severe toxicity	Although this dose-escalation model, limited the rates of clinically significant pneumonitis, dose-limiting toxicity occurred and was dominated by late radiation toxicity involving central and perihilar structures. The identified dose-response for damage to the proximal bronchial tree warrants caution in future dose-intensification protocols using hypofractionation.
Khalil AA, et al (2015)	To monitor the incidence of RP following the introduction of IMRT.	Single centre, Prospective Cohort	87	Histologically confirmed NSCLC receiving curative thoracic radiotherapy	IMRT (delivered using 4 – 8 beam arrangements) was introduced in three phases, with increasing dose constraints for lung with each subsequent phase. Phase-I (12 patients) using V20 < 40%.	Incidence of Radiation Pneumonitis	Introducing IMRT combined with chemotherapy for NSCLC resulted in higher incidence of severe (≥grade 3) or fatal RP, compared to 3D-CRT. Introduction of new dose constraints, especially V5 could reduce the incidence of lethal RP in patients treated with IMRT.

					Phase-II (25 patients) using V20 and MLD. Phase-III (50 patients) using V20, MLD & V5 ≤ 60%.		
Zhang W, et al (2015)	To analyse the effects of hypofractionated-SIB-IMRT (Hypo-SIB-IMRT) on medically inoperable patients with special stage II (T 2b-3 N 0 M 0) NSCLC.	multi-centre (3 centres), Single arm, Phase 2 / Prospective study	28	Medically inoperable patients with special stage II (T 2b-3 N0 M0) NSCLC	Hypo-SIB-IMRT was delivered with 75Gy to GiTV, 60Gy to CTV, and 45Gy to PTV in 15 fractions once daily on consecutive weekdays in 3 weeks	Overall survival	Owing to the favourable long-term survivals, LC and minimal toxicities in current study, Hypo-SIB-IMRT may be considered for special stage II (T2b-T3 N0 M0) NSCLC patients without lymph nodes metastasis who are medically inoperable.
Martinussen HMA, et al (2016)	To investigate the incidence of isolated nodal failures (INF), after FDG-PET based selective nodal irradiation with IMRT, in stage III NSCLC	Single centre, Single arm, Prospective, observational study	183	Histological or cytological confirmed NSCLC, stage IIIA or IIIB	IMRT with chemotherapy concurrently (conCRT) or sequentially (seqCRT) or IMRT alone	Isolated nodal failures in local or regional LNs. Secondary endpoints: OS, PFS, patterns of failure and toxicity	FDG-PET-CT based selective nodal irradiation with IMRT results in an INF-rate of 2.2%, which is comparable to INF-rates after 3D-CRT, and may thus be considered safe
Kim JO, et al (2017)	To determine the MTD of hypofractionated IMRT for unresectable or inoperable NSCLC in the setting of concurrent cisplatin/etoposide chemotherapy	Single centre, Single arm, Phase 1	12	Biopsy or cytology proven NSCLC, unresectable or inoperable stage II or III	48 Gy in 20 daily fractions using IMRT, followed by 1 of 3 defined boost dose levels using hypofractionated IMRT concurrently with cisplatin/etoposide chemotherapy 16.8 Gy/7 ($EQD_2 \cong 76$ Gy/38), 20.0 Gy/7 ($EQD_2 \cong 84$ Gy/42), and 22.7 Gy/7 ($EQD_2 \cong 92$ Gy/46).	MTD, defined as the dose at which ≥30% experienced dose-limiting toxicity, with DLT defined as any acute non-haematological toxicity related to the RT ≥ grade 3, which occurred within 90 days from the start of RT	Hypofractionated IMRT was well tolerated and provided meaningful local control. The maximum tolerated dose of RT in this setting lies beyond an EQD2 of 92 Gy/46 and further dose escalation in this setting is warranted.
Wanet M, et al (2017)	To assess the feasibility of an individualized FDG-PET-guided dose escalation boost in NSCLC patients and to assess its impact on local tumour control and toxicity	2 centres, Single arm, Phase 1/2	13	Histologically proven NSCLC, stage II–III, with primary greater than 3cm and no bulky LN involvement	Dose escalation using increased fraction dose within the individual PET-based PTV using IMRT with a SIB until the pre-defined OAR threshold was reached. RT was used with concurrent or sequential chemotherapy	Feasibility, local control and toxicity	Non-uniform, individualized PET-guided dose escalation using IMRT is feasible and enables good local control, at acceptable toxicity rates. Dose escalation in centrally located tumours with mediastinal invasion must be performed with great caution in order to avoid severe late toxicity.
Jeter MD, et al (2018)	To establish the MTD of image-guided, IMRT or proton therapy (IMPT), both with a simultaneous integrated boost (SIB), for patients with stage II–IIIB	Single centre, Single arm,	15 treated	Pathologically proven NSCLC, either unresectable stage II–IIIB disease or recurrent	Dose escalated, image-guided, IMRT or proton therapy (IMPT), both with a simultaneous integrated boost (SIB),	MTD to SIBV, at which no more than 30%	Our results indicate that an SIBV dose of 72 Gy (CGE) is the MTD to be given with

	NSCLC receiving concurrent chemoradiation therapy.	Phase 1	(17 consented)	disease after surgical resection, fit for concurrent chemoradiation	along with concurrent chemoradiation therapy.	patients have acute dose-limiting toxicity	image-guided IMRT or IMPT, for the planned randomized phase II study.
Ohri N, et al (2018)	To examine the strategy of using dose-painted IMRT, based on pre-treatment PET metrics in the setting of locally advanced NSCLC.	Single centre, Single arm, Phase 2	35	Adult patients with stage IIB-III NSCLC	Concurrent chemotherapy with 25-fraction course of dose-painted IMRT over 5 weeks. Dose of of 65 Gy (2.6 Gy/fraction) for high-risk lesions vs 57 Gy (2.28 Gy/fraction) or 52.5 Gy (2.1 Gy/fraction) for low-risk lesions	The absence of high residual metabolic activity (maximum SUV > 6) in treated lesions on PET, 12 to 16 weeks after completion of IMRT	Dose-painted IMRT based on pre-treatment PET metrics with concurrent chemotherapy yields high rates of metabolic response and local disease control for locally advanced NSCLC
De Ruysscher D, et al (2019)	To investigate if individualized, accelerated, isotoxic dose escalation radiotherapy (INDAR) delivered with IMRT would improve the OS of stage III NSCLC patients treated with concurrent chemotherapy and radiotherapy	Single centre, Single arm, Phase 2	185	Histological or cytological confirmed stage III NSCLC with no prior thoracic RT and a work-up according to national guidelines (staging PET-CT scan and MRI or contrast-enhanced CT brain)	individualized, accelerated, isotoxic dose escalation radiotherapy (INDAR) delivered with IMRT	Overall survival. Secondary endpoints: loco-regional relapses and toxicity	INDAR with IMRT concurrently with chemotherapy did not lead to a sign of an improved OS in unselected stage III NSCLC patients
Glinski K, et al (2020)	Prospective study of accelerated hypofractionated RT (AHRT) with concurrent full-dose chemotherapy to evaluate the toxicity and efficacy of such an approach for stage III NSCLC.	2 centres, Single arm, Phase 1/2	Stopped at 92/100	clinically stage III, pathologically confirmed NSCLC	3D-CRT or IMRT-planned RT: 58.8 Gy /21 fractions (2.8 Gy/fraction, 4 weeks) with 2 cycles of 3-weekly chemotherapy using cisplatin and vinorelbine	Non-hematological or hematological toxicity (grade $\geq$ 3) related to treatment within six months of the start of treatment; and the OS two years after the start of chemo-RT.	Survival rates are encouraging, but the observed rate of toxic and probably toxic deaths was of potential concern. The use of AHRT with concomitant full dose chemotherapy continues, but patients with large PTV and major vascular abutment or presence of significant haemoptysis before treatment are excluded due to increased risk of toxic death.
Li J, et al (2020)	To explore the feasibility and effectiveness of hypofractionated tomotherapy in patients with stage III NSCLC who are not eligible for surgery or concurrent chemo-RT.	single centre, Single arm, Phase-1 dose escalation	43	Histologically or cytologically confirmed stage III NSCLC, inoperable or refused surgery	Hypofractionated IMRT using HT, 70 Gy and 60 Gy administered in 15–25 fractions over a period of 3–5 weeks	OS rate and PFS rate	Tomotherapy is an effective treatment option for stage III NSCLC patients who were medically inoperable or refused concurrent chemotherapy, with lower incidence of side effects
Haslett K, et al (2021)	Treatment intensification using isotoxic IMRT	Multi centre, Single arm, Feasibility study	37	Histologically or cytologically confirmed stage III NSCLC Unsuitable for CCRT	2 cycles of platinum-based chemo, then RT delivered in 1.8-Gy fractions twice daily, dose was increased until a maximum dose of 79.2 Gy was	Delivery of isotoxic IMRT to >60 Gy (EQD2) Suitability, acceptability, recruitment, grade $\geq$ 3	Isotoxic IMRT is a well-tolerated and feasible approach to treatment intensification

					reached or 1 or more of the OAR met predefined constraints	non-hematological toxicity	

HT: helical tomotherapy, OAR: organs at risk, MTD: maximum tolerated dose, IFRT: involved-field radiotherapy, ENF: elective nodal failure, LF: Local failure, LPFS: local progression-free survival, TTP: time to progression, OS: overall survival, PFS: progression-free survival, V20: proportion of lung receiving 20Gy or more, expressed as percentage, MLD: mean lung dose, RP: radiation pneumonitis, SIB: simultaneous integrated boost, SIBV: SIB volume, GiTV: gross internal target volume, CTV: clinical target volume, PTV: planning target volume, LC: local control, INF: isolated nodal failures, FDG-PET: fluoro-deoxy-glucose positron emission tomography, CT: computed tomography, EQD_2: cumulative equivalent dose in 2 Gy fractions, DLT: dose limiting toxicity, IMPT: intensity modulated proton therapy, Chemo-RT: chemoradiation, AHRT: accelerated hypofractionated RT, CCRT: concurrent chemoradiation

Table 3.3B: Outcomes from prospective, non-randomised studies on IMRT or VMAT for inoperable, LA NSCLC – focused on radiation-related questions

Reference	Median FU (months)	Median OS (months)	1-year survival	2-year survival	3-year survival	5-year survival	Median PFS (months)	1-year PFS	2-year PFS	Acute dysphagia or oesophagitis < grade 3	Acute dysphagia or oesophagitis ≥ grade 3	Oesophageal stricture or ulceration ≥ grade 3	Acute lung toxicity (RP) < grade 3	Acute lung toxicity (RP) ≥ grade 3	Late lung toxicity	Grade 5 RP or fatal haemoptysis or oesophageal perforation
Adkison JB, et al (2008)	8.1	18		46.8%						15% – grade 2	0	0	13% – grade 2	0		
Yu, HM, et al (2008)	38	38	65.80%	55.70%		25.30%	33 LPFS			12.7% (n=10) – grade 2	1.27% (n=1)		17.7% (n=14) – grade 2	3.8% (n=3)		
Bral S, et al (2010)	16	17	65%	27%				66% LPFS	50% LPFS	33% – grade 2	2.5% (n=1)		43% – grade 2 or more	10%		2/40 - RP
Cannon DM, et al (2013)	17	16			29%					48% – grade 2	0	0	16% (n=12) – grade 2	1 – grade 4		5/79 RP
Khalil AA, et al (2015)	17	17.5												30% overall		11.5% (n=10) RP 16% - phase I/II 4% - phase III
Zhang W, et al (2015)	41	46.5	93%	85%	61%			92%	79%	7.1% (n=2) – grade 1			28.6% (n=8) – grade 1 & 2		5 patients (17.9%) - grade 1 pulm fibrosis	
Martinussen HMA, et al (2016)	58.0	19.5	69.7%	42.3%			15.0	60.00%	35.20%		15.5% (1.5% – grade 4)			3.1% (n=4)	n=1 grade 5	1/183 RP
Kim JO, et al (2017)	22	21.7	58.3%							33.3% (n=4) – grade 1	0	0	8.33% (n=1) – grade 2	0		
Wanet M, et al (2017)	29.28	Not reached	84.60%	52.80%	52.80%			53.90%	46.20%		23.1% (n=3)	7.7% (n=1)		23.1% (n=3)		15.4% (n=2)

																Fatal haemoptysis
Jeter MD, et al (2018)	25	38.6	82.4%							13.3% (n=2)	11.1%		0	13.33% (n=2)		6.66% (n=1) grade 5 RP (78Gy-IMPT)
Ohri N, et al (2018)	5.5 (entire cohort)	Not reached		52%			7.0		23%		6% (n=2)	3% (n=1)		6% (n=2)	3% (n=1)	
De Ruysscher D, et al (2019)		19.8	68.6%	43.8%	34.1%	24.3%				43.8% (n=81) – grade 2	21.6% (n=40)	0	2.7% (n=5) – grade 2	3.2% (n=6)		
Glinski K et al (2020)	21.5	38		68%	50%		25				14% (n=13)			3	2.17% (n=2) grade 3	1.1% (n=1) Oesophageal perforation 3.26% (n=3) Fatal haemoptysis
Li J, et al (2020)		34.23	97.70%	74.40%	55.90%		25	79.10%	53.50%	18.6% (n=8) – grade 1/2	0		16.28% (n=7) – grade 1/2	0	11.6% (n=5) grade1/2; 7% (n=3) grade 3	
Haslett K, et al (2021)	25.4	18.1		33.6%					23.9%		5.4% (n=2)			0	8.6% (n=3) grade 3 Dyspnoea 2.9% (n=1) grade 4 lung infection	8.1% (n=3) RP, bronchopulmonary haemorrhage, acute lung infection

FU: follow-up, OS: overall survival, PFS: progression-free survival, RP: radiation pneumonitis, LF: Local failure, LPFS: local progression-free survival, TTP: time to progression, IMPT: intensity modulated proton therapy, LC: local control

Table 3.4: Non-Randomised Controlled Trials on IMRT or VMAT for inoperable, LA NSCLC - focussing on systemic therapy or patient reported outcomes

Trial (ref)	Patients	Treatments/Study design	N	Outcome	Results (OS/PFS)	Results (toxicity)	Conclusion
Jensen AD, et al (2011)	histologically proven NSCLC stage III, unfit for concurrent chemoradiotherapy	Intervention: IMRT (66Gy) using 4DCT and weekly (7 cycles) cetuximab, given as loading dose 1 week before RT, during and followed by a 13 X weekly maintenance period Single centre, single arm, Phase-II	30	Toxicity and feasibility of the combination regimen	Median FU: 19 months Median OS: 19.6 months 1-yr survival: 66.7% 2-yr survival: 34.9% Median PFS: 8.5 months	**Acute dysphagia or oesophagitis ≥ grade 3** 3.3% (1/30) **Acute lung toxicity (RP)** **≥ grade 3** 3.3% (1/30) **Grade 5 toxicity** 10% (3/30), not treatment related	Combined radioimmunotherapy with cetuximab was safe and feasible, especially in elderly patients with multiple comorbidities.
Bearz A, et al (2013)	cytological or histological confirmation of NSCLC, Stage III	Intervention: Concurrent weekly Docetaxel dosage was scheduled as 10 mg/m2 for the first 3 patients; if no severe toxicity occurred, the dose was escalated in cohorts of 3 patients and 3 mg/m2 were added to every cohort, up to 38mg/m2/week Single centre, Single arm, Phase-1, dose finding study for docetaxel	33	MTD of weekly Docetaxel concurrent with IMRT	Median OS: 24 months 1-yr survival: 68.6% 2-yr survival: 43.8% 3-yr survival: 34.1% 5-yr survival: 24.3% Median PFS: 20 months	**Acute dysphagia or oesophagitis ≥ grade 3** 3% (1/33)	Concurrent weekly Docetaxel with HT are feasible, and even with Docetaxel at 38 mg/m2/week, no dose limiting toxicity was observed.
Komaki R, et al (2015)	Previously untreated, locally advanced (stage IIIA or IIIB), inoperable NSCLC	Intervention: Erlotinib for 6 days a week added to concurrent chemo-RT using IMRT (63Gy in 35 fractions) and weekly paclitaxel and carboplatin, followed by 2 cycles of 3-weekly consolidation chemotherapy	46	Disease control, PFS, OS, toxicity	Median FU: 37 months Median OS: 36.5 months 1-yr survival: 82.4%	**Acute lung toxicity (RP)** **≥ grade 3** 6.5% (3/46)	Toxicity and OS were promising compared with other trials (RTOG 0324 & RTOG 0617), but time to progression or disease control did not meet expectations of improvement. The prevalence of distant failures underscores the need for more effective systemic therapy.

		Single centre, single arm, Phase-II			2-yr survival: 67.4% 5-yr survival: 35.9% Median PFS: 14 months (TTP)		
Lu Y, et al (2016)	Unresectable, histologically or cytologically confirmed lung adenocarcinoma, stage IIIA/IIIB	Intervention: Thoracic IMRT at 60–64 Gy in 30–32 fractions, concurrently with two cycles of 500 mg/m2 pemetrexed, with nedaplatin doses escalating from 60 mg/m2 (level 1) to 70 mg/m2 (level 2) and 80 mg/m2 (level 3), followed by three cycles of consolidation chemotherapy Single centre, single arm, Phase-I	15	To determine the MTD	Median FU: 26.3 months Median OS: 30 months 1-yr survival: 58.3% Median PFS: 12 months	**Acute dysphagia or oesophagitis ≥ grade 3** 20% (3/15) **Acute lung toxicity (RP)** **≥ grade 3** 6.7% (1/15)	Full dose 500 mg/m2 of pemetrexed and nedaplatin 70 mg/m2 could be used safely with thoracic IMRT for inoperable stage III lung adenocarcinoma
Nguyen PAH, et al (2019)	Locally advanced NSCLC	Concurrent chemotherapy with Linac-based rotational IMRT, followed by consolidation chemo or Durvalumab or surgery and consolidation chemo	32	Quality of life as patient-reported outcome (PRO) using validated questionnaires (EORTC QLQ-C30), encompassing global quality of life scores or global health status (GHS), functional status (FS) and symptom scores (SS), collected at baseline, during therapy, at therapy stop and till 1 year after therapy end, every 3 months	Median FU: 19.6 months Median OS: 24.3 months 1-yr survival: 84.6% 2-yr survival: 52.8% 3-yr survival: 52.8%	**Acute dysphagia or oesophagitis ≥ grade 3** 25% (8/32) **Oesophageal stricture or ulceration ≥ grade 3** 3.1% (1/32) **Late lung toxicity** 3.1% (1/32) – grade 4, needs O_2 continuously	The assault on health-related quality of life during concurrent chemoradiation for locally advanced lung cancer is considerable. Loss of physical and role functioning persists up to 6 and 9 months after therapy end, respectively. Measuring PROs can help to identify issues for improvement of the value of care delivered.

4DCT: 4-dimentional computed tomography, MTD: maximum tolerated dose, HT: helical tomotherapy, TTP: time to progression, EGFR-TKI: endothelial growth factor receptor-tyrosine kinase inhibitor, Chemo-RT: chemoradiation, PFS: progression-free survival, OS: overall survival, DLT: dose limiting toxicity, FU: follow-up, RP: radiation pneumonitis, LF: Local failure, LPFS: local progression-free survival, TTP: time to progression, IMPT: intensity modulated proton therapy, LC: local control

Chapter 3 – Supplementary material:

EMBASE – Search History (carried out on 8/10/2020): 710 publications

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2. lung neoplasm*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. (lung adj2 cancer).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
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6. VMAT.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
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13. rapidarc.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 4 and 14
16. limit 15 to (full text and english language)

MEDLINE – Search History (carried out on 8/10/2020): 1008 publications.

1. lung tumor/ or lung cancer/
2. lung neoplasm*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
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13. rapidarc.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 4 and 14
16. limit 15 to english language

Chapter 4

A hypothetical prospective external validation of the decision support tool that predicts the requirement for using IMRT over 3D-CRT for locally-advanced NSCLC: The study design

Introduction

Radiotherapy planning for locally-advanced non-small cell lung cancer (NSCLC) is complex and often involves trade-offs between coverage of planning target volume (PTV) and sparing of the organs at risk (OARs) (17,103). Critical organs like spinal cord often overlap with the nodal target volume, creating challenges for the RT planner.

Three-dimensional conformal radiotherapy (3D-CRT), is widely used for planning and delivery of radiotherapy for lung cancer. The advantages of 3D-CRT include: no contouring of control/planning structures, simpler forward planning and plan assessment, and no requirement for patient-specific quality assurance (52). However, many cases of locally-advanced NSCLC cannot be planned satisfactorily using simple or multi-segment 3D-CRT. This is because in order to create a plan that could be delivered safely, i.e., without unacceptable doses to OAR (as outlined in Table 4.1) it often resulted inadequate PTV coverage (17,18,102). Table 4.1 shows the OAR constraints used for planning with the priorities defined for the planning algorithms.

Intensity modulated radiotherapy (IMRT) is a more complex technique that allows the planners to create an acceptable and safe radiotherapy plan. IMRT plans necessitate stringent image guidance and robust quality assurance because they typically display a steep dose gradient that renders the plan susceptible to motion interplay (17,18,52). Therefore, it creates better conformity at higher doses but this is associated with a tradeoff in terms of low dose spillage in the lung (52). IMRT requires specific training for staff, additional contouring of planning structures, more complex planning including

automated optimisation, careful plan evaluation and patient-specific quality assurance before treatment delivery (17,18). In addition, most contemporary IMRT planning uses volumetric modulated arc radiotherapy (VMAT) which requires use of a more expensive planning licence (46).

IMRT may not confer any clinically significant dosimetric advantage for many patients where a 3D-CRT plan satisfies all the planning criteria (103,104). Therefore, it is often used where 3D-CRT cannot produce an acceptable radiotherapy plan, i.e. where both PTV coverage is satisfactory and OAR constraints are being met, as listed in Table 4.1 (103,105).

Table 4.1: Dose constraints for organs at risk, and plan evaluation criteria

Volume	Metric	Criteria	Priority
PTV	D95	≥ 95%	1
	D107	< 1cc	2
	Dmax	<110%	2
Lung-PTV	V20	< 35%	2
	V10	< 50%	2
	V5	<70%	2
	Mean	<18 Gy	2
Spinal Cord	Dmax	< 48 Gy (Conventional fractionation) < 44 Gy (Accelerated radiotherapy)	1
Heart	Mean	< 26 Gy	3
	V30	< 46%	3
Esophagus	Dmax	≤ Prescribed dose	4

(1= highest priority and must be satisfied; 4= lowest priority)

We developed a predictive model which could estimate the probability that acceptable PTV coverage would require the use of IMRT planning technique (46). At the time of development of this model, we specified that the cross-validated concordance-index (C-index) be 0.80 or better, and be available as a nomogram. This model was internally validated on a separate cohort of patients that were not used to develop this tool. This model is meant to enable the planner to choose the planning modality viz. 3D-CRT or IMRT, with a good degree of confidence. The primary utility of this tool is aimed at saving the time a dosimetrist would use, for creating a 3D-CRT plan which would be found inadequate, before deciding to change the planning approach to IMRT (46).

In order to use the model, the planner has to look at the 5 variables in the model (some of which are described in Figure 4.1) and note down points for each of the five variables, as described in Table 4.2. If the total of the points is 98 or greater, then the probability of requiring IMRT to produce an acceptable plan is greater than 50% and we recommend that the planner proceeds with IMRT(46).

The variables used in the predictive model are:

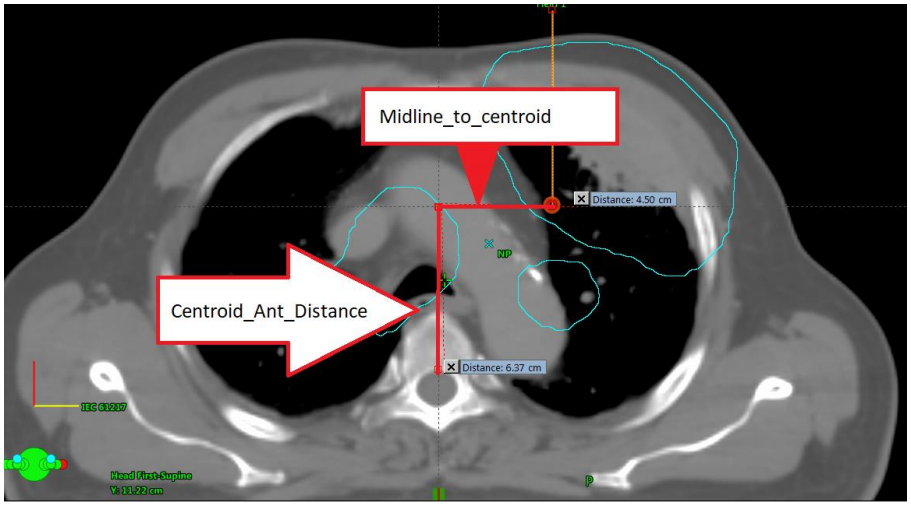
1. The ratio of the PTV to the total lung volume (TLV).
2. The lateral distance (in cm) from midline to the PTV centroid (The centroid or the geometric centre of the PTV is the arithmetic mean position of all the points within the PTV, and is created by the planning software package).
3. The distance of the PTV centroid with respect to the spinal canal - anterior distance of the PTV centroid from the anterior border of the spinal canal along the midline.
4. The cranio-caudal extent of the PTV in cm.
5. The distance of PTV across the midline (i.e., extent of PTV crossing midline in cm).

Figure 4.1 shows an example of planning CT image with the variables displayed on the image and described in the legend. Table 4.2 shows the numerical summary of the nomogram showing how to convert the variable

values into points, which can then be recorded and added in the right-hand column. An example of using this scoring system based on the CT image from Figure 4.1 is displayed in the right-hand column in Table 4.2. From Figure 4.1, the PTV_TLV_Ratio was 0.2, thus, giving a score of 19. The points for other variables are similarly extracted.

In this chapter, I would like to outline the study design of a hypothetical prospective study that aims to externally validate the predictive model in a cohort of patients treated in multiple hospitals, different from where it was created. We will also explore the real-world gains in reduction of treatment planning time achieved by using this planning technique.

Figure 4.1: The variables described on the CT image (copied from the supplementary of the article in Appendix 5)

<table>
<tr>
<td> 
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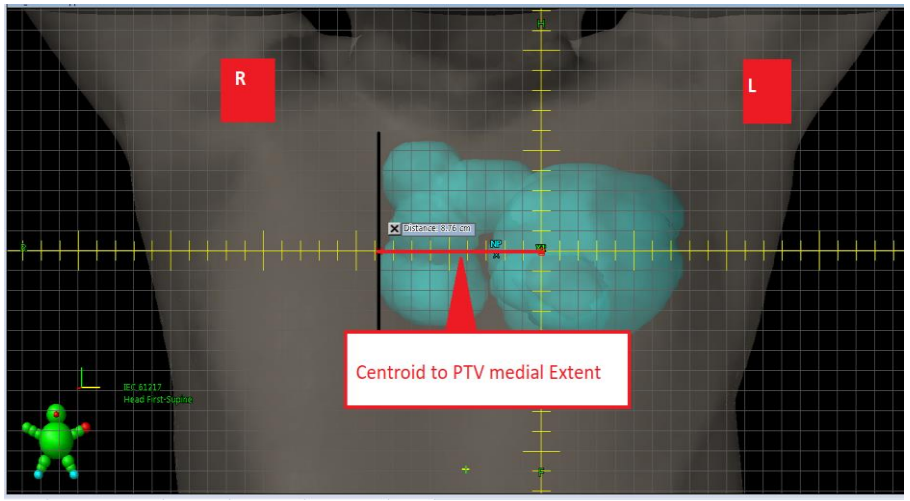
<td> 
</td>
</tr>
<tr>
<td>Measurements on axial slice at level of Centroid
1. Centroid_Ant_Distance = Distance from mid of anterior spinal canal to the centroid of PTV along midline
2. Midline_to_Centroid = Distance from midline to the PTV Centroid</td>
<td>Measurement on the frontal Beam’s Eye View
1. Centroid to PTV medial extent: Distance measured between the centroid to the medial most extent of the PTV. In this patient the primary tumor is in the left side so measurement is towards the right side.</td>
</tr>
<tr>
<td colspan="2">Dist_PTV_to_midline = Centroid to PTV medial extent - Midline_to_Centroid
This measures the extent PTV crosses midline. This value will be negative if PTV does not cross the midline.
PTV_CC_Extent: Cranio-caudal extent can be measured either on the frontal BEV projection of PTV or from the superior and inferior most extent of PTV on the axial slices on the Planning CT</td>
</tr>
</table>

Table 4.2: Numerical summary of the nomogram for predicting probability of needing IMRT in NSCLC patients
(Copied from the supplementary of the article in Appendix 5)
Instructions: Note the points for each variable based on the value recorded from the planning CT in the right-hand column. Sum to get the total points and check the resulting probability of requiring an IMRT plan from the bottom table. If the predicted probability is >50% (equivalently, total score ≥98) then proceed with IMRT.

Nomogram																	**Example calculation**
Variable	**Variable Values and Points**																**Points Received (Actual Value)**
PTV_TLV_Ratio	**0**	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1**	**1.1**					
Points	*0*	*9*	*19*	*25*	*26*	*25*	*23*	*22*	*21*	*19*	*18*	*16*					***19 (0.2)***
Midline_to_Centroid (cm)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**							
Points	*10*	*9*	*8*	*7*	*6*	*4*	*3*	*2*	*1*	*0*							***6 (4.5cm)***
PTV_CC_Extent (cm)	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**			
Points	*8*	*6*	*4*	*2*	*1*	*0*	*3*	*9*	*17*	*24*	*31*	*38*	*46*	*53*			***1 (10.5cm)***
Centroid_Ant_Distance (cm)	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Points	*57*	*47*	*37*	*26*	*16*	*7*	*1*	*0*	*1*	*3*	*5*	*7*	*8*	*10*			***1 (6.37cm)***
Dist_PTV_to_Midline (cm)	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Points	*0*	*7*	*13*	*20*	*27*	*33*	*40*	*47*	*53*	*60*	*67*	*73*	*80*	*87*	*93*	*100*	***100 (8.76cm)***
														Total of Points			***127***

Total of Points	**76**	**84**	**90**	**94**	**98**	**102**	**107**	**112**	**121**
Probability of requiring IMRT	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9

Rationale for external validation

The performance of prediction models needs to be assessed in external validation studies with independent data from different samples. External validation helps establish the generalizability of the prediction model in terms of clinical transportability or statistical reproducibility (106). To externally validate a model is to evaluate its predictive performance (calibration and discrimination) using a separate data set from that used to develop the model (107,108).

External validation studies are often based on small and local datasets, thereby assessing the performance of a prediction model in a limited and specific setting or small population. However, it is increasingly recognised that the predictive performance of a model tends to vary across settings, populations and periods (109). Heterogeneity in model performance across populations, settings, and periods is rarely assessed as that would necessitate multiple external validation studies, to fully appreciate the generalizability of a prediction model (106,109).

Objective 1: To carry out external validation of the predictive model for these patients, after 3D-CRT plans have been attempted for all patients.

Objective 2: To document and analyse time taken to produce every 3D-CRT radiotherapy plan, before the patient participants are exposed to the decision tool.

Materials and Methods

Study design: Multi-centre, prospective, cohort study.

Target population: Patients with NSCLC who will be treated with curative intent using high dose RT with or without chemotherapy.

Inclusion criteria:

- Stage-III or locally-advanced NSCLC
- Radical RT or chemoradiation.

- Adequate lung function tests

Exclusion criteria:

- Prior lung surgery
- Prior radiotherapy in the thoracic region
- Inadequate lung function tests
- Any contra-indication for radiotherapy
- Radical RT not possible

Patient participants: Patients requiring radical radiotherapy for locally-advanced NSCLC.

Planner participants: Experienced and independent planners or dosimetrists who are responsible for planning radical radiotherapy for locally-advanced NSCLC.

Outcome predicted by the model: Decision on whether an acceptable 3D-CRT plan could be achieved or an IMRT plan would be necessary for appropriate PTV coverage and for meeting OAR constraints detailed in Table 4.1.

Primary outcome: Accuracy of the model in predicting that patients would need IMRT to try and achieve a satisfactory plan (110–112).

Secondary Outcomes:

1. Positive predictive value that IMRT will be required in patients with planning scans scoring ≥98.
2. Negative predictive value for IMRT.
3. Total time taken to produce an acceptable plan for each patient (WP1 and WP2).

4. To quantify the planning time saved in the real-world setting by using the model (WP1).

Defining outcome measures:

- Accuracy of the model in predicting that patients would need IMRT.
- Positive predictive value for IMRT for patients with scores ≥98.
- Negative predictive value for IMRT for patients with scores ≥98.
- Time saved (based on the cohort of IMRT plans) would be estimated from the mean time spent attempting 3D-CRT planning prior to IMRT in patients with scores ≥98.
- In a real-world setting, the difference of the mean of the total planning times for all patients before and after implementing the nomogram.

Table 4.3: A 2x2 table showing the 3D-CRT planning outcomes with nomogram score

	Nomogram score	
	<98	≥98
3D-CRT acceptable	TN	FP
3D-CRT not acceptable	FN	TP

Accuracy = (TP+TN)/ (TP+TN+FP+FN) (110–112)

Positive Predictive Value = TP/(TP+FP)

Negative Predictive Value = TN/(TN+FN)

Where:

- **True positive (TP)** = the number of cases correctly predicted as requiring IMRT
- **False positive (FP)** = the number of cases incorrectly predicted as requiring IMRT
- **True negative (TN)** = the number of cases correctly identified as successfully planned by 3D-CRT
- **False negative (FN)** = the number of cases incorrectly identified as successfully planned by 3D-CRT

Bias: the various sources of bias will be minimized. To avoid selection bias, we will offer this study to all patients who meet the inclusion criteria.

Sample size: 200 patients

Historically, the rule of ten events per variable based on 2 simulation studies was widely used (113–115). In the context of the current study, it was felt to yield a sample size of 50, not deemed large enough to result in sufficient events (113–115). Peek and colleagues examined the influence of sample size when comparing multiple prediction models, and concluded that a substantial sample size is required (116). Based on a hypothesis testing framework, Vergouwe *et al*., suggested that at least 100 events and 100 non-events are required for external validation of prediction models developed using logistic regression (117), with arguing for up to 200 events (108). An event is defined as a failure of 3D-CRT to generate an acceptable plan. A non-event is defined as successfully producing an acceptable 3D-CRT plan. The total sample size is 200.

Statistical analysis:

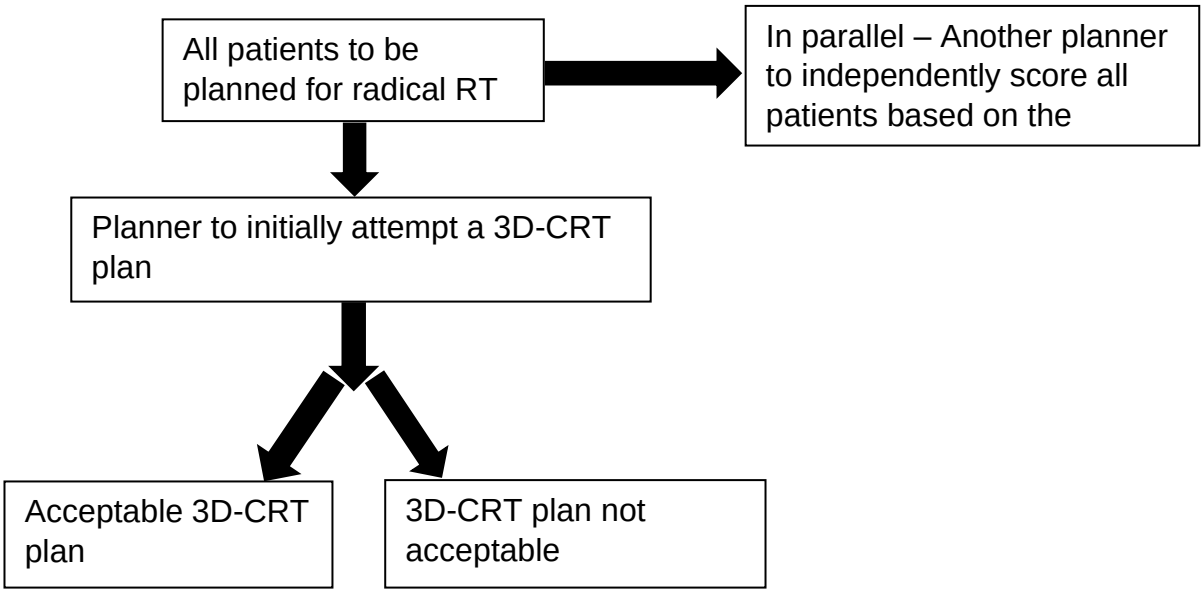
Descriptive statistics would be used for demographics and baseline clinical characteristics for all of the patients.

All 200 patients would be analysed and descriptive data on number of attempts and time taken for the 3D-CRT radiotherapy plan would be presented with their mean and standard deviation, median, interquartile range and minimum and maximum.

This cohort of 200 patients would be analysed for accuracy of the decision model in predicting the requirement for IMRT for a patient, positive predictive value and negative predictive value for requiring IMRT.

In the same patient cohort, the decision tool or nomogram is to be scored and documented by a different planner. After the planning attempts and nomogram-based scoring have been completed, the table (Table 4.3, above) is to be filled in based on whether scores <98 or ≥98.

Figure 4.2: Flow chart for the all of the patients
A 3D-CRT plan is to be attempted on all of these patients.



Potential limitations of the proposed external validation study:

- The limitation of this study is that we are doing this study within a set timescale, and may not be generalizable across periods. Heterogeneity in model performance across populations, settings, and periods is rarely assessed (109). External validation studies are often based on small and limited or local datasets and therefore, assess the performance of the

prediction model in a specific population or setting (109). In order to mitigate some of these limitations, we have designed a multi-centre study.

- Non-representative samples – the prediction model was generated based on planning data on lung cancer patients in a single tertiary cancer care centre in Eastern India. Unless the validation study is run at another similar cancer centre in India, the inherent differences in the healthcare systems across countries, that are reflected in differences in target volumes such as delayed presentation, more advanced stage, bulky volumes of NSCLC, could impact the validation study. Other differences are differences in levels of obesity, body mass index (BMI) and smaller lungs.
- The planners would develop and hone their skills at 3D-CRT planning for NSCLC as we go along this study, and the planning skill-set applied is not uniform throughout the study. Differences in perspective and threshold at which the planners and physicists would abandon 3D-CRT before opting for IMRT could be different and could potentially impact the validation of this decision model.

Potential impact of the validation study:

In the course of the validation study, the performance of the model would also be assessed. If any systematic difference or inaccuracy is identified with regards to the nomogram, they would be investigated in a thorough and transparent manner in order to understand the causes of the discrepancy. Any model re-calibration or updating that may result from this validation study would be presented and described.

Another potential impact of the validation study could be to widen the usage of the tool across other similar centres which would reduce resources required for lung planning as it had in the original centre.

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Chapter 5

General discussion and future perspectives

Changing landscape within the last decade

Non-Small Cell Lung Cancer (NSCLC) is a leading cause of cancer related deaths in the UK and worldwide [1–4]. About a quarter of all patients with NSCLC present with locally-advanced disease [3–5]. Radical chemoradiotherapy (either concurrent or sequential) is the standard of care in patients with stage-II or III NSCLC who are inoperable or have declined surgery [6].

Advances within the last decade include routine use of staging investigations such as whole body PET, MRI brain and staging EBUS, with TBNA as necessary [6]. CCRT was established as the standard of care for fit patients with LA-NSCLC, after Auperin and colleagues demonstrated survival advantage compared with SCRT in a meta-analysis [7]. SCRT or radical RT is used where concurrent treatment is deemed inappropriate [8] or if systemic therapy is contra-indicated [6,9–11].

After initial hesitation due to concerns around underdosing of tumour caused by interplay and potentially increased lung toxicity due to low-dose bath, IMRT and VMAT made a relatively late entry in lung cancer. These and other technical challenges relevant for IMRT in lung cancer have been discussed in Appendix 1 [12]. In LA-NSCLC, IMRT was initially used for patients with a large disease volume, complex tumour shapes and challenging tumour positions, where using 3D-CRT would lead to unacceptably high doses of radiation to OARs [12–15]. Technical challenges and concerns about IMRT for lung cancer were carefully assessed and had been reviewed before this treatment was accepted into routine practice and supported by guidelines [12,13]. Evidence pertaining to the use of IMRT in lung cancer evolved over time and was initially

retrospective in nature. Prospective studies have since been published and a systematic review of prospective evidence has been described in chapter 3.

Other radiotherapy-related advances within the last decade are more widespread use of dosimetry algorithms that include heterogeneity correction, the use of 4DCT for planning [16] and daily online CBCT imaging which reportedly increased planning and treatment delivery accuracy [17,18]. Advances in systemic therapy either as induction (sequential) chemotherapy prior to radiotherapy or upon relapse, as well as maintenance Durvalumab have improved outcomes [7,19–21].

Within the RTOG 0617 trial, IMRT was associated with lower rates of severe pneumonitis and cardiac doses and therefore routine use of IMRT for LA-NSCLC was suggested [31]. Dose escalation studies reported increased toxicity and toxicity-related deaths, therefore caution is required with patients with large PTV or vascular abutment [32–34]. Although studies are few and sample sizes are small, it has been suggested that dose escalation using hypofractionation could be attempted cautiously using SIB [35–37].

Radiobiological predictive models are used to help estimate the risk of radiation pneumonitis based on radiation dose distribution. Mean lung dose and V20 (proportion of normal lung receiving at least 20 Gy, expressed as percentage) are widely used predictors for radiation pneumonitis [29,30]. Models for normal tissue complication probability (NTCP) are based on published data from the period 1995-2005 when such IMRT/VMAT were not in routine use and much larger volumes of OARs were routinely irradiated using relatively simple and non-conformal radiation techniques [29,29,31]. Moreover, most of the models are from an earlier era when doses have historically been driven (dumped) through the heart, to minimize lung damage. Results of the RTOG0617 study have shown more severe toxicity and more treatment related deaths from higher doses of radiation to the heart [19]. Major cardiac events after high-dose thoracic RT are relatively common and may occur earlier than historically understood [32], and there is a need for early recognition and treatment of cardiovascular events [33]. It may no longer be

acceptable to minimise radiation exposure to normal lung at the expense of delivering very high doses to the heart [33].

Relevance of the submitted publications

After obtaining higher specialist training, research fellowship experience and consultant experience in the NHS, I had moved to Kolkata (India) to help develop lung cancer services at a philanthropic (not-for-profit) comprehensive cancer hospital. The submitted publications (Appendices 1-6) are focussed on the development and implementation of IMRT and VMAT for treatment of NSCLC, at this newly commissioned cancer centre in Eastern India. As the IMRT and VMAT techniques evolved and were integrated into clinical service, between 2013 and 2018, the processes and outcomes were audited and reported in these submitted papers.

The context and significance of the submitted published papers (appendices 1-6) and how the papers link within this thesis are already discussed in chapter-2. Aspects and challenges that are unique to this context are analysed and reported as follows:

- CHART (Appendix 3) was delivered using VMAT for patients where 3D-CRT could not result in a satisfactory and safe RT plan. This publication describes how the accelerated RT regimen was used in the real-world setting, for patients not suitable for chemotherapy, in a non-Caucasian population. This dose-fractionation was particularly valuable for patients who had travelled long distances for treatment. This shorter treatment regimen helped patients and their accompanying relatives return home sooner, reducing the logistic and financial burden of cancer [22].
- It had been demonstrated in a phase-III RCT that IMRT enabled comparable survival despite having been used in patients with larger volume tumours [23]. The audit of outcomes with analysis of patients with larger tumours (Appendix 6) showed that using IMRT made the delivery of

radical radiotherapy including CCRT feasible in large volume LA-NSCLC, in a real-world setting [24]. The tumour volumes and PTV were much larger than had been reported in the published RCT (i.e., RTOG 0617 trial).

- A decision model to predict the need to use IMRT for LA-NSCLC with a high degree of accuracy was developed and validated using a discrete cohort of patients (Appendix 5). It was expected that using this model could significantly reduce the treatment planning time for complex LA-NSCLC patients requiring IMRT, by removing the need for attempting 3D-CRT planning for these patients [25].

Conclusion from the submitted papers

VMAT was shown to enable more patients to receive radical doses of RT, with good PTV coverage, where 3D-CRT techniques had failed to generate an acceptable plan (Appendix 2). For each treatment fraction using conventional fractionation, VMAT resulted in greater number of monitor units, however had a shorter treatment delivery time [26].

Radical RT, particularly CCRT, was found to be feasible, safe, and well tolerated in the studied patient population, and resulted in survival benefits comparable to the published literature (Appendix 4) [27]. It was suggested that CCRT be routinely considered for all patients with inoperable LA-NSCLC, who are fit and have good ECOG-PS. Accelerated RT using CHART using 3D-CRT or VMAT (as necessary) was also shown to be feasible, safe and well tolerated as an effective, single modality treatment for NSCLC patients, who are not suitable for chemoradiation (Appendix 3) [22].

Radical radiotherapy including CCRT in large volume LA-NSCLC was made feasible by using IMRT, resulting in non-inferior survival outcomes, when compared to relatively smaller target volumes treated within a large, multi-centre, RCT (RTOG 0617) [24,27]. The updated systematic review (chapter 3)

did not show any direct impact of VMAT on toxicity, local control, and survival in patients with inoperable, locally advanced lung cancer. Despite the absence of prospective or randomised evidence supporting IMRT over 3DCRT for lung cancer, the case can be made for using IMRT for NSCLC patients with larger volume disease and more advanced stage (IIIB) [24].

Impact on clinical outcomes – how they fit within the contemporary literature

A recent review of the lung cancer services in India, found our reported survival outcomes for radical RT for NSCLC to be favourable compared with reports from other Indian centres [24,27,28]. Radical treatment using conventionally fractionated RT and concurrent cisplatin-based doublet chemotherapy resulted in outcomes that were comparable to contemporary reports from UK institutions [29] and a large, multi-centre, phase-III RCT [19]. This was despite the fact that 43% of the treated patients had stage IIIB NSCLC, compared with 32% reported by Iqbal *et al*., [24,29,30]. Besides, the median planning target volume (PTV) of 693 cm^3 was also greater compared with 450 cm^3 reported in the RTOG 0617 trial [19,24,30].

In summary, the papers describe the work in sequential or incremental steps that took a new lung cancer service from delivering conventional RT to technically-advanced RT for LA-NSCLC in a way that maximised clinical benefit to patients. This brought radical and curative-intent RT to more patients in that setting (CCRT, SCRT, hypofractionated RT or CHART), and maximised optimum use of limited resource (nomogram helping save planners time, as well as managing with limited VMAT licences). Furthermore, clinical benefits of having implemented these changes have been demonstrated through published audit data.

Future perspectives

After setting-up the lung radiotherapy service at the Tata Medical Center at Kolkata to high standards, I moved back to the UK in 2018. Therefore, future perspectives for my thesis are in the context of the National Health Service. Within the UK, a randomised phase-II study of accelerated, dose-escalated, sequential chemo-radiotherapy in NSCLC (ADSCaN) comparing different schedules against conventionally fractionated radiotherapy has now closed to recruitment in 2021 [43]. CONCORDE is a phase-I platform study currently recruiting patients, seeking to establish the toxicity profiles of multiple novel radiosensitisers targeting DNA repair proteins in patients treated with sequential chemoradiotherapy [44].

Up-to-date studies are needed for systematic assessment of toxicity (to both lung and heart) from highly modulated radiotherapy techniques such as IMRT/VMAT, in the context of modern multi-modality lung treatments. Studies are also needed for exploration of approaches towards reducing toxicity, as clarity and consensus are lacking on how to optimally balance radiation dose between the heart and lungs. These studies need to have translational sub-studies incorporated within them, for investigating imaging and circulating biomarkers and correlating them with clinical toxicity.

IMRT and VMAT enables safer approaches to treatment intensification by allowing OAR sparing and is well established in LA-NSCLC. I believe that VMAT should be used to help drive up standards in the context of high dose palliative radiotherapy. We are developing a study to investigate the safety and efficacy of reducing the number of radiation fractions and treatment duration, by using shortened hypofractionated accelerated palliative radiotherapy, aided by VMAT planning and delivery and accurate online volumetric verification imaging [45].

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Appendix 1

Pitfalls and Challenges to Consider before Setting up a Lung Cancer Intensity-modulated Radiotherapy Service: A Review of the Reported Clinical Experience

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Abstract

Intensity-modulated radiotherapy (IMRT) is being increasingly used for the treatment of non-small cell lung cancer (NSCLC), despite the absence of published randomised controlled trials. Planning studies and retrospective series have shown a decrease in known predictors of lung toxicity (V20 and mean lung dose) and the maximum spinal cord dose. Potential dosimetric advantages, accessibility of technology, a desire to escalate dose or a need to meet normal organ dose constraints are some of the factors recognised as supporting the use of IMRT. However, IMRT may not be appropriate for all patients being treated with radical radiotherapy. Unique problems with using IMRT for NSCLC include organ and tumour motion because of breathing and the potential toxicity from low doses of radiotherapy to larger amounts of lung tissue. Caution should be exercised as there is a paucity of prospective data regarding the efficacy and safety of IMRT in lung cancer when compared with three-dimensional conformal radiotherapy and IMRT data from other cancer sites should not be extrapolated. This review looks at the use of IMRT in NSCLC, addresses the challenges and highlights the potential benefits of using this complex radiotherapy technique.

Statement of Search Strategies Used and Sources of Information

The aim of this overview was to review the clinical experience of intensity-modulated radiotherapy (IMRT) for lung cancer after summarising the development of IMRT technique in this setting. In order to review the clinical experience of IMRT for lung cancer, a PUBMED search was carried out on 23 April 2014. The search was limited to articles in English print and used the following parameters: lung cancer AND clinical outcome AND IMRT (53 results); non-small cell lung cancer AND IMRT (148 results). This yielded 201 publications. Of the returned articles, we included studies reporting clinical outcome data after the use of IMRT in non-small cell lung cancer (NSCLC). References of the selected articles were also searched and further studies with relevant clinical data were identified and selected for this review. Relevant selected planning and dosimetric studies showing potential advantages of IMRT over three-dimensional conformal radiotherapy in lung cancer were examined and included. Case reports and hypofractionated stereotactic radiotherapy studies and studies on other tumour types were excluded. Where institutions have multiple publications, the previous publication was included only if it gave useful additional information. In total, five institutions have reported actual clinical outcome data on IMRT for NSCLC. Seven publications from five institutions were identified and included (Tables 3 and 4). Repeat analyses with a longer follow-up and more patients were available and were included from two institutions. Technical IMRT planning and delivery challenges and concerns in the setting of thoracic cancers were identified by studying the selected and relevant articles and published guidelines. Specific searches were carried out, pertaining to individual questions/problems about IMRT.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1-3]. Non-small cell lung cancer (NSCLC) ac-counts for over three-quarters of all lung cancer cases. Surgery for early lung cancer (stage I, II and some IIIA) is the treatment option of choice, although there are no published phase III data

comparing surgery with chemoradiotherapy. However, less than 20% of patients with NSCLC are suitable for surgery [4]. Radical radiotherapy with curative intent is the primary treatment option for patients with stage III NSCLC, with the potential for providing long-term local disease control. In many of these cases, surgery has no added survival advantage over radical chemoradiotherapy [5]. The long-term survival rate with definitive radiotherapy is typically low at 15% in 5 years [6]. The radical radiotherapy schedule is usually at least 60Gy in 30 fractions, using 2Gy fractions daily over 6 weeks [7]. An alternative schedule for radical radiotherapy delivering 55Gy in 20 fractions has also been used, mainly in the UK [8].

The dose-limiting organs at risk (OAR) for radical lung radiotherapy are normal lung, spinal cord, heart and oesophagus. The percentage of lung [minus gross tumour volume (GTV)] receiving a dose of at least 20Gy (V20) and the mean lung dose (MLD) have both been used to define lung tolerance. Various radiotherapy guidelines have described lung tolerance and recommend improvement or modification of the radiotherapy plan until V20 decreases to less than 32-35% and MLD to under 20Gy [9,10]. In locally advanced lung cancer, dose constraints to these OARs can be difficult to satisfy with three-dimensional conformal radiotherapy (3DCRT) due to a large disease volume and challenging tumour positions. This is particularly common in patients with mediastinal node-positive peripheral tumour, involved contralateral lymph nodes (N3 disease) or tumours close to the spinal cord. This may result in unacceptably high doses of radiation to the spinal cord or to a substantial proportion of normal lung. Given this limitation, in radiotherapy centres without a lung intensity-modulated radiotherapy (IMRT) service, many patients are treated with high dose palliative radiotherapy to avoid exceeding a normal tissue tolerance [11,12].

Survival from high dose palliative radiotherapy for NSCLC is even lower than survival rates from definitive radical radiotherapy, and this modality has been addressed in a recent Cochrane review of 3708 patients from 14 randomised controlled trials. For selected patients with a good performance status, high dose palliative radiotherapy resulted in a modest increase in survival (5% at 1

year and 3% at 2 years) [13], but typical outcomes remain poor, with a median survival of 9 months. The largest clinical trial in this review, with 509 patients, was the Medical Research Council trial published in 1996 [11].

This limitation can be overcome with the introduction of forward- and inverse-planned IMRT in lung cancer. IMRT involves highly conformal radiotherapy combined with modulation of fluence along the beam profile [14-17]. By controlling or modulating the radiation beam into multiple small beamlets, IMRT conforms the radiation dose to an irregular shaped target volume in all three dimensions. This advanced mode of high-precision radiotherapy uses a computer-controlled linear accelerator to deliver high precise radiation doses to the planning target volume (PTV) with a steep dose fall-off near the normal critical structures in the vicinity of the target [14-17]. Here we have summarised data from relevant planning studies, clinical studies and retrospective series and discuss the technical challenges and solutions and the rationale for using IMRT in selected cases of locally advanced lung cancer.

Materials and Methods

In this review, we summarise the development of the IMRT technique for locally advanced lung cancer. We start by addressing technical radiotherapy planning challenges and concerns in the setting of thoracic cancers. Second, we look at the relevant planning studies showing potential advantages of IMRT over 3DCRT in lung cancer. Third, we review and summarise the available clinical data and published prospective studies on IMRT in lung cancer. Finally, we discuss the limitations of comparing the outcome of IMRT with historical literature on 3DCRT and outline the potential of this promising technology.

In order to review the clinical experience on IMRT for lung cancer, a PUBMED search was carried out on 23 April 2014. The search was limited to articles in English print and used the following parameters: lung cancer AND clinical outcome AND IMRT (53 results); non-small cell lung cancer AND IMRT (148 results). This yielded 201 publications. Of the returned articles, we included studies reporting clinical outcome data after the use of IMRT in NSCLC.

References of the selected articles were also searched and further studies with relevant clinical data were identified and selected for this review. Case reports and hypofractionated stereotactic radiotherapy studies and studies on other tumour types were excluded. Where institutions have multiple publications, the previous publication was included only if it gave useful additional information. In total, five institutions reported actual clinical outcome data on IMRT for NSCLC. Seven publications from five institutions were identified and included. Repeat analyses with a longer follow-up and more patients were available and included from two institutions. Certain published dosimetric and planning studies [18-26] were also selected, reviewed and summarised in the section on planning studies, to address the relevant issues and to facilitate the discussion.

Radiation Planning for Radical Treatment for Lung Cancer

Radical radiotherapy for lung cancer is planned using various planning modalities from 3DCRT to volumetric modulated arc radiotherapy (VMAT) and tomotherapy.

3DCRT – refers to three-dimensional computed tomography image-based planning. Linear accelerators equipped with sophisticated computer-controlled multileaf collimator (MLC) systems accurately shape the beam aperture. Arrangements of multiple static beams are used in all three dimensions and non-coplanar beams may also be used. Most of the beams enter through the ipsilateral lung and off-cord beam arrangements may be used where necessary. With this technique, three to four beams are typically used with varying gantry angles, differential weighting, different apertures shaped with MLCs. To further improve the conformity and the dose distribution, conventional beam modifiers such as wedges, partial transmission blocks or compensating filters may also be used. The dose is usually normalised at or close to the isocentre, such that the ICRU recommendations on PTV coverage between 95 and 107% are satisfied [27]. The three-dimensional dose matrix is computed with three-dimensional treatment planning software. With a fixed dose rate, energy and a fixed field size in the treatment machine, monitor units

are calculated. Treatment position verification is carried out with the help of digitally reconstructed radiographs generated in the treatment planning system from the planning computed tomography dataset.

Forward-planned IMRT – this planning technique is juxtaposed between 3DCRT and IMRT. It is a more than a conventional 3DCRT and like a simplified IMRT plan. Forward IMRT plans are achieved by manually adding subfields with various weights and evaluating the dose distribution. In each non-automated iteration of the process, the planner introduces changes to revise the plan, typically producing a limited number of subfields. The treatment delivery uses static fields in a step and shoot manner.

Inverse-planned IMRT – IMRT is an advanced radiotherapy planning technique that delivers non-uniform (i.e. intensity-modulated) beams in order to produce a highly conformal dose distribution [18]. This is an inverse-planning process that uses computerised optimisation. This necessitates a formal description of the requirements using a mathematical objective function and constraints, which are then used by the program to find the solution. After the design of initial beam geometry, the desired dose-volume constraints for the PTV and OARs are fed into the treatment planning system. The treatment planning system optimisation algorithm then divides each beam into many small beamlets (i.e. pencil beams that together make up the IMRT beam) and then iteratively alters the beamlet intensities, until the three-dimensional dose distribution conforms to the prior-specified dose objectives, as closely as possible. After the optimal beam intensities and the resulting dose distribution has been achieved, the treatment planning system then calculates the MLC leaf sequence motions that will achieve this dose distribution and the dose is recalculated. The use of IMRT for lung cancer has been shown to allow a reduction in the MLD, the V20 for lung and the maximum dose to the spinal cord [12,18-21].

VMAT – a form of dynamic IMRT where the dose to the target volume is delivered in a full 358-degree gantry rotation with varying gantry speed [28]. With the gantry motion, the MLC positions and the fluence-output (dose rate) also vary continuously. A typical VMAT plan consists of one to four arcs. The

arcs are either one or more full arcs with skipped angles (arcs restricted by avoidance sectors) or two or more partial arcs. The collimator angle, for a VMAT plan is not zero, but typically tilted at 20-45 degrees in either direction [28]. This is a rotational IMRT that can be delivered using conventional linear accelerators with conventional MLCs.

Tomotherapy – yet another mode for delivering intensity-modulated arc therapy. The tomotherapy treatment system delivers radiation in a spiral (helical) delivery pattern [29]. It consists of a linear accelerator attached to a slip ring just like a computed tomography scanner machine and travels around the patient in unison with 120 pairs of MLCs (binary MLC for fluency modulation) and a translational sliding couch. Tomotherapy plans are created using an inverse treatment planning system based on a superposition/convolution dose calculation algorithm. A good correlation was found between the quality of the helical tomotherapy plans and the IMRT plans, with helical tomotherapy being slightly better in many cases [29].

Planning Issues and Challenges with Intensity-modulated Radiotherapy for Lung Cancer

IMRT is aided by automated optimisation techniques that design beam modulation according to a clearly defined set of treatment objectives [18]. This has been made possible by improved computing power of planning systems, good planning software and computer-controlled treatment units. Clinical implementation of the technique has been challenging due to the additional experience, training and resources needed to account for the additional complexity of treatment planning and quality assurance [18,30].

Although the advantages from the use of IMRT seemed promising, the National Cancer Institute guidelines in 2002, aimed at ensuring safety and comparability, suggested caution with the use of IMRT for intra-thoracic cancers [31].

Subsequent guidelines stressed the importance of quality assurance programmes to ensure the accurate delivery of radiotherapy, appropriate

corrections for tissue heterogeneity and target organ motion, patient immobilisation and appropriate imaging to reduce motion artefacts [31]. American Society for Radiation Oncology (ASTRO) guidelines and other publications provide recommendations about the practice of IMRT and detailed documentation before using IMRT for thoracic tumours [32-36].

The respiratory motion may cause artefacts during image acquisition. These motion artefacts occur because different parts of the organ or tumour move in and out of the computed tomography slice window during image acquisition. These motion artefacts manifest themselves during target and normal tissue delineation and may also affect dose calculation accuracy. Currently adopted methods for managing respiratory motion during image acquisition are slow computed tomography scanning, inhale and exhale breath-hold computed tomography scanning and four-dimensional computed tomography (4DCT) scanning [37]. Other methods of accounting for respiratory motion after image acquisition include respiratory gating and real-time tumour tracking [37].

According to ICRU 62, the PTV is obtained from the clinical target volume plus an additional margin for intra-fraction motion, inter-fraction motion and set-up error [38]. Radiation delivery in the presence of intra-fraction organ motion may cause a smearing/blurring of the dose distribution calculated from static planning scan images. As IMRT results in a greater conformity of dose around the target volumes, it makes them highly susceptible to systematic errors in delineation and geometric uncertainty; therefore, adequate margins must be incorporated into the treatment plan [35]. Quantifying the margin for the clinical target volume in each individual case for accurate dose delivery can be challenging. A steep gradient with a rapid fall-off at the edges of the target volumes also necessitates robust quality assurance of immobilisation and treatment verification [35].

Dose dumping may be seen when critical structures are incompletely delineated and appropriate dose constraints are not properly assigned. OAR delineation must extend well beyond the cranial and caudal extent of the PTV, otherwise non-coplanar fields may be assigned through part of that OAR and radiation passing through them will not be represented in the dose-volume

histogram [35]. Doses to the other non-critical structures should also be monitored. Depending on the treatment planning technique (static IMRT, Rapid Arc or tomotherapy) different strategies may be adopted to avoid dose dumping. With static IMRT, avoiding non-coplanar beam arrangements would help to reduce this problem. Delineation of dummy (avoidance) structures and assigning dose constraints to these structures is a common method for avoiding dose dumping [39]. Giving high constraints to avoidance structures, using more than one arc for better dose modulation (increased control points) or using avoidance sectors for normal tissue sparing are some of the methods to minimise dose dumping with VMAT. In the tomotherapy Hi-Art system the concept of partial block (delineated structures that allow exit beams but not beam entry) and complete block (delineated structures that do not allow any beam entry or exit) is used to reduce the chances of dose dumping. The clinician must carefully examine the dose distribution and isodose lines on every slice of the treatment plan in all three planes to identify any inadvertent dose dumping [39].

IMRT is characterised by inhomogeneous beam intensity and dose distribution, which makes single prescription points unsatisfactory and a mean dose is often prescribed to the target volume [36]. Heterogeneous dose distribution may be troublesome in the presence of organ motion, such as in the lungs and upper abdomen [40]. Respiratory tumour motion during imaging, planning and delivery of radiation therapy potentially leads to a blurring effect and interplay effect. The interplay effect is well recognised between moving sub-fields (segments) and moving lung tumour and has raised concerns about coverage and dosimetry. With IMRT (unlike 3DCRT), the entire PTV is not always covered by a beam in all its segments. IMRT may only irradiate a part of the target volume with any given segment of a field. However, various studies with fractionated IMRT schedules (of 30 fractions or more) have shown that the dosimetric effect of this interplay is probably less than 1%, and these studies did not show unpredictable hot and cold spots within the target volumes [23-26]. For similar conventional fractionation the effects of interplay are probably blurred or ‘washed out’ [23-26] and the dose variation due to respiratory motion in IMRT is comparable with 3DCRT [24].

Multiple beam angles from intensity modulation may increase the integral radiation dose delivered to the lungs resulting in a larger volume of normal lung tissue receiving a greater low-dose radiation (low-dose bath) [21,41]. Longer treatments using more monitor units may result in greater radiation leakage through the MLC leaves, leading to a higher total body dose, in addition to the low-dose bath [35]. The long-term clinical effects of this low-dose bath on gas-exchange and respiratory symptoms are not completely understood. The higher total body dose may also lead to an increased incidence of secondary malignancies [42,43]. However, the possibility of secondary malignancies may not be of major concern in patients with locally advanced (stage III) NSCLC, where 5-year overall survival is less than 15% [6]. Off-axis delivery (using asymmetric jaws) of irregularly shaped fields is not routinely commissioned for low density tissue (in all departments) and therefore the delivery accuracy may be uncertain. An ongoing dosimetric audit is necessary in individual departments to confirm that the dose distributions being delivered are accurate and reliable.

The major challenges and solutions with the use of the IMRT technique for lung cancer patients have also been summarised in Table 1 [35].

Table 1: IMRT for lung cancers- Facts, problems and solutions.

Fact	Practical problems	Answer/Solution	Reference
High conformity of dose aroundtarget volume	highly susceptible to systematic errorsin delineation and geometric uncertainty	adequate margins must be incorporated into the treatment plan	Galvin et al [35].
	Steep gradient with rapid fall-off at theedges of the target volumes	the quality assurance of immobilisation and treatment verification with appropriate image guided RT must be robust	Galvin et al [35].
Heterogeneous dose distribution	single prescription points are unsatisfactory	a mean dose is prescribed to the targetvolume	ICRU Report 83 [36], Galvin et al [35].
Appropriate dose constraints may not be properly assigned toall the different tissues and organs in the path of the beams	Dose dumping (deposition of higher than usual dose of radiation at an unintended location) may be seen when critical structures are incompletely contoured	OAR contours must extend well beyond the cranial and caudal extentof the PTV	Galvin et al [35], Chatterjee et al [39].
	Excess dose may be deposited in organs that are traditionally non critical(such as heart) that do not require irradiation	Doses to the non-critical structures, such as skin or muscle tissue, shouldbe monitored All relevant OARS should be contoured and dose constraints applied in the IMRT optimization.	Galvin et al [35].
Critical structures (OARs) maybe incompletely contoured	non-coplanar fields may be assigned through critical structures and radiation passing through them will not be identified or represented in the DVHs	Coplanar beam arrangements are usedby most planners for lung IMRT to minimise this problem.	Galvin et al [35].
Unlike 3D CRT, with IMRT,the entire PTV is not always covered by the beam in all its segments IMRT may only irradiate a partof the target volume with any given segment of a field	Potential interplay between moving subfields (segments) and moving lungtumour is a matter of concern	The dosimetric effect of this interplayis probably less than 1% if the treatment is delivered over 30 fractions or more	Bortfeld [23], Chui [24], Duan [25], Jiang [26].
		For similar fractionation, dose variation due to respiratory motion inIMRT is comparable to 3D CRT	Chui et al [24].
		the effects of interplay are probably blurred or “washed out” with multiple fields over a fractionated course of radiotherapy	Bortfeld [23], Chui [24], Duan [25], Jiang [26].
		Various studies with fractionated IMRT schedules did not show unpredictable hot and cold spots within the target volumes because of interplay between tumour motion andmulti-leaf collimator movement	Bortfeld [23], Chui [24], Duan [25], Jiang [26].

Multiple beam angles from intensity modulation may increase the integral radiationdose delivered to the lungs Longer treatments using moremonitor units may result in greater radiation leakage through the MLC leaves and other shielding, leading to a higher total body dose. [35]	A higher mean lung dose and a larger volume of normal lung tissue receivinga greater low dose radiation (low dose bath). [21,41] The long-term clinical effects of this low-dose bath on breathing and gas-exchange are not well understood This could also lead to an increased incidence of secondary malignancies. [42,43]	Clinically, this should not be of majorconcern in patients with locally advanced (stage-III) NSCLC; some ofwho would otherwise have received high dose palliative radiotherapy and would have a median survival of 9 months.	Macbeth et al [11].
Often large irregularly-shapedtarget volumes	Off-axis delivery (using asymmetric jaws) of irregularly-shaped fields is notroutinely commissioned by physics departments for low density tissue and the delivery accuracy is therefore not known	Ongoing dosimetric audit is needed inindividual departments to confirm thatthe dose distributions being delivered are accurate and reliable	Warren [49], Galvin[35], Bezjak [41].

Planning Studies

Various planning studies have shown the benefits of IMRT either as a result of better normal tissue sparing [19,20,22] or enabling dose escalation [45]. Studies (stage I-IIIB) have reported reductions in the V20, the percentage volume of lung receiving more than 20Gy, of between 8 and 15%, compared with 3DCRT [20,21,46,47]. Some studies have shown an advantage with IMRT to the dose to the heart, whereas some studies did not find any benefit [19,46-48]. However, the results of the Radiation Therapy Oncology Group (RTOG) 0617 trial (a prospective clinical trial) have established dose-volume limitations for the heart that would be incorporated in future RTOG lung cancer trials [49]. Important planning studies for lung cancer that have looked at IMRT and compared it with other forms of planning (including 3DCRT) have been reviewed and summarised in Table 2. These are widely cited earlier studies that comprehensively describe the planning details on how improved target coverage and reduction in dose to the lungs and other OARs were achieved using different IMRT solutions. The last planning study in Table 2 by Warren et al. [44] looked at the feasibility of isotoxic radiotherapy with dose escalation using IMRT, which is a relatively new concept in lung cancer.

Studies using IMRT in the treatment of lung cancer have also shown significantly reduced doses to the oesophagus [19-21]. Another study has shown that optimised many-field IMRT plans allow dose escalation to the PTV, at a similar level of oesophageal sparing and without unacceptable worsening of dose distribution to the normal lung, in cases of oesophagus overlapping PTV [52]. Another planning study by the same author investigating the dose to the heart, in irradiation of middle and lower lung tumours, showed that the use of non-coplanar fields and IMRT dramatically reduced the dose received by the heart, with the largest benefit seen when the two techniques are combined [53].

A recent study on IMRT for lung cancers looked at the clinical planning trade-offs between OAR sparing and PTV coverage. By focussing on two of the relevant OARs (normal lung and oesophagus) and keeping the ‘weights and priority’ for the other organs constant, they simplified the analyses and

concluded that the sparing of these OARs was linearly related to PTV coverage [54]. Two separate planning studies have compared 6 MV with 18 MV photons for IMRT treatment for lung cancer. Neither of the studies showed any advantage from using the higher energy for this situation [55,56].

Various investigators have shown the feasibility of single photon emission computed tomography (SPECT) for mapping the spatial distribution of lung perfusion, thereby defining functional lung [57-59]. SPECT-guided IMRT has been shown, in planning studies, to divert dose away from higher functioning lung, with the potential for reducing the number of high-grade pneumonitis cases that develop after radiotherapy, while preserving target coverage [57-60]. These planning studies have shown a significant reduction in dose-function histograms [57] or functional V20 and mean perfusion-weighted lung dose in stage III patients with inhomogeneous lung perfusion [58-60].

Table 2: Planning studies comparing IMRT with other forms of RT planning, looking at radiotherapy doses to lungs

Authors	Aims/ Summary of the project	Methods	Results	Clinical relevance
Liu et al [20].	To investigate the effect of IMRT on the potential of spreading low doses to large volumes of normal tissues (lung) in such treatment	Retrospective treatment planning study, where nine beam IMRT and 3D CRT plans were created for 10 NSCLC patients (Stage I–IIIB)	IMRT was shown to reduce the median V-20 and the mean lung dose (MLD) by 8% and 2Gy, respectively	It is possible to reduce the volumes of low doses (such as the >10-Gy volume and >20-Gy volume) for thoracic normal tissues using IMRT
Murshed et al [19].	To investigate dosimetric improvements with IMRT with respect to tumour dose conformity and normal tissue sparing compared with 3D CRT	Forty-one patients with stage III-IV and recurrent NSCLC who underwent 3D CRT were re-planned with IMRT using 9 equidistant coplanar 6-MV beams	The median absolute reduction in the V-20 and V-10 was reported as 10% and 7%, respectively. This reportedly reduced the total lung mean dose (MLD) by >2Gy and resulted in a reduction of 10% in the risk of radiation pneumonitis. A marginal increase in the maximum dose to the spinal cord and the V-5.	IMRT planning significantly improved target coverage and reduced the volume of normal lung irradiated above low doses. The spread of low doses to normal tissues can be controlled in IMRT with appropriately selected planning parameters.
Grills et al [21].	To evaluate four different techniques of radiation therapy (RT) used to treat NSCLC and to determine their efficacy in meeting multiple normal-tissue constraints while maximizing tumour coverage and achieving dose escalation.	IMRT was compared with 3 other radiotherapy techniques, namely, optimised 3D CRT using multiple beams, limited 3D CRT using 2-3 beams and traditional radiotherapy using elective nodal irradiation (ENI) to treat the mediastinum. For 18 patients with inoperable non-small cell lung cancer (stage I-IIIB).	IMRT was shown to meet all the normal tissue constraints in node positive patients and was shown to enable delivery of 25-30% higher doses than 3D CRT and 130-140% higher doses than traditional radiotherapy and ENI. In node positive patients IMRT reduced the V-20 and mean dose by about 15% compared to 3D CRT.	IMRT was of limited additional value in node negative patients. Patients with node positive (stage III) NSCLC or those with target volumes close to the oesophagus are thought to derive maximum dosimetric advantage.
Christian et al [18].	This study compared intensity-modulated RT (IMRT) with three-dimensional conformal RT (3D-CRT) in reducing the dose to the lungs	Planning study (10 patients), where inverse-planning tool was used to produce a beam-angle optimised six-field non-coplanar 3D CRT plan on each patient [Christian JA]. This was then compared with 5 IMRT plans on each patient (3, 5, 7, 9 equidistant coplanar field arrangements and a 6-field non-coplanar plan).	IMRT (except for 3 field coplanar IMRT) was shown to significantly improve the conformity of the plan and reduce the dose to the lungs compared with 3D CRT. Nine coplanar IMRT beams were shown to be significantly better than 5 or 7 coplanar IMRT beams.	Although the 9-beam plan was “theoretically” the best solution, the investigators reported the 5-beam solution with equidistant gantry angles to be a pragmatic approach, with a good balance between best theoretical outcome and practical plan delivery.
Rosca et al [50].	Looked at comparing 7 different planning techniques for mediastinal lung targets, aiming to reduce lung volume receiving low doses of radiation.	Treatment plans generated for 13 cases of NSCLC with targets including mediastinal lymph nodes, to both 60Gy and 74Gy prescription doses. Seven different planning techniques were used: conformal, hybrid conformal/ intensity-modulated radiation treatment (IMRT), 7 equidistant IMRT beams, 2 restricted beam IMRT plans, a full (360 degree) modulated arc, and a restricted modulated arc plan.	Is was shown that all planning techniques that allow lateral or lateral-oblique beams result in higher lung volumes receiving a low dose bath.	The area under the lung dose-volume histogram curve below 20Gy, the V0-20 integral parameter, was proposed as alternative measure of lung sparing and as a parameter to be minimised during IMRT optimisation, for further studies.
Komosinska et al [51].	Investigated whether IMRT (5 coplanar beams) offered any advantage compared to 3D CRT for patients with small lung volumes.	From a database of 200 patients, 10 patients with the smallest lung volumes were identified and 3D CRT and IMRT plans were created to deliver 66Gy in 33 fractions. Of these 10 patients, safely usable 3DCRT plans for 66Gy could not be produced for 4 patients and usable IMRT for 3 of these patients.	MLD was lower for five IMRT plans and two 3DCRT plans, and the decrease in MLD with IMRT was seen for cases with large PTV and high PTV/lung volume ratio. V-5 was 47% for 3DCRT and 57% for IMRT. V-15 or higher was lower for IMRT	V-5 was lower for all 3DCRT plans and V-15 or higher was lower for IMRT. IMRT is promising for cases with small lung volumes, especially when associated with large PTV.
Warren et al [49]	Dosimetric planning study comparing IMRT and 3D-CRT to deliver isotoxic treatment using twice daily radiotherapy.	Retrospective dose-escalated plan produced for 20 patients with stage II/III NSCLC using 3 methods: (i) 3-5 beams 3D-CRT; (ii) 7 beams inverse-planned conformal RT; (iii) 7 beams IMRT. The number of fractions was increased, in increments of 1.8Gy per fraction twice-daily, until one or more organ at risk tolerance dose was exceeded or a maximum dose of 79.2Gy was reached.	The median escalated doses were 70.2, 66.6 and 64.8Gy for IMRT, 3DRT and inverse-planned conformal radiotherapy, respectively. IMRT allowed a significant dose increase in comparison with the othertwo methods ($P < 0.05$).	IMRT allows greater dose escalation compared with conformal radiotherapy where the brachial plexus and spinal canal were close to the PTV. However, limited escalation in prescription dose beyond 70.2Gy twice-daily (82.8Gy BED10, 69Gy EQD2) is possible in disease close to the central mediastinum.

Retrospective Clinical Series

The literature on the use of IMRT in NSCLC is limited to a few prospective studies and mostly single-centre retrospective series on patients with stage I-III disease. These retrospective series are heterogeneous and it is difficult to draw firm conclusions from the analysis. Therefore, individual papers are discussed below and relevant information has been tabulated for easy reading (Tables 3, 4).

A retrospective series of 55 patients, from the Memorial Sloan Kettering Cancer Center, with stage I-III NSCLC, with large tumour volumes (GTV 100 cm3), suggested promising outcomes from lung IMRT treatment [61]; with a median follow-up of 26 months, 2-year overall survival for stage I/II and III were reported as 55 and 58%, respectively. The median survival was reported as 25 months. Grade 3 acute pulmonary toxicity was seen in six (11%) patients and grade 3 late pulmonary toxicity was seen in two (4%) patients.

Govaert and colleagues [62] from Nijmegen Medical Centre have published their retrospective series with stage III NSCLC treated with IMRT alone or with (sequential or concurrent) chemotherapy. In their review of 86 patients, the overall survival rate for patients receiving 66Gy was reported to be 71% (±11%) after 1 year and 56% (±14%) after 2 years, with a median survival of 29.7 months. Metastasis-free survival was 73% (±11%) after 1 and 2 years. Treatment-related oesophageal toxicity was significantly greater in patients receiving concurrent chemotherapy [62].

Liao et al, [63] from MD Anderson reviewed 91 patients who were treated with 4DCT aided planning and IMRT and compared the outcome with 318 patients treated with computed tomography/3DCRT. They suggested a therapeutic benefit with improved overall survival (hazard ratio 0.64; P = 0.039) and decreased grade 3/4 pneumonitis (hazard ratio 0.33; P = 0.017) with 4DCT/IMRT [63]. However, it is worth noting that 4DCT has an effect on the assessment of target motion, target definition, margins and greatly affects the radiotherapy planning process and is therefore potentially a confounding factor.

The largest clinical experience (the MD Anderson experience) of IMRT for inoperable NSCLC with long-term outcome data was published by Jiang and colleagues [64]. This was retrospective review of 165 patients with stage III-IV NSCLC treated over a 2-year period until the end of 2006. Concurrent chemoradiotherapy was delivered using IMRT in conjunction with 4DCT to inform radiotherapy planning. The median follow-up time was 16.5 months for survivors. The median survival was 21.6 months and the 2 year and 3-year survival rates were 46 and 30%, respectively. Grade 3 (or higher) radiation pneumonitis was seen in 11% at 6 months and 14% at 12 months. A high percentage of patients who experienced grade 3 oesophagitis later developed grade 2 or 3 oesophageal stricture.

In another series from Beijing, Shi et al, [65] reported their experience of 94 patients at a median follow-up of 10.5 months. The patients had locally advanced NSCLC and were treated using IMRT with concurrent chemotherapy. Eleven (11.7%) patients developed severe (grade 3 or higher) acute radiation pneumonitis (SARP). In multivariate analysis, normal tissue complication probability (NTCP) values and V10 were the most significant factors associated with SARP. V10 is the proportion of whole lung (minus GTV) receiving a dose of at least 10Gy, expressed as a percentage. The incidences of SARP in the group were 43.5% and 1.4% for NTCP values of >4.2% and 4.2%, respectively. Similarly, the incidences of SARP were 29.2% and 5.7% for V10 of >50% and 50%, respectively [65].

A series of publications from the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam looked at oesophageal and pulmonary toxicity where NSCLC patients were treated with hypofractionated IMRT (66Gy/2.75Gy/24 fractions) to the lung with concurrent low-dose daily cisplatin [66-68]. No significant difference was identified in the incidence (grade 2) of acute oesophageal toxicity between patients treated with 3DCRT and IMRT with concurrent chemotherapy [66].

Shirvani et al, [69] reported an interesting study analysing 3986 patients from The Surveillance, Epidemiology, and End Results (SEER) – Medicare database. The authors concluded that practice factors rather than sound

clinical rationale accounted for increased utilisation of IMRT for NSCLC, between 2001 and 2007 [69]. Rates of acute toxicity in the oesophagus and lung were similar between IMRT and 3DCRT. Chronic toxicities and survival were not analysed in this study.

Table 3: Retrospective clinical series (Treatment and planning parameters)

Author	Number of patients receiving IMRT	Timescale (for IMRT arm where relevant)	Diagnosis and stage	Technique / Beams	Chemotherapy	Dosimetry
Jiang et al [64]. Update from the MDACC	165	2 years (Jan 2005 – Dec 2006)	III – IV NSCLC (89%) I – II NSCLC (11%)	IMRT (all) 4DCT (79%) No 4DCT (21%)	RT alone: 8% Concurrent: 82% Concurrent alone: 25% Other: 9%	Median GTV 124.6cc (4.3-730) Median PTV 739cc (99-2221)
Govaert, 2012 [62]. Nijmegen Medical Institute	86	3 years (Mar 2008 – Feb 2011)	IIIA-IIIB NSCLC (83%)	IMRT with 6 co-planar beams, 10MV photons	Pre-RT: 42 Concurrent: 37 RT alone: 7	
Liao et al [63]. MDACC	91	2 years (2004 –2006)	Unresectable locally advanced NSCLC	4DCT & IMRT	Concurrent: all	Median GTV 199cc (+/-165) MLD 24.9Gy (17.5-32.3) V20 34.4 (33.2-35.6) V10 49.3 (47-51.6) V5 64.5 (61.6-67.4)
Sura et al [61]. MSKCC	55	4 years (2001 – 2005)	Inoperable, stage I – IIIB & recurrent NSCLC	IMRT 6MV photons	RT alone: 13 Pre-RT: 29 Concurrent: 13	Median GTV 136cc (4-1060) Median PTV 459cc (63 -1890)
Shi et al [65]. Beijing Cancer Hospital & Institute	94	(May 2005 – Sept 2006)	IIIA, IIIB - NSCLC	IMRT (all)	Induction: 73 concurrent: all	MLD 11.59 (6.53-18.11)
Uyterlinde et al [67]. The Netherlands Cancer Institute, Amsterdam.	153	2008 – 2010	IIIA, IIIB – 88.2%	4DCT & IMRT	Concurrent – 66.7%-full course.	
Chen et al [68]. The Netherlands Cancer Institute, Amsterdam.	171	2008 – 2011	IIIA, IIIB - 90%	4DCT & IMRT	Concurrent – 71.9%-full course.	

Table 4: Retrospective clinical Series (Toxicity and Outcome).

Author	Number of patients receiving IMRT	Oesophageal Toxicity(=/> Grade 3 toxicity)	Pulmonary Toxicity(=/> Grade 3 toxicity)	Median follow-up(survivors)	Local control and Survival indices
Jiang et al [64]. Update from the MDACC	165	Acute: 29 patients (18%) Stricture: 4 patients	11% at 6 months 14% at 12 months1 patient - fibrosis	31 months (16.5 months forall patients)	1.8 years Median survival Local control 57 % at 2 years and 41 % at 3 years (LRFS) Overall survival 46 % at 2 years and 30 % at 3 years (O.S)
Govaert, 2012 [62]. Nijmegen Medical Institute	86	Nil	Nil	17 months (12 months for all patients)	29.7 months Median survival (for patients who received full dose) Overall survival 71 % at 1 year and 56 % at 2 years (O.S) (for patients who receivedfull dose)
Liao et al [63].MDACC	91	2 (6%) (Grade 3: 1, Grade 4: 1)	Nil	8 months	Median survival 13 months Overall survival 56% at 12 months
Sura et al [61].MSKCC	55	Early: 2 (4%) Late: 0	Early: 6 (11%) Late: 2 (1 with grade-5)	26 months	Median survival 25 months Local control Stage I/II: 50% Stage III: 58% Overall survival 57 % at 2 years
Shi et al [65]. Beijing Cancer Hospital & Institute	94		6 (6.4%) - grade 3 2 (2.1%) - grade 4 3 (3.2%) - grade 5	10.5 months	

Uyterlinde et al[67]. The Netherlands Cancer Institute, Amsterdam.	153	Early: 20% Grade 3		23 Months	
Chen et al [68]. The Netherlands Cancer Institute, Amsterdam.	171	Late: 18.71% Grade 3			

Prospective Clinical Trials

A prospective randomised phase III study with two-by-two factorial design involving 544 patients from 185 institutions compared standard dose (60Gy) versus high dose (74Gy) conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage III NSCLC. The planned interim analysis showed no advantage but possible detriment from high dose radiotherapy with more treatment-related deaths and more severe toxicity. The exact reasons for this are unclear, but possible explanations by the investigators are extended treatment duration, higher doses of radiation to the heart, compliance in the high dose group and uncertain cause of death; IMRT was used for planning and treatment in under half of the patients in both arms (46% and 47%) [49].

Interestingly, the percentage of heart volume receiving 5Gy (V5) and V30 were found to be important predictors of overall survival on both univariate and multivariate analyses and were recognised as predictors of patient death. The trial protocol suggested non-binding dose-volume guidelines for the heart. Therefore, when trying to limit radiation exposure to normal lung, the heart volume probably received greater doses of radiation therapy. Specific heart toxicity outcomes in this trial were not tracked. Variability in heart contouring was also noted within the submitted plans and secondary analysis is planned to assess heart dose-volume effects on overall survival after re-contouring heart structures (pericardium, atria and ventricles). Future lung cancer trials through RTOG will include heart dose-volume limitations [49].

Quality of life analysis of the RTOG 0617 trial showed significantly worse quality of life on the high dose arm (74Gy) at 3 months. The reported decline in quality of life was significantly lower with the use of IMRT (versus three-dimensional), suggesting that improved radiotherapy treatment techniques may help to enhance the therapeutic window for these patients [70].

Seventy-nine patients with NSCLC were enrolled in another prospective single-institution phase I trial of dose-escalated hypofractionated radiotherapy without concurrent chemotherapy [71]. These patients were staged using positron emission tomography-computed tomography, planned using 4DCT

and treated using helical tomotherapy. Total radiotherapy doses ranged from 57 to 85.5Gy in 25 daily fractions over 5 weeks using IMRT. The maximum tolerated dose was defined as the maximum dose with 20% risk of severe toxicity and was identified as 63.25Gy in 25 fractions. No grade 3 pneumonitis was reported. However, with a longer follow-up period, grade 4-5 toxicity occurred in six patients and was correlated with total dose (P = 0.004). Late grade 4-5 toxicities were attributable to damage to central and peri-hilar structures and correlated with dose to the proximal bronchial tree [71].

Discussion

Despite the absence of randomised controlled trials in NSCLC comparing IMRT with 3DCRT, it has been widely accepted in routine practice in many centres around the world.

Comparison of the experience with IMRT with large randomised clinical trials from the pre-IMRT era is difficult for several reasons [63]. First, modern diagnostic and staging investigations, such as the routine use of positron emission tomography, in the more recent IMRT series may potentially cause stage-migration in some patients, making comparisons difficult. Second, variability of dose algorithms for heterogeneity correction may affect how doses of radiation to the tumour and normal tissues are calculated [63]. Third, the use of 4DCT (respiration-correlated scans) for planning has led to a major shift in treatment planning and dosimetry. Fourth, patients may receive systemic therapy either as induction (sequential) or concurrent chemotherapy or on relapse, thereby confounding the outcome data. Lastly, early identification and better management of toxicity from treatment may also have an effect on outcome [63].

The real benefit from IMRT lung is therefore difficult to quantify as there are few published completed prospective randomised clinical trials using this technique. Guidelines published by the IMRT indications expert panel from Canada have identified situations where IMRT for lung cancer seems to be of particular benefit [41]. They include: tumour in close proximity to OAR, target

volumes such that fields (portals) probably include a large volume of lung and where dose escalation is attempted without an increase in normal tissue toxicity. They further suggest caution with radiation doses to the normal lung, as V20 may be improved at the expense of an increase in V5 or V10, as the integral dose remains constant and is merely deposited elsewhere. Bezjak et al. [41] recommended a maximum V10 of 50% and V5 of 65% with a caution that lower dose spillage must be monitored. However, these recommendations are not supported by high level evidence.

A recent review suggested minimum requirements for the safe delivery of IMRT for lung cancer [30]. This review discussed the advantages and disadvantages from IMRT in the setting of the additional experience, training and resources needed to account for the additional complexity of treatment planning and quality assurance. Among other requirements, they listed a 4DCT planning scan, a type B algorithm for dose calculation and cone beam computed tomography verification. A risk assessment of interplay effects from the IMRT technique and fractionation used was also deemed necessary before setting up the IMRT service. The quality assurance for the technique should include a dedicated machine IMRT quality assurance program and a patient-specific IMRT quality assurance program including independent monitor unit verification [30]. The need for increased contouring and planning time, and rigorous quality assurance will probably affect the resources of the radiotherapy department [30]. Although, published data on this in the setting of locally advanced lung cancer are scarce, treatment times will probably be shorter, leading to greater treatment machine availability with VMAT, when compared with tomotherapy or IMRT [30,72,73].

Quite a few trials involving IMRT for lung cancer are in progress. The results of the ongoing National Cancer Institute trials on chemoradiotherapy using IMRT for lung cancer (such as NCT01166204, NCT01266512, NCT01166191) are eagerly awaited. NCT00921739 is looking at organ-sparing with IMRT for locally advanced thoracic malignancies. Other trials are looking at isotoxic IMRT with dose escalation (NCT01836692), positron emission tomography-

guided boost (NCT01024829) or positron emission tomography-guided adaptive radiotherapy (NCT01507428).

With the available current advances in technology there could be a tendency of incentivising technically complex and resource intensive radiotherapy. The above review highlights and addresses the implications on the routine use of IMRT in lung cancers. It has been shown that IMRT may enable radical radiotherapy, with limited and manageable toxicity, in patients where previously only high dose palliative radiotherapy was possible. Usually, in these cases either the tumour is close to an OAR or the target volumes are very large. In these situations, IMRT should be used in patients with a good performance status. IMRT treatment must be preceded by a well thought out and written protocol, which must conform to specific dose constraints for OARs and PTV coverage. All new centres starting IMRT for lung cancers should therefore audit their safety and outcome data to ensure effective and safe radiotherapy.

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Appendix 2

Actual gains in dosimetry and treatment delivery efficiency from volumetric modulated arc radiotherapy for inoperable, locally advanced lung cancer over five-field forward-planned intensity-modulated radiotherapy

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Abstract

Aims: Volumetric modulated arc radiotherapy (VMAT) is used for inoperable, locally advanced non-small cell lung cancer, where three-dimensional conformal radiotherapy (3D-CRT) cannot yield an acceptable plan.

Methods: The planning and treatment data were prospectively collected on the first 18 patients treated using VMAT plans. We analyzed the actual dosimetric gain and impact on treatment, compared with complex multisegment 3D-CRT (five-field forward-planned intensity-modulated radiotherapy [IMRT]) that were generated for treatment. Proportion of planning target volume (PTV) receiving 95% dose (PTV-V95%) conformity index (CI), conformity number (CN), dose homogeneity index (DHI), monitor units (MUs), and treatment time were also analyzed.

Results: The PTV coverage (PTV-V95%) was improved from a median of 91.41% for 5-F forward-IMRT to 98.25% for VMAT ($P < 0.001$). The CI improved with a mean of 1.12 for VMAT and 1.31 for 5-F forward-IMRT ($P < 0.001$). The mean DHI improved from 1.15 for forward-IMRT to 1.08 for VMAT ($P < 0.001$). The mean CN improved from 0.62 for forward-IMRT to 0.87 for VMAT ($P < 0.001$). No significant increase in the low-dose bath (V5, V10 and mean lung dose) to the lung was seen. Significantly higher number of MUs ($P < 0.001$) and shorter treatment delivery times ($P = 0.03$) were seen with VMAT.

Conclusion: VMAT resulted in improvement in target volume coverage, demonstrated by PTV-V95%, CI, CN, and DHI, without any increase in the low-dose bath to the lung. For conventional fractionation, VMAT requires more MUs ($P < 0.001$) but has a shorter treatment delivery time ($P = 0.03$) per fraction.

Introduction

Lung cancer is a leading cause of cancer death across the world [1-3]. A majority of patients with non-small cell lung cancer (NSCLC) in India present with locally advanced (Stage IIIb; AJCC Cancer Staging Manual, 7th Edition, 2010) and metastatic (Stage IV) disease [4-6]. Radical radiotherapy combined with chemotherapy given with curative intent is the primary treatment option for most patients with Stage III disease; however, the survival remains poor with a 3-year survival rate of 24% [7]. The radiotherapy strategies that aim to improve local control and survival of these patients with inoperable, locally advanced NSCLC include dose escalation, altered fractionation, individualized radiotherapy administration, and advanced modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT) [8,9].

IMRT is well established as an advanced form of highly conformal radiotherapy (CRT) where the intensity of the beam is varied across its profile. This allows carefully sculpted dose distributions and steeper dose gradients with narrower margins than previously possible. VMAT is based on a similar inverse planning process but allows continuous delivery of radiation in a moving arc by simultaneously varying the gantry rotation speed, positions of the multileaf collimator (MLC), and dose rate. VMAT is increasingly being used because of shorter treatment times [10-12]. IMRT or VMAT has been shown to decrease the dose to the spinal cord and normal lung tissue and to improve tumor coverage [13-17]. The proportion of whole lung excluding planning target volume (PTV) (whole lung volume − PTV) receiving a dose of at least 20Gy (V20) expressed as percentage and the mean lung dose (MLD) expressed in Gy are established predictors of lung toxicity, and it is aimed to keep them below 32%–35% and 20Gy, respectively [18-20]. In locally advanced disease, the dose constraints to organs at risk (OAR) may be impossible to meet with adequate PTV coverage using with three-dimensional CRT (3D-CRT) planning, and until recently many of these patients often received palliative radiotherapy [17-21].

Numerous retrospective series have been published showing improved local control rates with IMRT for NSCLC [22-25]. We had reviewed the published evidence including various guidelines, recommendations, and reports for the practice and documentation of IMRT pertaining to lung cancer, before implementing this practice at our centre [26-30].

The current study is not a typical planning study but aims to review our initial planning and treatment experience with patients with inoperable, locally advanced NSCLC. These patients were planned with multisegment 3D-CRT (five-field forward-planned IMRT), which was routine for NSCLC with large tumor volumes or complex shapes, before deciding that VMAT plans were necessary. This was because it provided better PTV coverage while maintaining satisfactory OAR constraints. We also describe the planning methods used and analyse the actual dosimetric gain and the impact on treatment efficiency from VMAT compared to five-field forward-IMRT.

Methods

Patient selection

The first 18 patients with inoperable, locally advanced NSCLC, who were treated with VMAT at our centre, were included in this prospectively planned study. They were treated with VMAT plans from March 2012 to May 2014. These patients were initially planned using 3D-CRT and found to be unsuitable for a radical dose of radiotherapy, based on established dose constraints to the OARs and PTV coverage parameters. Our standard practice was to create a 3D-conformal plan using three or four fields. If the dose volume parameters for tumor coverage were not met or OAR dose was too high, a forward-planned multisegment five-field plan was generated. In all of the patients, multisegment 3D-CRT using five-field and numerous subfields were attempted multiple times (ranging from 3 to 6 times) before a decision was made in favour of a VMAT plan. The most optimal forward-IMRT plan (after review by a radiation oncologist and a physicist) was selected for each patient, prior to attempting a

VMAT plan. Therefore, this was not a typical planning study where alternative plans are created in hindsight for academic comparison.

Treatment planning

Standard (helical) and slow (axial) computed tomography (CT) scans were acquired in quick succession, with the patient lying in treatment position at the same sitting. The gross tumor volume was delineated on the slow scan to obtain the tumor encompassing volume including the entire motion envelope to yield the internal target volume (ITV). Information from staging positron emission tomography (PET) using fluorodeoxyglucose was used to inform and help tumor and involved lymph node (or ITV) delineation. However, the PET images were not fused with planning images or directly used for planning. The clinical target volume (CTV) was obtained by a margin of 5 mm for subclinical extension, around the ITV, where appropriate. The PTV was defined by a margin of 1 cm around the CTV and 1.3 cm in the craniocaudal direction to account for organ and tumor motion and setup errors. The CTV and PTV margins were decided as per the European Organization for Research and Treatment of Cancer guidelines [19,20]. The spinal cord and lung were outlined as OARs, and esophagus and heart were contoured for dose evaluation purposes. The aim of planning was to ensure that the PTV received coverage of 95%–107% for a prescribed dose of 60Gy in 30 fractions. A satisfactory target volume (TV) coverage for treatment was defined as V95% of ≥95% (95% of the PTV should receive a dose equal to or higher than 95% of the prescription dose) and a V107% of 1 cc or less (a maximum of 1 cc of the PTV should receive a dose >107% of the prescribed dose). Our dose criteria for OARs are summarized in Table 1.

Table 1: Dose constraints for organs at risk

Organ	Dose-volume parameter		Reference
Lung	V20	<35%	[17-19]
	V10	<50%	Locally agreed practice
	V5	<70%	[30]
	Mean	<18 Gy	[18,19]
Spinal cord	Maximum	50 Gy	[18,19]
		48 Gy	Locally agreed practice

The eclipse treatment planning system (version 10.0.42, Varian Medical Systems, Palo Alto, CA, USA) was used to generate all the plans. The typical planning process used for forward-IMRT and for VMAT for lung cancers used by the authors has been described in an earlier publication [30]. Identical planning objectives and dose constraints for OAR were used for both types of plans.

The multisegment 3D-CRT (forward-IMRT) plans comprised 5 beam angles were optimized according to target localization. Most of the beams were made to enter through the ipsilateral lung, and off-cord beam arrangements were used wherever possible. With this technique, the 5 beams were used with varying gantry angles, differential weighting, and different apertures shaped with high-definition MLC. Thirty-two pairs of MLC used had a thickness of 2.5 mm, and the remaining 28 pairs had a thickness of 5 mm. The MLC were set to cover at least 5 mm more than the PTV margins. The plans were normalized at the isocentre, which was placed in the tumor region of the PTV, avoiding bone, or air cavity. The multisegment plan was achieved by manually adding subfields with various weights and evaluating the dose distribution. In each nonautomated iteration of the process, the planner introduced changes to revise the plan, producing multiple subfields. Each multisegment 3D-CRT plan had an average of about ten subfields, and the minimum number of monitor units (MUs) for each subfield was 4. The plans were optimized to meet the

dose constraints for the TVs and the OAR. A 3D dose matrix was computed with 3D treatment planning software. With fixed dose rate, energy, and fixed subfield size in the treatment machine, the MUs were calculated. The final dose calculations were performed using an analytic anisotropic algorithm (AAA). The best multisegment five-field forward-IMRT plan for each patient that was closest to meeting the target doses and OAR constraints was also identified by the treating radiation oncologist and archived on our system. A comparative analysis was carried out between the best multisegment 3D-CRT (forward-IMRT) plan that was achieved and the VMAT plan that was actually used to treat the patients as identical planning objectives and dose constraints were used for both types of plans.

For VMAT (RapidArc), the progressive resolution algorithm was used for dose-volume optimization where MLC positions, dose rate (fluence output), and gantry rotation speed are simultaneously optimized in five levels with increasing resolution to fulfil the desired objectives [31]. Multiresolution dose calculation algorithm was used for fast dose estimation during optimization. The final dose calculation was performed using AAA at a grid size of 2.5 mm. Each VMAT plan comprised 2–4 (full or partial) arcs. The full arcs often had skipped angles (arcs restricted by avoidance sectors). The collimator angle, for a VMAT plan, ranged from 20° to 45° in either direction [31].

Data and statistical analysis

To compare the VMAT and multisegment forward-IMRT plans, the dose distributions and the dose-volume histograms were generated and evaluated in accordance with the dose constraints in Table 1. The comparison and analysis were carried out by a physicist, a physician, and a statistician with a focus on TV coverage indices and OAR constraints. Conformity index (CI), conformity number (CN), and dose homogeneity index (DHI) have been computed based on the equations as described in Table 2.

Table 2: Formulae for the indices used for plan quality evaluation

Number/index	Formula	Legend	Reference
Conformity index$_{RTOG}$	V_{RI}/TV	V_{RI} TV	[32,33]
Conformity number	$TV_{RI}/TV \times TV_{RI}/V_{RI}$	TV_{RI} TV V_{RI}	[34,35]
Dose homogeneity index$_{RTOG}$	I_{max}/RI	I_{max} RI	[33,36]

V_{RI}=Volume of the reference isodose; TV=Target volume; TV_{RI}=Target volume covered by the reference isodose; I_{max}=Maximum isodose in the target; RI=Reference isodose; RTOG=Radiation Therapy Oncology Group

The CI was first proposed by the Radiation Therapy Oncology Group (RTOG) in the year 1993 for the evaluation of stereotactic radiotherapy plans and was also described in report 62 of the International Commission on Radiation Units and Measurements (ICRU) [32-34,37]. It is defined as the ratio of the volume delineated by the reference isodose (RI) and the TV. This RI is defined by the RTOG as the prescription isodose. A CI equal to 1 would represent absolute conformation. With traditional 3D-CRT, the CI of between 1 and 2 is considered satisfactory [35-37]. However, the CI as defined by RTOG, although widely used in studies, fails to account for the degree of spatial intersection of the two volumes. It is possible to have a CI of 1 while the PTV and prescribed isodose volume, although measured to be equal, are separated from each other. As this is merely a ratio of two different volumes, it must be combined with visual assessment of the entire treatment plan including dosimetry and dose-volume histograms [34].

However, the CN is a product of two ratios, where the first ratio defines the quality of coverage of the TV and the second ratio defines the volume of healthy normal tissue covered by the prescription isodose (i.e. receiving a dose greater than or equal to the prescribed dose). This number (CN) takes into

account the irradiation of both TV as well as the delineated normal tissues. This number ranges from 0 to 1, where 1 represents the ideal situation [34,35].

Duration of time taken by planners for each of these plans was not recorded prospectively, and therefore could not be analyzed. The MUs and beam-on times were computed and compared. The treatment delivery time of the multisegment 3D-CRT plans was obtained by treatment delivery to a phantom and was compared with treatment delivery time for VMAT obtained from the actual radiotherapy treatments.

We compared the two different radiotherapy modalities (RapidArc and multisegment forward-IMRT) to see if there was a statistically significant difference for each of the parameters (V-95%, PTV-V95%, DHI, CN, CI, MLD [PTV], V20, V10, V5, max spinal cord dose) between VMAT and multisegment forward-IMRT. As the VMAT plan was used to treat each of these 18 patients and the best forward-IMRT plan achieved was saved for each patient, we have paired data. As the sample size was 18, the two-tailed Wilcoxon signed-rank test was used instead of the paired *t*-test. Differences were reported to be statistically significant at $P \leq 0.05$.

Results

Tumor and lung volume details are presented in Table 3. Each VMAT plan comprised 2–4 arcs with a median beam-on time of about 3 min. The median of the computed beam-on time for the forward-IMRT plans was 2.98 min and for VMAT was 2.62 min. The MU delivered for VMAT plans was significantly higher at 655.0 compared to 286.6 MUs calculated for the forward-IMRT plans ($P < 0.001$).

Table 3: Tumour and lung volume characteristics

Description	Mean	Range
PTV (ml)	850.17	350-2230
Cranio-caudal extent of PTV (cm)	13.68	7.75-19.5
Whole lung volume (ml)	2972.9	1587.4-4065
Ratio of PTV: Whole lung Volume	0.293	0.15-0.59

PTV= planning target volume

Planning target volume coverage

The total volume of tissue receiving >95% of the prescribed dose (within the 95% isodose lines) was significantly higher for forward-IMRT with a median value of 1044 cc compared to 874.5 cc ($P < 0.001$). The TV coverage (assessed by PTV-V95%) was seen to improve significantly with VMAT as seen in Table 4. The improvement in CN was significant with a mean of 0.87 with VMAT when compared with 0.62 for multisegment 3D-CRT. The CI also showed a significant improvement with VMAT. Figures 1 and 2 illustrate some examples of improvement in tumor coverage and conformity by VMAT from our patient series. As mentioned earlier, this was because the planners and physicists had manually created the most acceptable five-field forward-IMRT plan that could potentially be delivered. This often meant that the safety of the patient (in terms of maximum spinal cord doses and lung doses) was weighted more important than better target coverage for large- or complex-shaped tumors, examples are seen in Figures 1 and 2. The dose distribution was also found to be better with VMAT with less heterogeneity within the TV as evaluated using DHI. The median DHI improved from 1.15 for forward-IMRT to 1.08 for VMAT.

Table 4: Analysis of comparison of volumetric modulated arc radiotherapy with five field multisegment forward intensity modulated radiotherapy

	VMAT		Multisegment forward IMRT		P
	Mean	**Med (range)**	**Mean**	**Med (range)**	
V5% lung	63.39	63.81 (30.18-91.5)	57.98	61.3 (25.8–86.72)	0.37
V10% lung	42.29	44.70 (21.72–72.17)	43.25	41.95 (18.06–69.82)	0.83
V20% lung	24.29	25.39 (9.11–33.81)	24.79	23.44 (8.6–44.04)	0.86
Mean lung dose (Gy)	17.99	17.92 (8.9–26.31)	19.02	19.55 (8.82–28.22)	0.55
Maximum spinal cord dose (Gy)	41.02	42.37 (27.4–45.51)	43.89	43.81 (18.71–61.61)	0.26
Maximum spinal cord PRV dose (Gy)	45.08	45.61 (30.12–49.26)	45.90	45.72 (20.31–62.07)	0.74
V95% (cc)	948.62	874.49 (400.36–2174.00)	1177.39	1044.05 (491.90–2686.80)	<0.001*
PTV V95%	97.87	98.25 (93.45–99.91)	92.15	91.41 (82.9–98.89)	<0.001*
Conformity index	1.12	1.12 (0.97–1.24)	1.31	1.20 (1.00–2.28)	0.028*
Conformality number	0.87	0.88 (0.78–0.92)	0.62	0.64 (0.43–0.75)	<0.001*
Dose homogeneity index	1.08	1.07 (1.05–1.18)	1.15	1.13 (1.06–1.37)	<0.001*
Treatment delivery time	4.17	4.0 (3.00–7.00)	5.54	6.11 (3.30–8.41)	0.03*
Beam on time	3.06	2.98 (1.55–4.95)	3.00	2.62 (1.54–4.84)	0.04*
Monitor units	638	655 (403–967)	286.61	275.5 (235–446)	<0.001*

*Statistically significant. PTV=Planning target volume; VMAT=Volumetric modulated arc radiotherapy; IMRT=Intensity modulated radiotherapy; PRV=Planning at risk volume; V95%=Volume within 95% isodose; PTV V95%=Volume of PTV within 95% isodose

Figure 1: Better TV and tumour coverage in the second (VMAT) plan; suboptimal coverage of the TV to meet the dose constraints for the spinal canal in the first plan

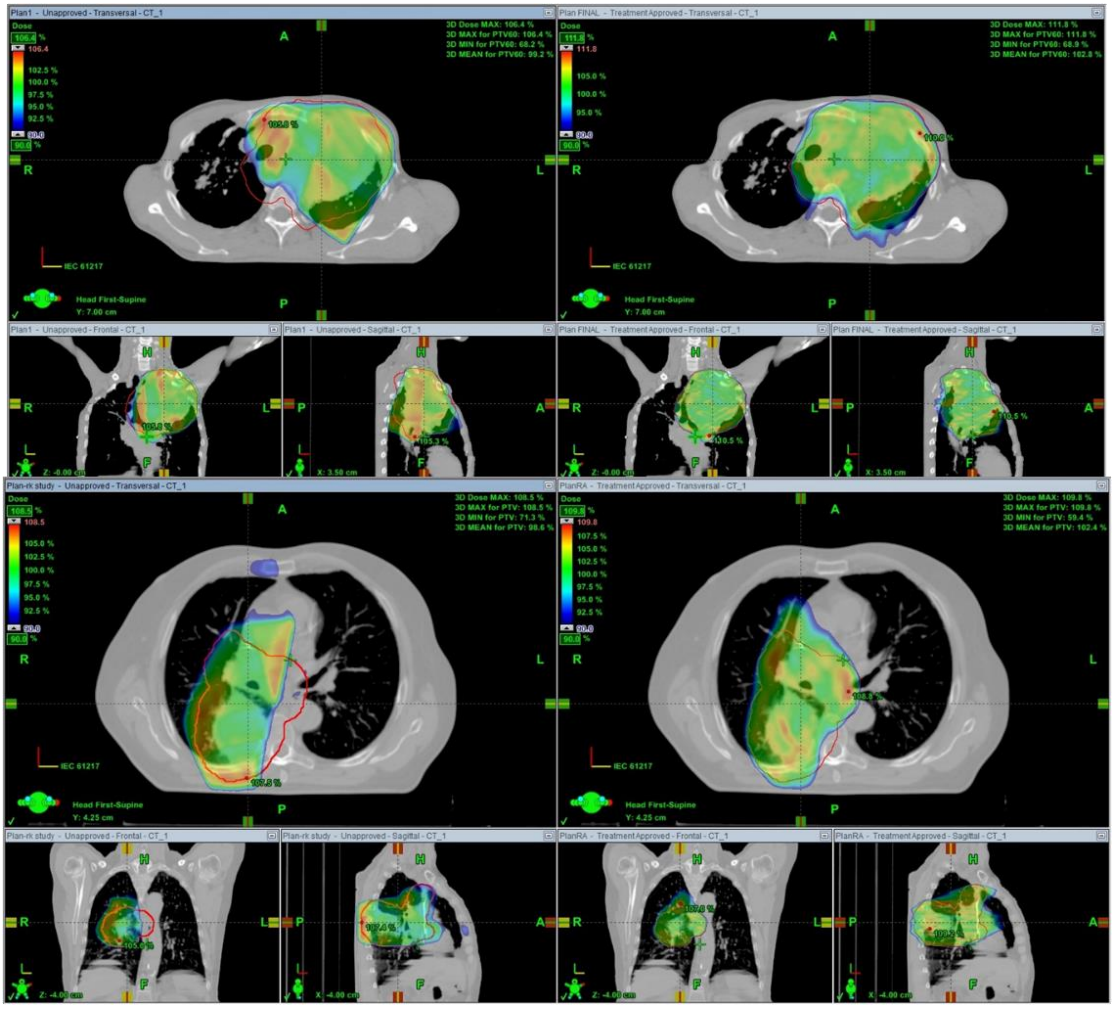
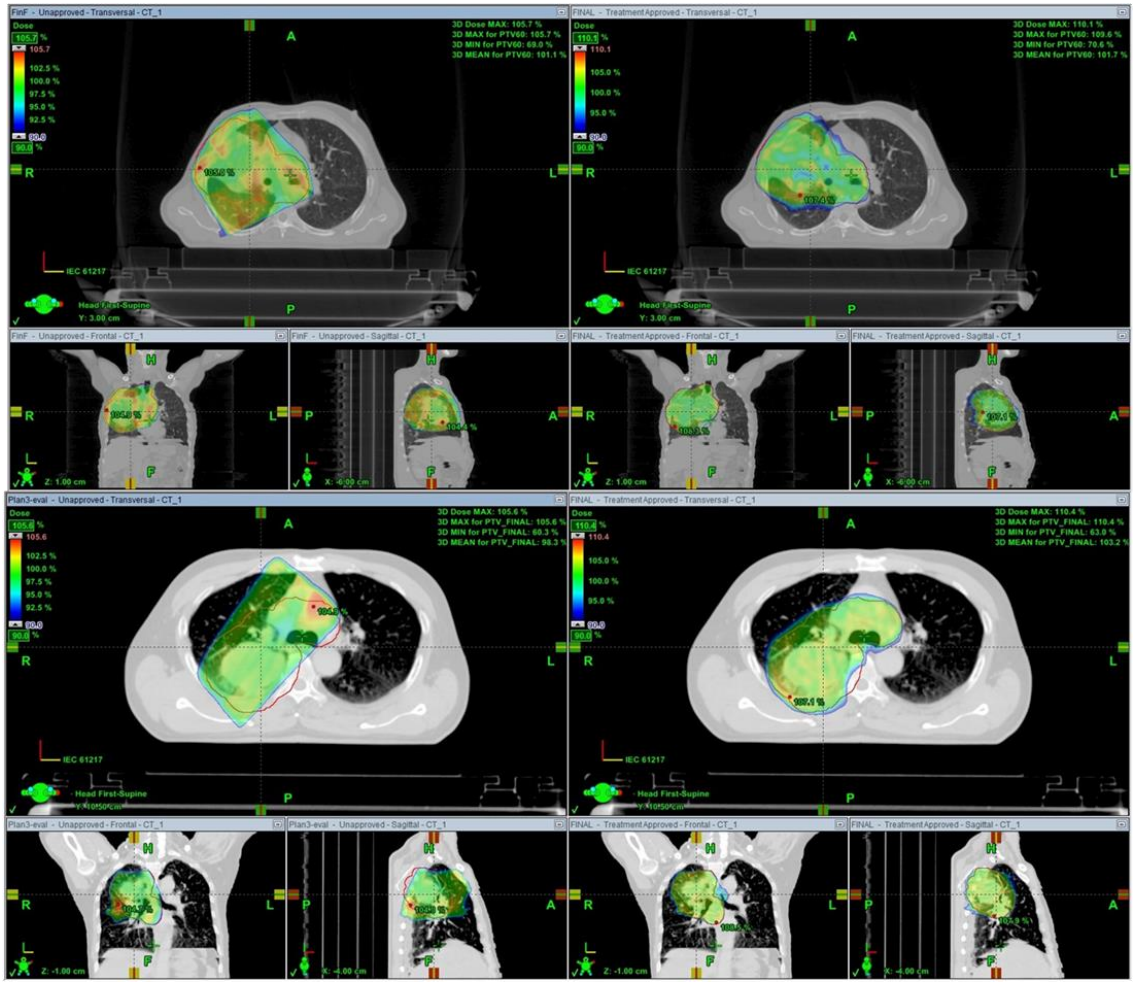


Figure 2: Better conformity in the second (VMAT) plan; poorly conforming high dose volume treating much more normal tissue outside the planning target volume in the first plan



Organs at risk sparing

The VMAT plan satisfied the OARs constraints by improving the mean of the MLD and mean of the maximum spinal cord dose, while maintaining satisfactory PTV coverage and made radical radiotherapy with curative intent possible. The outcome of the analysis between the two different types of radiotherapy plans is displayed in Table 4. A statistically significant difference was seen for CI, CN, DHI, MU, beam-on time, and total treatment time between the VMAT and the forward-IMRT group as displayed in Table 4. For other parameters, the difference between the groups was statistically not significant. The worsening in these lung dose parameters was also statistically not significant.

Discussion

On comparison with five-field forward-IMRT, VMAT was shown to improve the TV coverage in the current study, without any worsening of the doses to the relevant normal tissues. In addition, VMAT was associated with a nonsignificant trend toward improvement in the MLD and maximum spinal cord dose, and a slight worsening in V10 and V5, which was not unexpected and other reported studies have shown similar results [14,15]. The CI and the CN were found to be significantly improved. The DHI was not a major endpoint for our analysis but was computed to see if there was any significant impact on this as a result of using VMAT. The DHI was shown to have improved significantly with VMAT compared to the forward-IMRT plans ($P < 0.001$).

Numerous planning studies have reported the dosimetric benefits of IMRT and VMAT when compared to 3D-CRT [13-17]. Previous planning studies have shown improvement in V20 from IMRT ranging from 8% to 15% over 3D-CRT [14-16]. However, in our study, the improvement in OARs dosimetry is not statistically or clinically significant for the reasons described below. Retrospective clinical series for NSCLC have been reported to show improved local control rates with IMRT [22-25].

The current study is important because it is based on prospective data from planning, plan evaluation, and clinical decision-making. The TVs in this study were large and had complex shapes in these patients with Stage III NSCLC. For these more advanced cases (N2 and N3 disease), our starting default solution is a manually created multisegment five-field forward-IMRT, conformed using MLC. It was retrospectively discovered that the PTV coverage was typically compromised by the planners and physicists in the forward-IMRT plans to ensure that the normal lung doses and maximum spinal cord doses were kept within the acceptable range [Figures 1 and 2]. At the time of planning, they believed that these plans would be used for treating these patients; therefore, the dose constraints for spinal cord and normal lung were strictly adhered to.

For VMAT planning, we made use of both partial arcs and/ or full arcs with or without skipped angles (arcs restricted by avoidance sectors) for optimal lung sparing using the method previously described as restricted modular arcs by Rosca *et al* [38]. The planned MUs for treatment delivery have been shown to be fewer with VMAT when compared with static IMRT [11,39,40]. However, as in the current study, it may be greater when VMAT plans are compared with complex 3D-CRT (or forward-IMRT). Overall time on the treatment couch has also been reported to be shorter with VMAT (mostly reported in other tumor sites) when compared with static IMRT [11,39], although the beam-on time may be longer as seen in locally advanced lung cancer setting in the current study.

VMAT planning algorithms depend on delineation of TVs (including PTV) and OARs to create a plan with the best combination of accurately conformed beams. The planning and dosimetry software provides the dose-distribution on each axial slice of the CT volume but does not indicate or quantify the TV coverage or the conformity of the entire plan. Two-dimensional radiotherapy and 3D-CRT plans are often evaluated by visual analysis of dosimetry on each axial slice of the CT planning scan dataset. However, overall understanding of more complex plans such as IMRT/VMAT makes dose-volume histograms

essential as a detailed comparison between several plans to choose the most desired plan may be difficult [34].

As the ITV was delineated on a slow CT scan to obtain the tumor encompassing volume including the entire motion envelope, the impact of interplay due to tumor motion should be fairly small. Several studies have shown that the dosimetric impact of interplay in conventionally fractionated (with 30 fractions or more) IMRT treatment was <1% as the effects of interplay are probably blurred or “washed out” [41-43]. The challenges and benefits of IMRT for lung cancer have been discussed by the authors in an earlier publication [30].

VMAT allows more patients to receive radical doses of radiotherapy in patients with lung cancer, with good PTV coverage. The TV coverage indices (PTV-V95%, CI, and CN) are important geometric parameters, although it is yet to be seen whether they are associated with local disease control or survival. Further studies are required to assess the impact of VMAT on toxicity, local control, and survival and to correlate with these indices, in patients with inoperable, locally advanced lung cancer.

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Appendix 3

Continuous hyperfractionated accelerated radiotherapy using modern radiotherapy techniques for non-small cell lung cancer patients unsuitable for chemoradiation

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Abstract

Introduction: The continuous hyperfractionated and accelerated radiotherapy (CHART) regimen of radiotherapy (RT) for non-small cell lung cancer is underused outside the UK. We present the first Indian experience of using CHART for patients, who were not suitable for chemotherapy or concurrent chemo-RT.

Methods: We retrospectively reviewed the data of patients treated using CHART at our institution between January 2014 and December 2015.

Results: Thirty-seven patients were treated using CHART. Planning methods and dosimetry parameters are described. Three-dimensional conformal RT was used for treatment planning and delivery in 23 patients and volumetric modulated arc RT was necessary for 14 patients. Patients in our series had a median age of 70 years (interquartile range 65.50–74.00) and 86.5% had Stage III disease. Median follow-up was short at 13.0 months. Actuarial rates of 1-year progression-free survival, 1-year overall survival (OS), and 2-year OS were 31.9%, 59.5%, and 28.5%, respectively. This treatment was well tolerated with manageable and some reversible acute esophageal toxicity (91.9% <Grade 3); (Common Terminology Criteria for Adverse Events version 4.03).

Conclusion: Our results indicate that CHART is feasible, safe, and well tolerated in Indian patients who are clinically found to be not suitable for either sequential or concurrent chemo- RT.

Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer death in the world [1,2]. Radical radiotherapy (RT) with curative intent is commonly used for inoperable patients (Stage: I–III) with NSCLC. The reported long-term survival rate is 15% in 5 years [2]. The typical radical RT schedule delivers 60Gy in 30 fractions, over 6 weeks, using 2-Gy fractions daily [3]. Concurrent chemo-RT is widely used for inoperable Stage II and III NSCLC [4].

Lung cancer cells undergo rapid proliferation with short doubling and repopulation during prolonged RT is well recognized. Hence, it is more efficacious to complete radiation within the shortest possible overall treatment time than conventional or prolonged fractionation [5-10]. A recent meta-analysis of lung RT schedules included data from 2685 patients from 10 randomized studies from 1970 to 2005. Of 2000 patients with NSCLC, at a median follow-up of 6.9 years, 1849 had died. The hazard ratio from altered fractionation schedules was 0.88 (95% confidence interval [CI]: 0.80–0.97), with reduction in the risk of death by 12% [11].

The continuous hyperfractionated and accelerated RT (CHART) regimen of RT, delivering 54Gy in 36 fractions of 1.5Gy/fraction delivered thrice daily (at least 6h apart) over 12 consecutive days, has provided strong evidence from a randomized trial that reducing tumor repopulation by shortening the overall treatment time results in improved local control rates and survival in NSCLC [7,8]. The CHART trial reported a 9% improvement in 2-year survival (29% vs. 20%, P = 0.004) [7]. The reduction in the relative risk of local progression was 21% (P = 0.033). Acute esophageal morbidity was higher, but no significant difference was reported in long-term toxicity [7]. More mature data confirmed the benefits and established that CHART was superior to conventional radical RT in inoperable NSCLC [8]. The CHART trial has not resulted in widespread change in practice because of logistical issues such as hospitalization and weekend treatment [9,12,13]. In addition, national holidays and planned machine maintenance can limit the number of weekends available for treatment. Compounding this was clinical concerns about acute mucosal side

effects, micrometastases, and distant failure [7,12,14]. Besides, radical RT was already evolving into combined modality treatment with platinum-based chemotherapy and conventional radical RT and CHART had not been compared with chemo-RT in the original study [9,13]. Therefore, in the UK, CHART is currently the recommended standard only when patients are prescribed radical RT alone (guidance.nice.org.uk/cg121) [15].

The recent Radiation Therapy Oncology Group (RTOG) 0617 study showed no benefit in improving outcomes from dose escalation using a longer treatment schedule [16]. With the evidence in favor of accelerated RT, there have been efforts to improve local control and survival in this setting of accelerated RT by intensification of treatment like addition of chemotherapy or dose escalation [9,11,12]. Recent CHART trials including MRC-INCH (using induction chemotherapy before CHART) and CHART-escalated dose (CHART-ED) have also used three-dimensional conformal radiation therapy (3D-CRT) but not volumetric modulated arc therapy (VMAT) for delivering RT. CHART-ED, a Phase I trial of intensifying CHART using dose escalation has been published recently [17]. CHART-ED was proposed as one of the dose escalation arms in ADSCaN trial [13,17]. CHART has also been combined with chemotherapy with better response rates, but reports of toxicity-related deaths have hindered progress [18,19]. Phase III randomized trials using induction chemotherapy combined with accelerated hyperfractionated RT failed to recruit the required number of patients [20,21]. Modern RT techniques (such as 3D-CRT, intensity-modulated RT [IMRT], or VMAT) are necessary toward the greater objective of dose escalation without increasing toxicities.

In our institution, concurrent chemo-RT is the treatment of choice for patients with inoperable, Stage II and III, NSCLC. However, toxicity from chemo-RT can be significant [4]. Patients who decline chemotherapy, or are not fit for chemotherapy (either because of comorbidity or poor general condition), are treated with radical RT alone [15]. It is this group of patients that CHART is used as an effective alternative to conventional RT alone.

The standard approach is 3D-CRT, keeping doses to spinal cord, normal lung, and esophagus as low as possible. With CHART, careful study of the dose-

volume histograms (DVHs) for spinal cord, esophagus, and normal lung are essential. When the target volume coverage or dose constraints to the organs-at-risk (OAR) were difficult or impossible to satisfy using 3D-CRT VMAT was used instead [22]. By applying advanced RT techniques such as VMAT, where necessary, CHART has been extended to patients who would previously not have been candidates for radical RT.

In this article, we present our experience of treating non-Caucasian NSCLC patients using CHART, including a subgroup of patients where VMAT was necessary. No previous comparable literature has been found on this group of patients. Apart from detailing our tumor and dosimetry parameters and early outcome data, we were primarily looking at the feasibility and safety of using CHART in our patient population and of combining CHART with VMAT.

Methods

Thirty-seven patients with confirmed NSCLC, by histology or cytology, received CHART at our hospital, from January 2014 to December 2015. They were deemed unsuitable for concurrent chemoradiation as they had either declined chemotherapy or were not fit for chemotherapy. Of the patients who were older than 70 years and had Eastern Cooperative Oncology Group performance status of 2, 7 patients (19%) declined concurrent chemotherapy. The rest of these patients (81%) were deemed unfit or unsuitable for concurrent chemoradiation, by the lung cancer multidisciplinary tumor board because of comorbidity (often two or more) such as history of poorly controlled angina, myocardial infarction, coronary bypass surgery or angioplasty, previous cerebral stroke, transient ischemic attacks, renal impairment, recent sepsis, debilitating arthritis, and poorly controlled diabetes. The epidemiological data, the response assessments, and the follow-up data were extracted retrospectively from the case records available on the electronic hospital management system. The planning dosimetric details were collected from the archived plan files in the treatment planning system (Eclipse version 10.0.42, Varian Medical Systems, Palo Alto, CA, USA). Considering the retrospective nature of the study, full exemption to consent from the patients

was granted by the Institutional Review Board of Tata Medical Centre (irb@tmckolkata.com).

Patients were staged with a whole-body positron emission tomography using fluorodeoxy glucose-computed tomography (FDG-PET-CT) and a magnetic resonance imaging of the brain. Lung function tests included spirometry and diffusing capacity of the lungs for carbon monoxide.

Treatment planning

Standard (helical) and slow CT scans (axial) were acquired in supine position, in quick succession, in the same sitting. The “slow scan” was an axial CT scan whereby the couch moved for the preset slice thickness and images were acquired and so on, for the entire volume of interest. The standard settings used at our centre aim to acquire axial slices of 2.5 mm thickness at a rate of four images per gantry rotation. Images of the tumor acquired during a slow CT scan approximate an internal target volume (summation of gross tumor volume [GTV] in all the phases of a respiratory cycle). Slow CT scanning is often used as a surrogate for 4D CT scan [23]. The GTV comprised the primary tumor and involved lymph nodes delineated on the helical scan. Information from staging FDG-PET was used in GTV delineation and the slow scan was used to obtain the volume including the entire motion envelope. The clinical target volume (CTV) was obtained using a margin of 5 mm around GTV. The planning target volume (PTV) was defined using a margin of 1 cm around the CTV and 1.3 cm in the craniocaudal direction. The craniocaudal margin was larger to account for the greater uncertainty due to respiratory motion in this direction. The spinal cord as visualized by the bony canal limits in all slices of the scan, and bilateral lungs were outlined as OAR. The esophagus (outer margin as visualized from the cricopharynx to the gastroesophageal junction) and heart (defined by the pericardial sac from the superior aspect of pulmonary artery to the inferior most clearly visible section) were contoured for dose evaluation.

A 3D-CRT plan was generated for all patients and the use of VMAT was decided on a case-by-case basis by the clinical oncologist and medical physicist, where they felt the 3D-CRT plan was not satisfying the dose-volume criteria for either the PTV or OARs [22-24]. This was usually because of large disease volume such as mediastinal node-positive peripheral tumor or involvement of contralateral lymph nodes (N3 disease) or challenging tumor positions such as tumors close to the spinal cord [25]. Of the 14 patients treated using VMAT in the current series, 8 had Stage IIIb (either N3 or T4 N2) lung cancer and 5 patients were staged as IIIa (often multi-station N2 nodes). They had bulky tumors resulting in significantly larger target volumes, with a mean PTV of 892.83 cc compared with 611.05 cc for patients treated using 3D-CRT ($P = 0.046$). Specific reasons for choosing VMAT for individual patients were not prospectively recorded at the time of planning.

The plans aimed to achieve PTV coverage of 95%–107% of the prescribed dose. Our dose criteria for OARs are summarized in Table 1. The Eclipse treatment planning system (version 10.0.42, Varian Medical Systems, Palo Alto, CA, USA) was used to generate both the 3D-CRT and VMAT plans. VMAT plans were generated using RapidArc (Varian Medical Systems, Palo Alto, CA, USA) which manipulates dynamic multileaf collimators, dose rate, and gantry positions to produce precise dose distributions. Our planning techniques for lung cancer using 3D-CRT and VMAT have been described in our earlier publication [22]. Every patient had a backup plan generated for tomotherapy, to ensure continuity of treatment in case of unplanned machine downtime. All patients receiving CHART underwent daily verification imaging with cone beam CT (CBCT) for at least 1 fraction and kV (electronic portal imaging devices) for the remaining 2 fractions. CBCT was restricted to 1 fraction/day to minimize radiation exposure and workload. Subgroup analyses have been carried out comparing the VMAT group and 3D-CRT group, comparing tumor parameters, dose-volume parameters, and acute toxicity.

All patients were admitted through the course of the treatment. All patients were then reviewed a week after completion of treatment and then on a

fortnightly basis until 6 weeks after completion of RT. A CT was carried out about 2.5–3 months after treatment to assess response.

Table 1: Dose constraints for continuous hyperfractionated and accelerated radiotherapy planning

Structure	Dose volume parameter
PTV	V95% of the prescribed ≥95%
Spinal canal (surrogate for spinal cord)	Maximum dose must be <44Gy
Whole lung - PTV	V20 must be <35%
	MLD must be <18Gy
Esophagus	V55Gy <50%
	V15Gy <60%
Heart dose	V30 to be <40Gy
	Mean dose to be <26Gy

PTV=Planning target volume; MLD=Mean lung dose

Statistical analysis

Statistical analysis was carried out using the statistical package SPSS version 23 (IBM, Armonk, New York, USA). The disease and treatment data were summarized. Subgroups, based on histology and treatment techniques, within the treated patients were compared using Mann–Whitney U-test, and Fisher's exact tests as appropriate. The survival analyses were performed using the Kaplan–Meier test and the subgroups within were compared using the log-rank test.

Results

The demographic details of the patients, tumor histology, and the clinical stage are detailed in Table 2. The tumor volumes and planning parameters are

detailed in Table 3. VMAT was used for 14 out of 37 patients with Stage III NSCLC. Although PTV size was not the only criterion for deciding in favor of VMAT, the median PTV was found to be significantly larger for patients requiring VMAT compared with patients treated using 3D-CRT (P = 0.046). The parameters for target coverage are detailed in Table 4. The proportion of PTV covered by the 95% dose distribution (PTV-95%) was found to be acceptable overall. There was a trend toward better coverage for the 3D-CRT group (P = 0.066), probably because of smaller PTVs. The indices of quality of coverage, namely, conformity $index_{RTOG}$ (CI_{RTOG} = prescription isodose volume/PTV) and conformity number ($CN = PTV_{PI}^2/PTV \times V_{PI}$, where PTV_{PI} = PTV covered by prescription isodose in cc) were significantly better with VMAT (P < 0.001) [26,27]. There was no difference in homogeneity $index_{RTOG}$ (HI_{RTOG} = maximum dose within PTV/prescription dose) between the VMAT and 3D-CRT groups (P = 0.344), probably because we had used a field-in-field technique for reducing the heterogeneity in dose distributions [26].

Table 2: Demographics

Patient characteristics		**All patients (n=37)**	**3D-CRT (n=23)**	**VMAT (n=14)**
Age, median (IQR)		70 years (65.50–74.00)	71 years (68.00–75.00)	66.5 years (64.75–71.50)
Gender	Male	31	20	11
	Female	6	3	3
Histology	Adenocarcinoma	15	10	5
	Squamous cell carcinoma	22	13	9
Stage	II	5	4	1
	III	32	19	13

3D-CRT=Three-dimensional conformal radiotherapy; VMAT=Volumetric modulated arc radiotherapy; IQR=Interquartile range

Table 3: Tumor volumes and parameters

Tumour volumes and parameters	**All CHART patients**		**3D-CRT patients**		**VMAT patients**		3D-CRT versus VMAT, *P* value, Mann–Whitney U-test
	Mean±SD	**Median (IQR)**	**Mean±SD**	**Median (IQR)**	**Mean±SD**	**Median (IQR)**	
GTV (cc)	174.33±165.1	129.04 (70.52–188.28)	131.39±95.04	118.38 (66.02–151.92)	244.89±227.11	166.75 (87.27–328.57)	0.101
PTV (cc)	717.67±366.63	626.7 (500.82–810.47)	611.05±248.17	621.5 (440.90–719.67)	892.83±738.88	784.99 (587.65–1119.12)	0.046*
PTV maximum length in any dimension (cm)	12.92±2.73	13.1 (11.70–14.42)	12.69±2.77	12.92 (11.42–14.25)	13.31±2.71	13.55 (12.20–14.66)	0.506
PTV craniocaudal length (cm)	12.02±3.20	11.5 (9.88–13.88)	11.86±2.97	11.5 (10.00–13.50)	12.29±3.66	11.9 (9.19–14.69)	0.889
Lung volume (cc)	2736.32±821.24	2474.36 (2219.31–3307.95)	2820.39±872.64	2601.05 (2219.01–3283.60)	2598.2±738.88	2357.05 (2137.65–3480.49)	0.769
PTV: Lung volume ratio	29.14±19.89	23.74 (18.74–31.63)	23.52±10.92	21.42 (16.11–30.17)	38.36±27.31	26.35 (20.16–48.42)	0.107

*Statistical significance. GTV=Gross tumor volume; PTV=Planning target volume; 3D-CRT=Three-dimensional conformal radiotherapy; VMAT=Volumetric modulated arc radiotherapy; SD=Standard deviation; IQR=Interquartile range

Table 4: Target coverage parameters, indices of conformality, and homogeneity

Target coverage characteristics	All CHART		3D-CRT		VMAT		3D-CRT versus VMAT, *P* value, Mann–Whitney U-test
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
PTV V90	98.0±1.61	98.03 (99.65–99.43)	98.26±1.47	98.4 (97.10–99.75)	97.53±1.78	97.65 (96.45–98.88)	0.219
PTV V95	95.68±5.32	97.38 (94.97–99.35)	96.84±4.14	98 (95.67–99.41)	93.77±6.56	95.84 (91.79–99.02)	0.066
PTV D5	103.75±1.35	103.70 (103.19–104.51)	103.65±1.4	103.6 (103.18–104.41)	103.93±1.29	103.96 (103.14–104.99)	0.567
PTV D95	95.92±2.80	96.16 (95.00–97.84)	96.61±1.92	96.76 (95.66–97.92)	94.79±3.63	95.60 (92.70–97.79)	0.175
Ratio of PTV V90: V20	4.48±1.42	3.97 (3.47–5.45)	4.25±1.14	3.77 (3.56–4.69)	4.85±1.78	4.4 (3.11–6.52)	0.429
V95 (volume in cc)	912.12±409.8	865.48 (635.01–1068.08)	905.75±373.12	868.68 (701.13–1083.34)	922.6±478.81	850.09 (574.39–1146.07)	0.793
CI_{RTOG}	1.32±0.31	1.34 (1.08–1.46)	1.49±0.28	1.42 (1.34–1.48)	1.04±0.09	1.05 (0.99–1.11)	<0.001*
CN	0.72±0.13	0.70 (0.65–0.84)	0.64±0.08	0.66 (0.64–0.69)	0.85±0.07	0.88 (0.78–0.89)	<0.001*
HI_{RTOG}	1.1±0.03	1.09 (1.07–1.12)	1.09±0.03	1.09 (1.07–1.11)	1.11±0.04	1.10 (1.07–1.14)	0.344

*Statistical significance. PTV=Planning target volume; 3D-CRT=Three-dimensional conformal radiotherapy; VMAT=Volumetric modulated arc radiotherapy; SD=Standard deviation; IQR=Interquartile range; CN=Conformity number; HI_{RTOG}=Homogeneity $index_{RTOG}$; CI_{RTOG}=Conformity $index_{RTOG}$

The doses to the OARs were found to be acceptable and are detailed in Table 5. The median V5 (proportion of lung receiving at least 5Gy, expressed as percentage) significantly increased from 50.8% to about 59% with the use of VMAT, when compared with the 3D-CRT group (P = 0.039). The maximum esophagus dose (57.3 vs. 55Gy; P = 0.002) and the V55 Gy (4.3% vs. 2.3%; P = 0.012) were significantly higher in the VMAT group when compared to the 3D-CRT group. No significant difference was found between the groups (VMAT and 3D-CRT) for other OAR parameters.

Dysphagia was the major acute toxicity, where 14 patients had Grade 1 and 12 patients had Grade 2 (Common Terminology Criteria for Adverse Events version 4.03) toxicity [28]. The overall breakdown of dysphagia based on 3D-CRT and VMAT patients is detailed in Table 6. Grade 3 dysphagia was seen in three patients, all of who received 3D-CRT. One patient who was treated using 3D-CRT had Grade 2 pneumonitis. None of the VMAT patients had any pneumonitis. There have been no incidence of long-term dysphagia or radiation-induced myelopathy.

Median follow-up is 13 months (inter quartile range – 4.0–20.5 months). Actuarial rate of 1-year progression-free survival (PFS) was 31.9%. Actuarial rates of 1-year and 2-year overall survival (OS) were 59.5% and 28.5%, respectively, seen in the Kaplan–Meier curve displayed in Figure 1. Subgroups analyses looking at the PFS and OS based on histology, the treatment groups, and the stage groups (II or III) did not show any statistically significant difference between the groups, possibly due to smaller patient numbers and a short follow-up.

Table 5: Doses to the organs-at-risk

Dose characteristics for OARs	All CHART		3D-CRT		VMAT		3D-CRT versus VMAT, *P* value, Mann–Whitney U-test
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Lung V20 (aim <35%)	23.49±6.24	24.25 (17.76–28.68)	24.09±5.54	25.18 (18.20–27.92)	22.49±7.36	22.37 (14.85–30.70)	0.526
Lung V10	36.86±8.89	37.65 (29.28–42.68)	35.25±8.29	36.95 (28.87–40.46)	39.50±9.52	40.24 (29.34–49.20)	0.231
Lung V5	53.97±11.11	53.27 (45.02–62.25)	50.77±9.30	50.93 (43.61–58.23)	59.21±12.15	63.35 (47.43–69.96)	0.039*
MLD (aim <18Gy)	13.04±2.53	13.17 (11.15–15.35)	12.98±2.44	13.11 (11.10–15.34)	13.14±2.75	13.84 (10.71–15.47)	0.745
Spinal canal maximum (aim <44Gy)	16.68±11.55	13.23 (7.68–19.79)	18.18±14.06	11.46 (7.49–34.20)	14.21±4.94	15.47 (8.87–18.80)	0.745
Length of esophagus in 95% isodose (recorded only)	6.01±4.30	5.75 (2.75–10.00)	5.23±4.53	5 (0.50–8.25)	7.29±3.69	6.75 (5.13–10.44)	0.165
Esophagus maximum dose (aim <60 Gy)	51.3±12.8	55.9 (53.5–57.0)	50.2±11.2	55 (50.7–55.95)	52.9±15.1	57.3 (56.1–58.8)	0.002*
Esophagus V55Gy (aim <50%)	4.0±5.8	1.1 (0–5.1)	2.3±4.4	2.3 (0–2.9)	6.6±6.8	4.3 (0.8–12.4)	0.012*
Esophagus V15Gy (aim <60%)	48.5±18.7	52.4 (39.6–61.5)	47.0±19.4	52.4 (36.5–57.3)	50.8±18.2	53.1 (39.8–66.3)	0.583
Heart mean dose, in Gy (aim <26 Gy)	14.88±7.70	16.39 (7.61–21.79)	13.58±7.42	12.17 (7.31–20.44)	17.02±7.94	17.25 (10.08–24.18)	0.231
Heart V30Gy, in % (aim <40%)	19.56±14.04	21.39 (5.71–31.11)	17.11±13.99	12.99 (5.16–27.97)	23.59±13.66	22.26 (12.99–35.16)	0.208

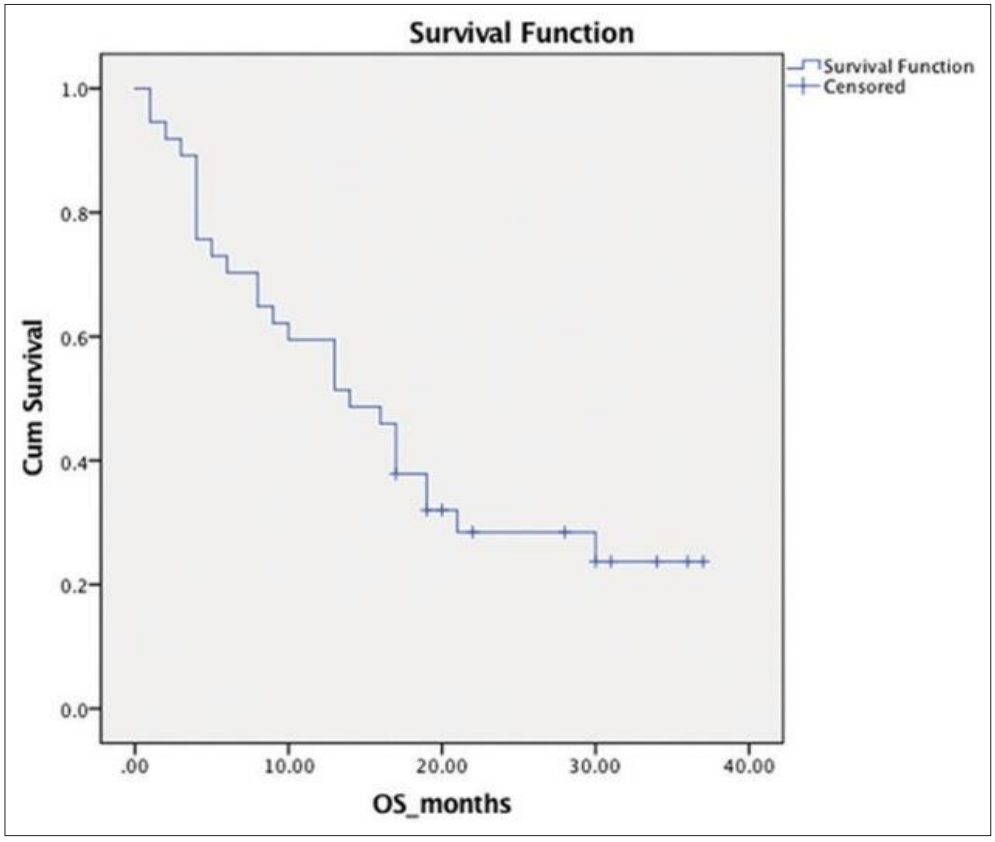
*Statistical significance. MLD=Mean lung dose; 3D-CRT=Three-dimensional conformal radiotherapy; VMAT=Volumetric modulated arc radiotherapy; SD=Standard deviation; IQR=Interquartile range

Table 6: Acute esophageal toxicity according to Common Terminology Criteria for Adverse Events version 4.03

Dysphagia	All CHART	3D-CRT	VMAT	3D-CRT versus VMAT, *P* value, Fisher's exact
Grade 0	8	6	2	Across all grade, *P*=0.46
Grade 1	14	8	6	
Grade 2	12	6	6	Grade 3 or more, *P*=0.275
Grade 3	3	3	0	

CHART=Continuous hyperfractionated and accelerated radiotherapy; 3D-CRT=Three-dimensional conformal radiotherapy; VMAT=Volumetric modulated arc radiotherapy

Figure 1: Kaplan–Meier curve for overall survival



Discussion

CHART has been an accepted form of radical RT since the CHART trial publications [7,8]. The CHART series presented in this paper is unique in many ways. This is the first paper to report on the clinical use of CHART for lung cancer outside the UK and Europe. In particular, this paper confirms that CHART is feasible and well tolerated in our non-Caucasian population.

The original CHART trial used conventional two-dimensional planning and limited the area of high-dose field (54Gy) when viewed anteriorly to 140 cm [27]. DVH for lung and other OARs were not possible at the time [18,19]. Since the initial CHART trial, there have been technological leaps in RT techniques. Experience is limited in combining these technologies with CHART. In the current series, modern RT techniques were used, with 37.8% (n = 14) receiving VMAT for reasons described earlier, and the rest receiving 3D-CRT. Elective nodal irradiation (ENI), which was standard during the initial CHART trial, is no longer used. With omission of the ENI and use of modern RT techniques (3D-CRT, IMRT or VMAT), it is possible to reduce excessive radiation doses to the spinal cord, esophagus, and normal lung. Computerized planning has made it possible to generate DVH data and to ensure that the doses to esophagus and normal lung are within tolerance. With CHART, the major toxicity concerns include damage to esophagus and lungs [7,8,14]. Both V-20 of lung and mean lung dose (MLD) have been shown to have correlation with the risk for radiation pneumonitis. A V-20 of 35% or less and a MLD value of <20 are acceptable constraints [23,24]. The V20 in our series (mean – 23.49%) was comparable to that of other contemporary studies such as the CHART-ED (mean – 25.4%). Similarly, the maximum dose to the spinal cord (mean – 16.68Gy) was well below the reported dose in CHART-ED study (mean – 34.7Gy). In our small series with early data, CHART using VMAT was well tolerated with manageable and reversible esophageal toxicity. In the current series, 86.5% of the patients had mainly Stage III NSCLC (n = 32), compared to about 61% in the original CHART study [7,8]. No patient with Stage I was present in our series. A significant proportion (36%) of patients in the original CHART trial had Stage I–II disease whereas the standard

treatment for most of these patients in contemporary practice would be surgery or stereotactic ablative body RT. Our patients were older compared to only 26% above 70 years in the original study, less fit and deemed to be unsuitable for chemotherapy or chemoradiation compared to the patients in the original study who were all classified performance status 0–1. Therefore, the patients in our series were very unlikely to receive any salvage therapy on progression.

The 1-year OS estimates of 59.5% observed in our series, although calculated at short median follow-up, is comparable with the published original CHART study with a 1-year OS of 63%. The survival figures are even more encouraging because the patients in our series were considerably more advanced stage than patients in the original CHART study and the latter CHART series published by Din et al., reporting a retrospective series from five UK centres treated with 3D-CRT having a 2-year OS of 34%with a minimum of 2-years of follow-up [7,29]. However, the slightly less OS estimate compared to that of the recent randomized trials of INCH and CHART-ED can be explained by the fact that these were largely poor performance status patients who were unfit for more intensive treatment.

The incidence of severe acute dysphagia, Grade 3 or more (8.11%), was also comparable with other studies which used 3D-CRT like the INCH (13%) and the CHART-ED (16.67%) while Din et al. reported 10%. Dysphagia was not graded in the original CHART study, but it reports severe dysphagia (restricted to fluids) have been 19%. There was very low incidence of Grade 2 or more pulmonary toxicity (<1%) compared to 16% reported incidence of pulmonary fibrosis at 2 years in the original CHART study and was comparable to the more recent CHART-ED which did not report any Grade 2 pulmonary toxicity. There were no cases of radiation myelopathy despite the more advanced nature of disease in our group of patients. This too is favorable compared to similar reports in the INCH and CHART-ED studies while Din et al, had 2% Grade 2 myelitis. Both pulmonary and neurological toxicity are known to be a late developing toxicity and hence will require more long-term follow-up to firmly comment upon. The use of VMAT and the use of DVH for analyzing the

dose distributions to the OARs have definitely helped in limiting the severe toxicities.

RT services are grossly inadequate in large areas of the developing world, particularly middle-income, lower middle-income, and low-income countries [30,31]. In our series, 16 patients (out of 37) had travelled long distances and 4 patients crossed international borders to undergo treatment for NSCLC. For these patients, accelerated treatments such as CHART have an added advantage of completing treatment within 12 days. These patients spend shorter time away from their homes, effectively reducing the logistic and financial burden of cancer.

The limitations of the present study were that this was a retrospective analysis of the patients who received CHART at our centre and also the short follow-up of the patients precludes strong conclusions on survival data.

Conclusion

CHART using 3D-CRT or VMAT (as necessary) was feasible and well tolerated for routine use in the non-Caucasian patient population and is an effective single modality treatment for NSCLC patients who are not suitable for chemoradiation. The main side effect was manageable and reversible acute esophageal toxicity. Clinical impact of this experience needs to be evaluated further for toxicity, local control, and survival. The authors feel that the next logical step in our setting would be carefully intensifying treatment by either dose escalation or by adding chemotherapy to CHART, in a well-designed clinical trial for patients who are eligible to undergo concurrent chemoradiation.

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Appendix 4

Radical radiotherapy or chemoradiotherapy for inoperable, locally advanced, non-small cell lung cancer: Analysis of patient profile, treatment approaches, and outcomes for 213 patients at a tertiary cancer centre

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Abstract

Introduction: Radical radiotherapy (RT) with curative intent, with or without chemotherapy, is the standard treatment for inoperable, locally advanced non-small cell lung cancer (NSCLC).

Materials and methods: We retrospectively reviewed the data for all 288 patients who presented with inoperable, locally advanced NSCLC at our institution, between May 2011 and December 2016.

Results: RT alone or sequential chemoradiotherapy (SCRT) or concurrent chemoradiotherapy (CCRT) was used for 213 patients. Median age was 64 years (range: 27–88 years). Stage-III was the biggest stage group with 189 (88.7%) patients. Most patients with performance status (PS) 0 or 1 received CCRT, whereas most patients with PS 2 received RT alone ($P < 0.001$). CCRT, SCRT, and RT alone were used for 120 (56.3%), 24 (11.3%), and 69 (32.4%) patients, respectively. A third of all patients (32.4%) required either volumetric-modulated arc radiotherapy (VMAT) or tomotherapy. Median follow-up was 16 months. The median progression-free survival and median overall survival (OS) were 11 and 20 months, respectively. One-year OS and 2-year OS were 67.9% and 40.7%, respectively. Patients treated using CCRT lived significantly longer with a median survival of 28 months, compared with 13 months using SCRT and RT alone ($P < 0.001$). On multivariate analysis, OS was significantly affected by age, stage group, treatment approach, and response to treatment.

Conclusion: RT including CCRT is feasible, safe, and well tolerated in our patient population and results in survival benefits comparable with published literature. CCRT should be considered for all patients with inoperable, locally advanced NSCLC, who are fit and have good PS.

Introduction

Lung cancer is a leading cause of cancer death across the world [1-3]. Non-small cell lung cancer (NSCLC) accounts for over three-quarters of all lung cancers. Surgery is the treatment option of choice for early lung cancer (Stages - I, II, and some IIIA; AJCC Cancer Staging Manual, 7th Edition, 2010) although there are no published randomized phase-III data comparing surgery with chemo-radiotherapy. However, less than 20% of patients with NSCLC are suitable for surgery [4].

The majority of lung cancer patients in India present with locally advanced (Stage-IIIA and IIIB) and metastatic (Stage-IV) diseases [4-6]. Radical radiotherapy (RT) with curative intent is the primary treatment option for most of these patients with stage-III disease, with the potential of providing long-term local disease control. The other usual reasons for using RT in patients without any distant metastases (Stages I to IIIA) are inoperability because of the stage, medically inoperable because of comorbidity, and patient preference. In Stage IIIB NSCLC and arguably many cases of Stage IIIA disease, surgery has no added survival advantage over radical chemo-radiotherapy [7]. RT (with or without chemotherapy) with curative intent is the primary treatment option for these patients (Stages - I, II, and III), with the potential of providing long-term local disease control. RT schedule is usually at least 60Gy in 30 fractions, using 2-Gy fractions daily over 6 weeks [8].

Concurrent cisplatin-based chemotherapy, in selected cases, has been shown to improve loco-regional control and overall survival (OS) [9,10]; however, survival for Stage III NSCLC remains poor with a 3-year survival rate of 24% [9]. The meta-analysis by Aupérin et al., and a subsequent Cochrane review established the superiority of concurrent chemoradiation therapy (CCRT) to sequential chemoradiation therapy (SCRT) for unresectable Stage III NSCLC, with 2- and 5-year absolute survival benefits of 10% and 4.5%, respectively [9,10]. However, CCRT also has a higher rate of Grade 3 or 4 esophagitis than sequential CRT or RT alone [9,10].

Despite advances in local and systemic therapies, the local control and survival remain poor, suggesting that a therapeutic plateau has been reached

with conventional approaches [3]. The radiotherapy strategies that aim to improve local control and survival of these patients with inoperable, locally advanced NSCLC are dose escalation, altered or modified fractionation, individualized radiotherapy administration, and advanced modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc radiotherapy (VMAT) [11-14].

We present our single-institution experience of treating NSCLC patients using RT with curative intent, using either radiotherapy alone or chemoradiation (sequential or concurrent). The management plan for each of these patients was decided by the lung cancer multidisciplinary team, guided by local protocols based on published evidence and guidelines. The objective of this large retrospective study was to assess outcomes in a large cohort of consecutive patients with inoperable and locally advanced NSCLC treated using radical doses of radiotherapy with curative intent, at our institution.

Materials and Methods

All patients who presented with non-metastatic (Stages I, II, and III) NSCLC and underwent RT for NSCLC with curative intent until December 2016 were searched from electronic medical records (EMRs) and radiotherapy records. From May 2011 to December 2016, 213 patients were identified as registered and treated with RT with curative intent for NSCLC at our hospital.

All patients with suspected lung cancer were staged using computed imaging, and histological or cytological diagnosis was obtained. Patients with no obvious metastases were further staged using a whole-body fluoro-deoxyglucose-positron emission tomography (FDG-PET) and magnetic resonance imaging of the brain. Pulmonary function tests comprising forced expiratory volume in 1 s and lung diffusion capacity for carbon monoxide (DLCO) were also carried out to assess fitness for surgery or high-dose radiotherapy.

All these patients were discussed at the lung cancer multidisciplinary team (MDT) meeting, and the optimum course of treatment was discussed and

decided upon. Patients with resectable tumors who were fit and willing for surgery underwent surgical resection. Stereotactic ablative radiotherapy (SABR) was used for patients with Stage I NSCLC who were medically inoperable because of comorbidities. Patients who were unresectable because of staging or technical reasons or medical reasons (comorbidities) or who decline surgery were considered for RT. Concurrent chemo-radiotherapy was the treatment of choice for all patients who were considered fit enough to tolerate this treatment. For patients who were comparatively frail or less fit, sequential chemo-radiotherapy was offered. For patients who were not suitable for chemotherapy because of comorbidity or had contraindications to chemotherapy, radiotherapy alone was used. Finally, some patients who were very frail, had suboptimal lung function, or had extensive nonmetastatic disease received palliative radiotherapy. This analysis excluded patients who received surgery, SABR, or palliative radiotherapy.

CCRT was delivered using conventional fractionation at 2Gy per fraction (usually 60Gy in 30 fractions), whereas SCRT was delivered using either accelerated hypofractionated radiation (55Gy in 20 fractions, at 2.75Gy per fraction) or conventional fractionation [15]. Most RT-alone treatments were either accelerated hypofractionated radiation or continuous hyperfractionated accelerated radiation therapy (CHART) using 1.5Gy per fraction, three times daily at least 6 h apart, for 12 consecutive days [16]. Three-dimensional conformal radiotherapy (3D-CRT) was our default technique, and rotational IMRT using VMAT was used only if necessary, for adequately covering the planning target volume (PTV) while satisfactorily meeting the dose constraints for organs at risks (OARs). Our decision on choosing between 3D-CRT and VMAT and the radiotherapy treatment planning has been described in an earlier article [14]. Image-guided treatment verification using orthogonal EPIDs or cone-beam imaging (CBCT) or megavoltage computed tomography (CT) (tomotherapy) was used for all of these patients.

The concurrent chemotherapy is typically delivered with standard fractionation (2 Gy/fraction) and usually comprises cisplatin and etoposide. Most patients received cisplatin 50 mg/m2 intravenously on days 1, 8, 29, and 36 with

etoposide 50 mg/m2 intravenously on days 1–5 and 29–33 [7,17,18]. The etoposide on days 2–5 and 30–33 was often changed to 100 mg/m2 orally, for patient convenience and easing chemotherapy workload.

During radiotherapy or CCRT, the patients are seen and reviewed by a clinical oncologist on a weekly basis and assessed for any toxicity and treated as appropriate. After completion of treatment, the patients are seen after 4 weeks to ascertain whether the side effects are settling as expected. Posttreatment response assessment CT is carried out at 10–12 weeks after treatment completion and response was documented according to the RECIST 1.1 criteria [19].

Statistical Analysis

Data were entered in Microsoft Excel (Released 2016. Microsoft Excel for Windows, Version MSO 16.0. Washington, USA). Data obtained were checked for completeness and consistency. Statistical analysis was done using SPSS statistical software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA). Frequencies, percentages, mean, median, interquartile range, and range were calculated for categorical variables. Exact test was used to determine the relationship between treatment received and performance status (PS). Survival was analyzed using Kaplan–Meier method, and log-rank test was used to compare factors. Cox proportional hazards analysis was used for multivariate analysis of survival outcomes. Hazard ratios were reported along with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant.

Results

Between May 2011 and December 2016, 288 patients were registered at our hospital with nonmetastatic (Stages I, II, and III) NSCLC. Of these, 37 patients received curative surgery and 9 patients received SABR for early NSCLC. A further 29 patients were treated with high-dose palliative radiotherapy (36–39

Gy using 3 Gy fractions) because they were found to be too frail (Eastern Cooperative Oncology Group [ECOG] PS 3 or 4) with comorbidity, had poor lung function, or the disease could not be encompassed within planning target volume that could be safely treated with a higher (curative) dose. All the remaining 213 patients were treated with RT with curative intent for NSCLC and have been analyzed.

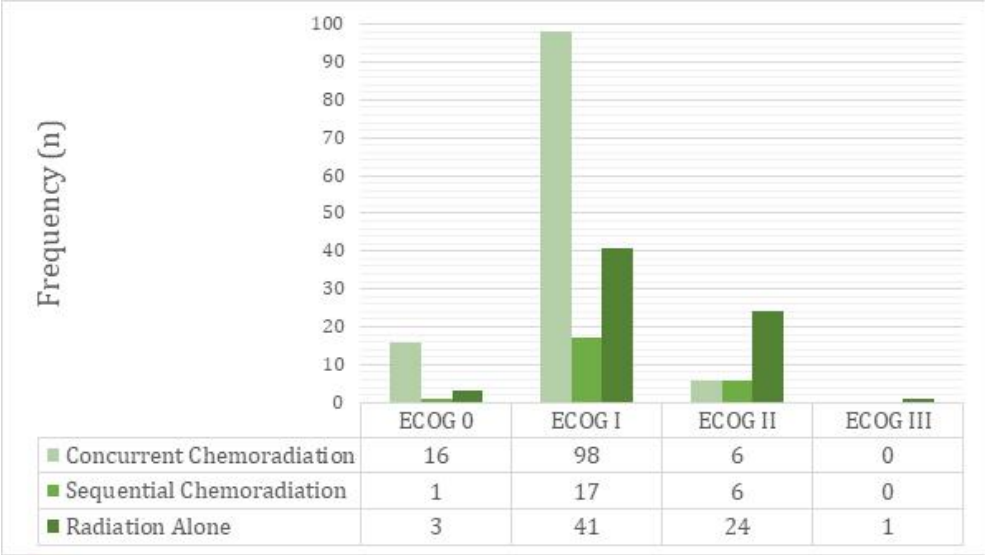
RT with or without chemotherapy was administered to 213 patients with a median age of 64 years (range: 27–88 years). The patient characteristics have been described in Table 1. A significant number of patients with ECOG performance scores (PS) 0 and 1 received CCRT whereas most patients with PS 2 received RT alone ($P < 0.001$), as shown in Figure 1.

Table 1: Demographics

Characteristics	**Subgroup**	**Patients, n (%)** **Total number=213 (100%)**
Age	≤70	164 (77)
	>70	49 (23)
Sex	Male	182 (85.4)
	Female	31 (14.6)
Biopsy/cytology	Biopsy	208 (97.7)
	Cytology	5 (2.3)
Histology	Adenocarcinoma	90 (42.3)
	Squamous cell carcinoma	111 (52.1)
	Large cell carcinoma	2 (0.9)
	Other NSCLC	10 (4.7)
PET-CT	Yes	202 (94.8)
	No	11 (5.2)
Location of primary	Central	107 (50.2)
	Peripheral	106 (49.8)
Laterality of primary	Right	134 (62.9)
	Left	77 (36.2)
	Bilateral	2 (36.2)

T-stage	T1	9 (4.2)
	T2	54 (25.4)
	T3	77 (36.2)
	T4	73 (34.3)
N-stage	N0	24 (11.3)
	N1	24 (11.3)
	N2	124 (58.2)
	N3	41 (19.2)
M-stage	M0	209 (98.1)
	M1	4 (1.9)
Stage group	I	1 (0.5)
	IIA	7 (3.3)
	IIB	12 (5.6)
	IIIA	108 (50.7)
	IIIB	81 (38.0)
	IV	4 (1.9)
ECOG PS	0	20 (9.4)
	1	156 (73.2)
	2	36 (16.9)
	3	1 (0.5)
Comorbidity	None	51 (23.9)
	1	54 (25.4)
	2	91 (42.7)
	>2	17 (8.0)
NSCLC=Non-small cell lung cancer; PET-CT=Positron emission tomography-computed tomography; ECOG PS=Eastern Cooperative Oncology Group performance scores		

Figure 1: Treatment approach with performance status



Radiotherapy

CCRT was administered to 120 (56.3%) patients, SCRT to 24 (11.3%) patients, and RT alone was used for 69 (32.4%) patients. RT alone included patients who received standard fractionation, accelerated hypofractionation (55Gy in 20 fractions), and CHART. The radiotherapy planning and delivery techniques included 3D-CRT in 144 (67.6%) patients and rotational IMRT (VMAT and tomotherapy) in 69 (32.4%) patients. The prescribed doses and the proportional breakdown of planning and delivery techniques are detailed in Table 2.

Table 2: Treatment Characteristics

Characteristics	**Subgroups**	***Patients, n(%) Total Number = 213(100%)***
Treatment	CCRT (16 patients also received NACT)	120 (56.3)
	SCRT	24 (11.3)
	RT alone	69 (32.4)
Prescribed dose	60 Gy in 30 fractions	123 (57.7)
	55 Gy in 20 fractions	30 (14.1)
	54 Gy in 36 fractions (CHART)	44 (20.7)
	64 Gy in 32 fractions	5 (2.3)
	66 Gy in 33 fractions	5 (2.3)
	60 Gy in 32 fractions	1 (0.5)
	54 Gy in 20 fractions	3 (1.4)
	56 Gy in 28 fractions	2 (0.9)
	50 Gy in 20 fractions	1 (0.5)
RT technique	3D-CRT	144 (67.6)
	IMRT-RapidArc®	61 (28.6)
	Tomotherapy	8 (3.8)
CRT=Conformal radiotherapy; CHART=Continuous hyperfractionated accelerated radiation therapy; 3D-CRT=Three-dimensional-conformal radiotherapy; RT=Radical radiotherapy; IMRT=Intensity-modulated radiotherapy; NACT=Neoadjuvant chemotherapy; CCRT=Concurrent chemoradiotherapy; SCRT=Sequential chemoradiotherapy		

Chemotherapy as a part of treatment

A total of 144 patients received some form of chemotherapy. Concurrent chemo-radiation was used in 120 patients. Cisplatin and etoposide [7,17,18] were the most commonly used regimens for concurrent use with radiotherapy and were used in 131 (91%) of 144 patients. Paclitaxel and carboplatin were used in nine (6.25%) patients. Other regimens used were carboplatin and etoposide, paclitaxel and cisplatin, and single-agent paclitaxel. Sixteen patients from the CCRT group also received some form of neoadjuvant chemotherapy. Neoadjuvant chemotherapy before definitive radiation (SCRT) was used in 24 patients. The neoadjuvant chemotherapy was decided according to the histological diagnosis with platinum and pemetrexed doublet used for adenocarcinoma, platinum, and gemcitabine doublet used for

squamous cell carcinoma, platinum and taxane (paclitaxel) doublet for NSCLC-NOS, or either of the other diagnoses [20]. The overall incidence of anemia, leukopenia, and thrombocytopenia is described in Table 3. Twenty-six patients required admission into hospital for the management of febrile neutropenia. Dose reduction in chemotherapy was necessary for 14 patients, whereas 106 patients did not undergo any dose reduction. Granulocyte-colony-stimulating factors (G-CSFs) and PEGylated G-CSF (peg-Filgrastim) were used in 30 and 12 patients, respectively.

Outcomes

Median follow-up was 16 months (interquartile range: 8–25 months). The Kaplan–Meier curves showing the progression-free and OS for the entire cohort are displayed in Figure 2a and b. The median progression-free survival and median OS were 11 (95% CI: 8.80–13.20) and 20 months (95% CI: 17.54–22.26), respectively. One-year and 2-year OS were 67.9% and 40.7%, respectively.

Fourteen patients died within 90 days of completion of treatment, resulting in a 90-day mortality of 6.6%. RT and chemotherapy-related toxicity documented in EMR is detailed in Table 3.

The patients treated with CCRT lived significantly longer with a median survival (MS) of 28 months compared with both SCRT or RT-alone groups, with a MS of 13 months ($P < 0.001$), as displayed in Table 4 and Figure 2c. The Kaplan–Meier curves comparing the progression-free and OSs for the CCRT and SCRT are displayed in Figure 2c and d. Patients with ECOG PS of 0 or 1 had significantly better outcomes compared with those with PS of 2 or 3. Patients who had at least stable disease (complete response, partial response, or stable disease) had better survival compared with patients who had progressive disease ($P < 0.001$).

Patients with Stage III disease formed the biggest subgroup with 189 (88.7%) patients, and comprised Stage IIIA (108 patients) and Stage IIIB (81 patients). MS for Stage IIIA patients was 22 months (95% CI: 19.45–24.54), compared with the MS for Stage IIIB patients at 17 months (95% CI: 11.89–22.12). This

difference in the survival between IIIA and IIIB did not reach statistical significance (P = 0.256).

On multivariate analysis, the OS was found to be significantly affected by age (up to 70 years or more than 70 years), stage group, treatment approach (CCRT, SCRT, or RT alone), and response to treatment, as displayed in Table 5.

Figure 2: Kaplan–Meier curves showing the following: (a) Overall survival. (b) Progression-free survival. (c) Overall survival, comparing concurrent chemoradiotherapy versus sequential chemoradiotherapy. (d) Progression-free survival, comparing concurrent chemoradiotherapy versus sequential chemoradiotherapy

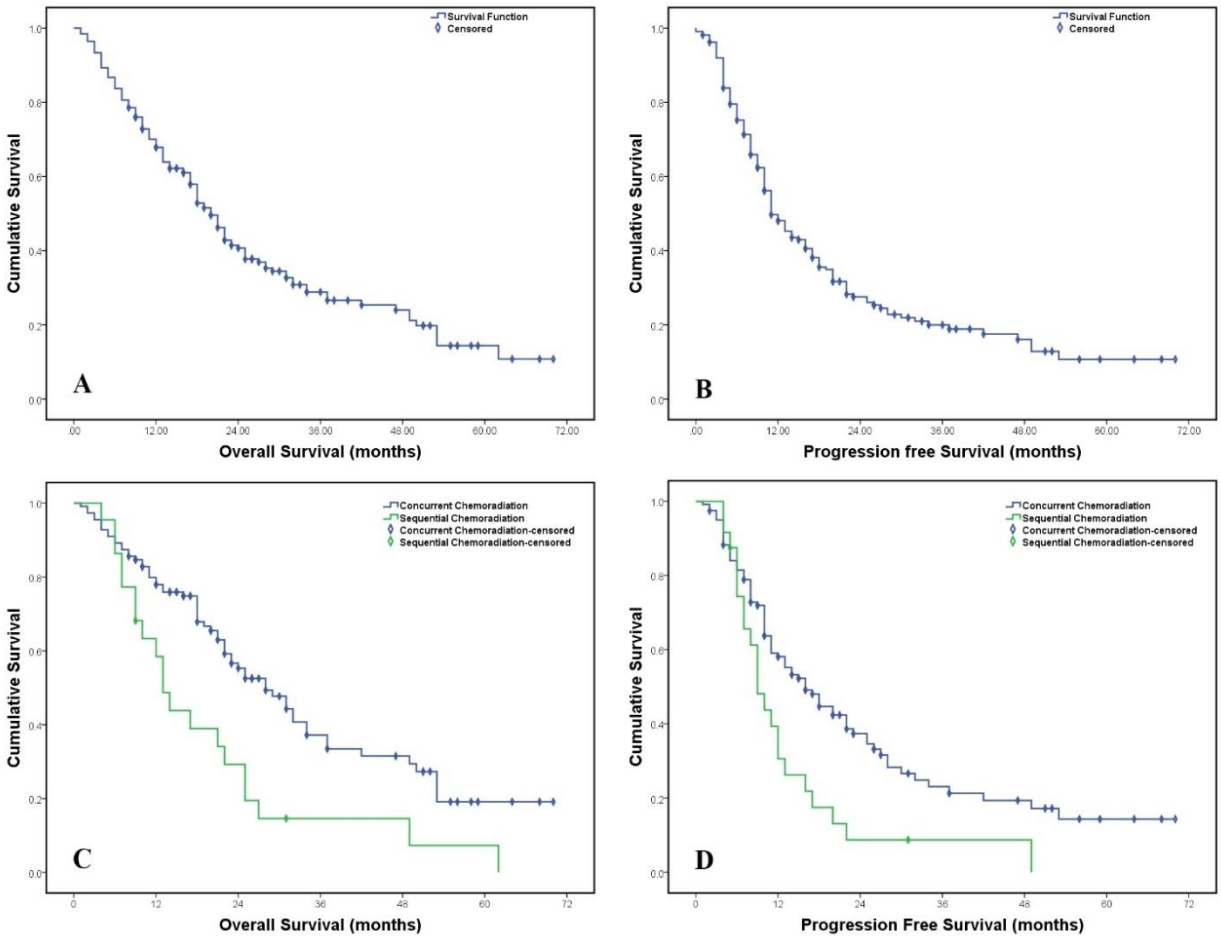


Table 3: Treatment-related toxicity

Characteristics	**Subgroup**	***n* (%)**
Analgesia requirement for odynophagia (*n*=213)	Nil intervention	20 (9.4)
	Anaesthetic gel	30 (14.1)
	Anaesthetic gel + paracetamol	103 (48.4)
	Anaesthetic gel + paracetamol + weak opioids	52 (24.4)
	Morphine	8 (3.8)
Dysphagia (*n*=213)	Grade 0	35 (16.4)
	Grade 1	97 (45.5)
	Grade 2	71 (33.3)
	Grade 3	10 (4.7)
	Grade 4	0
Inpatient admission due to febrile neutropenia (Chemotherapy-related; *n*=144)	Yes	26 (18.1)
	No	107 (74.3)
	Unknown (chemo elsewhere)	11 (7.6)
Anaemia (Chemotherapy-related; *n*=144)	No anaemia	7 (4.9)
	Grade 1	42 (29.2)
	Grade 2	64 (44.4)
	Grade 3	20 (13.9)
	Grade 4	0
	Unknown (chemo elsewhere)	11 (7.6)
Documented leukopenia (Chemotherapy-related; *n*=144)	No leukopenia	53 (36.8)
	Grade 1	26 (18.1)
	Grade 2	17 (11.8)
	Grade 3	17 (11.8)
	Grade 4	20 (13.9)
	Unknown (chemo elsewhere)	11 (7.6)
Thrombocytopenia (Chemotherapy-related; *n*=144)	No thrombocytopenia	50 (34.7)
	Grade 1	52 (36.1)
	Grade 2	16 (11.1)
	Grade 3	7 (4.9)
	Grade 4	8 (5.6)
	Unknown (chemo elsewhere)	11 (7.6)

Table 4: Analyses of factors affecting overall survival

Variable	Category	*n*	Median OS	95% CI	*P*
Age	≤70	164	22	18.99–25.01	0.111
	>70	49	16	12.08–19.92	
Histology	Adenocarcinoma	90	22	16.94–27.06	0.300
	Squamous cell carcinoma	111	19	15.84–22.16	
	Large cell carcinoma	2	10	-	
	Others	10	17	0.00–38.80	
T-stage	T1	9	53	-	0.714
	T2	54	18	15.29–20.71	
	T3	77	21	17.52–24.49	
	T4	73	20	13.34–26.66	
N-stage	N0	24	32	8.88–55.12	0.317
	N1	24	19	13.40–24.60	
	N2	124	22	18.03–25.97	
	N3	41	13	7.58–18.43	
M-Stage	M0	209	20	17.58–22.42	0.672
	M1	4	9	0.00–22.72	
Stage Group	I	1	3	-	0.002*
	IIA	7	53	-	
	IIB	12	11	5.16–16.84	
	IIIA	108	22	19.46–24.54	
	IIIB	81	17	11.89–22.12	
	IV	4	9	0.00–22.72	
ECOG PS	0	20	42	15.68–68.32	<0.001*
	I	156	21	17.96–24.04	
	II	36	14	9.34–18.67	
	III	1	3	-	
Treatment	CCRT	120	28	21.18–34.82	<0.001*
	SCRT	24	13	10.09–15.92	
	RT-alone	69	13	9.45–16.55	

Technique	3D-CRT	144	21	17.70–24.30	0.634
	IMRT	69	19	15.73–22.27	
Response (*n*=165) Unknown=48	CR	5	34	-	<0.001*
	PR	80	23	16.60–29.40	
	SD	57	24	19.47–28.54	
	PD	23	10	19.14–24.86	

*Statistical significance for *P*<0.05. ECOG PS=Eastern Cooperative Oncology Group performance scores; CCRT=Concurrent chemoradiotherapy; SCRT=Sequential chemoradiotherapy; RT=Radical radiotherapy; 3D-CRT=Three-dimensional-conformal radiotherapy; IMRT=Intensity-modulated radiotherapy; CI=Confidence interval; CR=Complete response; PR=Partial response; PD=Patient's disease; SD=Stable disease

Table 5: Multivariate analysis of predictors for overall survival

Variable	**Category**	**HR**	**95% CI**	***P***
Age	≤70 versus 70	0.47	0.24–0.92	0.027*
Histology	Adenocarcinoma	Reference		0.181
	Squamous cell carcinoma	1.51	0.94–2.46	
	Large cell carcinoma	0.40	0.07–2.29	
	Others	2.30	0.29–18.16	
T-stage	T1	Reference		0.668
	T2	0.96	0.26–3.53	
	T3	0.76	0.20–2.87	
	T4	1.33	0.31–5.66	
N-stage	N0	Reference		0.534
	N1	1.64	0.53–5.05	
	N2	1.72	0.46–6.48	
	N3	3.35	0.45–24.80	
M-stage	M0 versus M1	1.33	0.11–16.55	0.826
Stage group	IIA	Reference		0.012*
	IIB	16.05	2.64–97.52	
	IIIA	2.54	0.40–16.03	
	IIIB	1.33	0.11–16.09	
ECOG PS	0	Reference		0.828
	I	1.43	0.68–3.00	
	II	1.41	0.54–3.68	
	III	0.00	0.00–VH	
Treatment	CCRT	Reference		<0.001*
	SCRT	2.43	1.18–4.98	
	RT-alone	4.63	2.43–8.81	
Technique	3D-CRT versus IMRT	0.75	0.45–1.23	0.250

Response	CR	Reference		<0.001*
	PR	3.45	0.79–15.19	
	SD	2.54	0.55–11.68	
	PD	14.37	3.05–67.75	
*Statistical significance for *P*<0.05. ECOG PS=Eastern Cooperative Oncology Group performance scores; CCRT=Concurrent chemoradiotherapy; SCRT=Sequential chemoradiotherapy; RT=Radical radiotherapy; 3D-CRT=Three-dimensional-conformal radiotherapy; IMRT=Intensity-modulated radiotherapy; CI=Confidence interval; CR=Complete response; PR=Partial response; PD=Patient's disease; SD=Stable disease				

Discussion

The outcomes reported in this retrospective analysis suggest that radical dose of curative-intent thoracic radiotherapy (CCRT, SCRT, or RT alone) is a feasible treatment for inoperable, locally advanced NSCLC. If the patients are discussed in a multidisciplinary environment and the fitness, performance status, and comorbidities are carefully considered, the majority of patients can complete the prescribed treatment with manageable and acceptable toxicity. In the current study, the median OS for the entire study cohort was 20 months. Furthermore, CCRT was found to be significantly better, with a median OS of 28 months, than SCRT and RT-alone groups, both at 13 months (P < 0.001). In most of the trials that directly compared CCRT with SCRT, and were included in the meta-analysis by Aupérin et al., and the Cochrane review, the median OS was 16–17 months with CCRT and 13–15 months with SCRT [9,10,21]. There were several other trials that reported the use of CCRT but did not directly compare CCRT with SCRT. These trials report the median OS for standard CCRT ranging from 20 to 28.7 months [7,17,22,23]. Several retrospective series on CCRT for NSCLC report the MS from 18 to 22 months [24-27]. The patient number (n = 213) in this study, near-universal use of tissue diagnosis, FDG-PET staging, and the multidisciplinary approach to treatment according to a clear departmental policy would suggest that these results are

likely to reflect typical clinical practice for inoperable, locally advanced NSCLC in a tertiary-level cancer centre from India.

The vast majority (88.7%) of patients with inoperable, locally advanced NSCLC in the current study consisted of Stage III disease, consistent with other reported data from India [5,6]. Stage III NSCLC consists of a heterogeneous population, therefore a multimodality approach discussed and decided by multidisciplinary teams involving experts in surgery, radiation, and systemic agents is necessary. The distinction between Stage IIIA and IIIB disease is important because prognosis, treatment options, and long-term outcomes differ from one another. Furthermore, Stage IIIA disease needs to be differentiated as resectable or unresectable, usually depending on whether the nodal disease is single- or multi-station. A subgroup of stage IIIA patients are suitable for surgery [4,28]. However, Stage IIIB (T1–T4 N3, or T4 N2) involves lymph node metastasis in the contralateral thorax or supraclavicular fossa and/or an unresectable primary tumor, making surgical resection inappropriate [4,28]. Unresectable or inoperable Stage IIIA and Stage IIIB disease is treated using CCRT, while the management of potentially resectable IIIA is more complex and controversial [29] and often debated. Treatment options for IIIA disease include surgery with neoadjuvant or adjuvant chemotherapy, radiation, or both as well as definitive chemoradiation [29,30]. Long-term outcomes are poor, with a baseline 5-year OS of 15%–35% for Stage IIIA and 5%–10% for Stage IIIB [31].

In the landmark meta-analysis by Aupérin et al., CCRT improved OS over sequential CRT by an absolute benefit of 4.5% after 5 years, increasing 5-year OS rate from 10.6% to 15.1% (hazard ratio [HR] = 0.84) [9]. The locoregional progression was decreased by an absolute rate of 6.1% at 5 years, lowering the rate from 35% to 28.9% after CCRT. Although CCRT was found to improve OS and locoregional control, it did not lower distant disease progression compared to sequential CRT (HR = 1.04). CCRT, however, was associated with higher rates of Grade 3 or higher esophageal toxicity, which could reach up to 18%. The higher toxicity rates were deemed to be clinically acceptable and manageable [9].

Induction or consolidation chemotherapy in addition to CCRT has no additional benefit, as it has not been shown to improve 2-year OS or MS [18,32-34]. However, it could be considered in specific situations, especially for patients with bulky tumors where gross disease cannot be treated with radiation without leading to significant radiation-induced toxicity [35]. CCRT is better suited for and tolerated by patients with minimal comorbidities, favorable performance statuses, and minimal weight loss [32,36]. CCRT is used for relatively young patients (≤70 or 75 years old) with an ECOG PS of 0 or 1, weight loss <10% in the preceding 3 months, and minimal or no comorbidities [37]. The use of CCRT in the current study is in line with this view, as more patients with better ECOG PS received CCRT, as displayed in Figure 1.

An overview of 16 Phase II and III clinical trials by Stinchcombe et al., showed that elderly patients in CCRT trials experienced worse OS, more toxicity, and a higher rate of death, compared with younger patients [36]. A retrospective study of 381 patients who received CCRT for Stage III lung cancer showed that age >75 years (P = 0.009), DLCO ≤80% (P = 0.011), and gross tumor volume ≥100 cm3 (P = 0.001) were statistically significant factors for poor OS [38]. Severe oesophageal and lung toxicity and interruption of radiotherapy were more frequent in patients with multiple adverse predictive factors [38]. This finding was also consistent with earlier data from the Maastricht Cancer Registry, where older patients or patients with one or more serious comorbidity appeared to have inferior survival, and more than half of the patients with Stage III lung cancer were not eligible for CCRT [39].

Although CCRT was reported to be the most commonly used treatment approach for patients with Stage IIIB NSCLC in the Netherlands, the authors could not obtain accurate information on whether CRT was sequential or concurrent from the registry, and therefore elucidating the criteria on which the treatment selection was based was not possible [25]. However, Driessen et al., [40] have reported comorbidity, poor performance score, and patient refusal as the most common motives for not using CCRT. Despite the fact that relatively fit and younger patients were assigned to CCRT, treatment tolerance was worse for patients receiving CCRT, especially for those with severe

comorbidity. Only minor differences in survival between CCRT, SCRT, and RT were found, leading to suggestions that SCRT or RT alone might be more feasible options for the elderly [40]. A recent systematic review and meta-analysis of three trials and subgroup data from one individual patient data meta-analysis have highlighted the importance of not excluding fit patients from more aggressive treatment on the basis of age alone [41]. With the exception of increased haematological toxicity, CCRT appears to be tolerable in fit, elderly patients and should be the standard of clinical care [41]. Patients who are unlikely candidates to tolerate CCRT should still receive sequential CRT since it could still add some benefit over radiotherapy alone by increasing 5-year OS from 5% to 10% [10,42,43].

Treatment was generally well tolerated in the current study, but admissions during treatment and chemotherapy dose modifications were still common. The overall incidence of haematological toxicity is described in Table 3. Twenty-six patients required admission into hospital for the management of febrile neutropenia. In the absence of routine nasogastric feeding tube insertion, it is possible that the severity of oesophageal toxicity was underestimated. We accept that mild and moderate oesophageal and lung toxicity is often underreported in retrospective reviews. The reported rate of Grades 3-4 esophagitis in this study (10%) is lower than many others reporting CCRT (18%–40%) [9,32,44,45], and although the esophageal dose constraints were not specified for planning and dosimetry, certain parameters were recorded. However, the low event rate precludes the identification of predictive factors for severe toxicity.

The radiotherapy may be difficult and challenging in inoperable, locally advanced (mostly Stage III) NSCLC because of the tumor size and complexity of shape, usually as a result of the following situations: primary separated from nodes (with normal lung in between), T3 or T4 disease that is very close to vulnerable organs, and multiple N2 or N3 (contralateral nodes) disease. Complex and advanced radiotherapy techniques may be necessary to satisfy the dose constraints for the OAR [14]. A meta-analysis of 3795 patients with NSCLC randomized into 25 trials to compare higher (escalated) versus lower

RT doses of curative intent showed that, in trials with concurrent chemotherapy, higher radiation therapy doses resulted in poorer survival, possibly related to high levels of toxicity [46]. Where radiation therapy was used without chemotherapy, progressively higher radiation therapy doses resulted in progressively longer survival [46]. Therefore, modern radiation techniques should be considered to reduce toxicity wherever possible, such as IMRT, IGRT, respiration-gated RT, and adaptive RT [37]. In the current series, VMAT was necessary for treating 61 patients and tomotherapy was used for 8 patients. Altered fractionation was also used, wherever feasible, for patients who did not receive CCRT, i.e., who received SCRT or RT alone. Thirty patients were treated using accelerated hypofractionated radiotherapy (typically using 55Gy in 20 fractions, 2.75Gy per fraction, 5 days a week) in the current series. CHART was used for 44 patients.

The mean lung dose (MLD) and the proportion of lung receiving 20Gy expressed as a percentage (V20) are the most widely used and accepted lung dose constraints, with recommended MLD and V20 limits of <20–23Gy and <30%–35%, respectively, in clinical practice [47-49]. With IMRT gaining more acceptance for treating locally advanced lung cancers, monitoring the low dose bath to the normal lung is achieved by observing and recording the proportion of lung receiving 10 and 5Gy expressed as a percentage (V10 and V5, respectively) [14,50]. Although definite evidence-based guidance does not exist, some guidance is evolving around the dose volume constraints for V5 and V10 [37]. The RTOG 0617 study showed that, although the patients treated with IMRT had larger and more advanced tumors, IMRT was associated with less ≥ Grade 3 pneumonitis (7.9% vs. 3.5%, P = 0.039), and the lung volume receiving ≥5Gy (V5) was not associated with any ≥ Grade 3 toxicity, whereas the lung V20 was associated with increased ≥ Grade 3 pneumonitis risk in multivariate analysis (P = 0.026).[51] In the current series, 69 (32.4%) patients received rotational IMRT (VMAT and tomotherapy), with no difference in survival when compared with the 3D-CRT group.

An observational population-based study by Walraven et al., has reported a large variation in non- surgical treatment for stage III NSCLC, across

radiotherapy departments in Belgium and the Netherlands. A large variation was also observed between the two national registries of Netherlands and Belgium [52]. Over half of the Stage III NSCLC patients in the Netherlands (55%) and more than a third (35%) in Belgium were treated with CCRT. Higher age and higher N-stage were found to be significantly associated with the choice for SCRT [52]. Another study from Australia by Duggan et al., looked at guideline-recommended treatment (GRT) in routine clinical practice for 592 patients with Stage I–III NSCLC [53]. One-third of the patients did not receive GRT, and it was identified that Stage I–IIIA patients who were ECOG 2 and Stage III patients aged 70 years and older were less likely to receive GRT. The MS was 30 months in the GRT group and 16 months in the non-GRT group ($P < 0.001$) [53].

After carefully staging the patients with inoperable NSCLC, they must be assessed for fitness, ECOG PS, and considered for CCRT. The treatment must be in keeping with the current evidence-based recommendations and guidelines [53]. This would help reduce variations in the treatment of patients with a similar clinical profile. These challenging and often complex multimodality treatment plans for the management of locally advanced NSCLC patients require the close coordination of health-care professionals and should ideally be performed at centres with an experienced team whenever possible [54].

Conclusion

This large retrospective study suggests that using radical doses of thoracic radiotherapy with curative intent, either when used alone or when combined with sequential or concurrent chemotherapy for patients with inoperable, locally advanced NSCLC, is feasible and well tolerated in the patient population studied. Our outcomes are comparable to those published in randomized trials and large retrospective series. Given that progression-free and OS rates remain poor and both locoregional control and distant failure remain significant issues, continued progress is necessary with well-designed future studies.

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Appendix 5

Development and validation of a decision support tool to select IMRT as radiotherapy treatment planning modality for patients with locoregionally advanced non-small cell lung cancers (NSCLC)

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Abstract

Objective: Radiation planning for locally-advanced non-small cell lung cancer (NSCLC) can be time-consuming and iterative. Many cases cannot be planned satisfactorily using multisegment three-dimensional conformal radiotherapy (3DCRT). We sought to develop and validate a predictive model which could estimate the probability that acceptable target volume coverage would need intensity modulated radiotherapy (IMRT).

Methods: Variables related to the planning target volume (PTV) and topography were identified heuristically. These included the PTV, it's craniocaudal extent, the ratio of PTV to total lung volume, distance of the centroid of the PTV from the spinal canal, and the extent PTV crossed the midline. Metrics were chosen such that they could be measured objectively, quickly and reproducibly. A logistic regression model was trained and validated on 202 patients with NSCLC. A group of patients who had both complex 3DCRT and IMRT planned was then used to derive the utility of the use of such a model in the clinic based on the time taken for planning such complex 3DCRT.

Results: Of the 202 patients, 93 received IMRT, as they had larger volumes crossing midline. The final model showed a good rank discrimination (Harrell's C-index 0.84) and low calibration error (mean absolute error of 0.014). Predictive accuracy in an external dataset was 92%. The final model was presented as a nomogram. Using this model, the dosimetrist can save a median planning time of 168 min per case.

Conclusion: We developed and validated a data-driven, decision aid which can reproducibly determine the best planning technique for locally-advanced NSCLC.

Advances in knowledge: Our validated, data-driven decision aid can help the planner to determine the need for IMRT in locally advanced NSCLC saving significant planning time in the process.

Introduction

Three-dimensional conformal radiotherapy (3DCRT) is widely used as the curative treatment for patients with inoperable locoregionally-advanced non-small cell lung cancer (NSCLC) [1]. Intensity modulated radiotherapy (IMRT) is used if 3DCRT cannot yield an acceptable radiotherapy plan, as target volume coverage is unsatisfactory or organ at risk constraints are not being met or both [2]. However, there is a lack of conclusive evidence that IMRT improves outcomes when compared to 3DCRT [3–5]. In lung cancers, better conformity of IMRT is associated with a tradeoff in terms of low dose spillage in the lung. Additionally, IMRT needs robust quality assurance and stringent image guidance, because of the sharp dose gradients [6]. Hence, if an acceptable treatment plan can be generated, 3DCRT still remains the desirable technique [3–5].

For an individual patient with complex target volume geometry, complex multisegment 3DCRT planning is often attempted before a decision is made to go for IMRT [7]. The iterative nature of this planning makes this a time-consuming process. While experienced dosimetrists or planners may be able to judge the required treatment modality (3DCRT vs IMRT), this is an empirical decision in most cases. The time used in generating multiple complex 3DCRT plans may be saved if a decision support tool is available. Such a decision support system could inform the dosimetrist about the likelihood that IMRT treatment plan would be needed to satisfy the planning objectives, thereby saving time and effort spent in generating a complex 3DCRT plan.

The objective of the current study was to develop a data-driven, decision support tool employing simple to measure metrics from the planning scan, to determine if IMRT will be necessary for a given patient. In order to be clinically useful, we pre-specified that such a tool should have a cross-validated concordance-index (C-index) of 0.80 or better and be available as a nomogram. The model C-index is a measure of the goodness-of-fit for binary outcomes in a logistic regression model and is equal to the area under the curve for a receiver operating characteristic (ROC) curve [8]. If such a validated model could be developed, then we would also determine the time saved by

avoiding attempts at creating complex 3DCRT plans in a separate set of patients.

Materials and Methods

Patient population

Medical and radiotherapy planning records of consecutive patients with NSCLC (July 2013–December 2017) treated with curative intent radiotherapy at a tertiary cancer centre were retrieved. Treatment plans of 202 patients, of whom 93 had required IMRT, were analyzed. The final treatment plan for these patients had been evaluated and approved using standard planning criteria which are presented in Table 1 [9–12]. Eclipse treatment planning system (v. 10.0.42 till September 2017, and v. 15.1.52.01 subsequently, Varian Medical Systems, Palo Alto, CA) was used to generate all the plans. The authors have described the typical planning process used for generating complex 3DCRT and for IMRT (including volumetric arc therapy) plans for lung cancers in an earlier publication [13]. For all cases, the treatment plan evaluation and approval were done by senior medical physicists and senior clinical oncologists with more than 10 years of experience. Until mid-2014, for all patients, the planning process started with the development of a 3DCRT plan. If the planners failed to create a 3DCRT plan that achieved all of the objective criteria, they would attempt complex multifield and multisegment 3DCRT, before deciding on changing to an IMRT plan. As can be expected, for several cases, significant time would have been spent in iterating a 3DCRT plan before the decision for planning IMRT would be taken. Subsequently, as the team gained more experience senior physicists estimated whether IMRT was needed upfront.

Heuristic decision-making

At the start of the study, we asked an experienced clinical oncologist and a senior physicist to review the planning CT for 25 randomly selected patients from this data set. The oncologist and the physicist were free to visualize the target volumes, location and spread in the treatment planning system in any

manner required. They were then asked to decide if the patient would need an IMRT plan or would a 3DCRT plan adequately achieve the planning objectives shown in Table 1. The corresponding author noted the time taken for decision making as well as the decision itself on a separate sheet. The result of this heuristic decision-making process was then used to determine the accuracy benchmark for the decision support tool. In order to be useful, the decision support tool should have an accuracy equal to or better than that of this heuristic decision making.

Table 1: Institutional plan evaluation criteria

Volume	Metric	Criteria	Priority
PTV	D95	≥ 95%	1
	D107	< 1cc	2
	Dmax	<110%	2
Lung-PTV	V20	< 35%	2
	V10	< 50%	2
	V5	<70%	2
	Mean	<18 Gy	2
Spinal Cord	Dmax	< 48 Gy (Conventional fractionation) < 44 Gy (Accelerated radiotherapy)	1
Heart	Mean	< 26 Gy	3
	V30	< 46%	3
Esophagus	Dmax	≤ Prescribed dose	4

Model specification and development

After completing the heuristic decision making, both the clinical oncologist and the senior physicist were asked to describe the reasons that they felt influenced their choice. The factors identified were:

(1) Planning target Volume (PTV)

(2) The ratio of the PTV to the total lung volume

(3) The distance between midline to the PTV centroid

(4) The distance of the PTV centroid with respect to the spinal canal

(5) The craniocaudal extent of the PTV

(6) The distance of PTV across the midline

Based on these factors, the following quantitative metrics were identified for developing the model. We selected quantitative metrics to facilitate objective, measurable and reproducible estimation of the parameters for use in the decision support model (Figure 1).

(1) **Volume of the PTV:** This was measured in cubic centimetres (cc) from the treatment planning system (TPS).

(2) **Ratio of the PTV to that of the total lung volume (PTV_ TLV_ratio):** The TLV was the auto-segmented lung volume in the TPS. The volume was also measured directly in the TPS.

(3) **Lateral distance of the PTV centroid from the midline (Midline_to_Centroid):** Measured on the axial plane where the centroid was located. First, an anterior field of 10 × 10 cm was with the isocentre placed at the centroid of the PTV using the automatic centring algorithm of the TPS. The midline was taken as a straight line passing through the mid of the anterior vertebral body. The distance was measured using the distance measurement tool in the TPS.

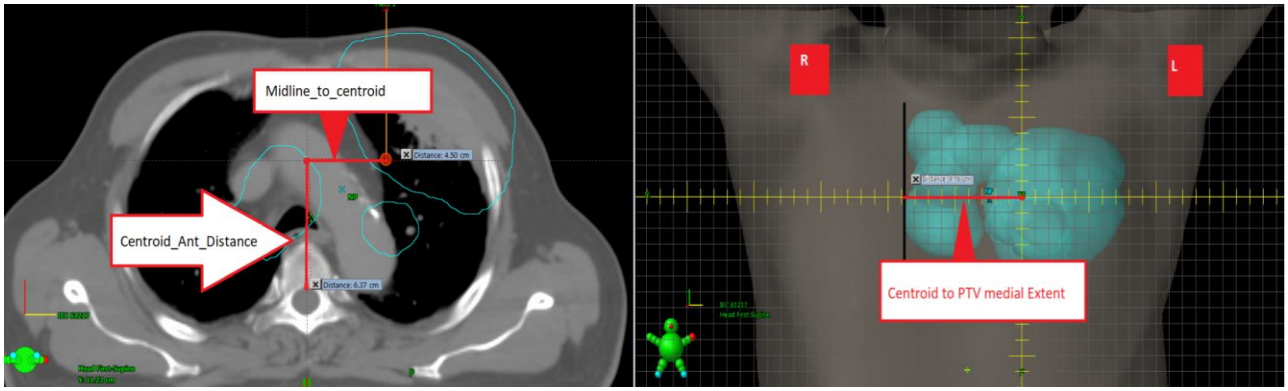
(4) **Centroid ventral distance (Centroid_Ant_Distance):** Anterior distance of the PTV centroid from the anterior border of the spinal canal along

the midline as measured on the axial plane where the centroid was placed. This distance was also measured in the same plane as above.

(5) **Extent of PTV crossing the midline (Dist_PTV_to_midline):** To measure this we first estimated the extent of the PTV which was medial to the centroid of the PTV on the frontal beam's eye view of the field. This value was subtracted from the lateral distance of the PTV centroid to the midline to obtain the distance by which the PTV crossed the midline, into the contralateral side- of the body. This method was adopted because the maximum extension of the PTV across the midline often lay in a plane which was different from the plane of the centroid.

(6) **Craniocaudal extent of the PTV (PTV_CCextent):** This was measured as the distance between axial slices having the superior most and the inferior most contours of the PTV.

Figure 1: Showing the measures to be obtained (See text and Appendix A) for details of the measurements.



These values were collected for all patients and a logistic regression model was developed to predict the probability that the patient would have a clinically acceptable plan using IMRT. We used the methodology outlined by Harrell et al to develop the model [14]. The detailed model development methodology followed is provided in (Supplementary Material 2). Briefly the process involved the following:

(1) Evaluation of the relationship between the variables and the independent variable. Differences in the mean values for the variables in IMRT vs 3DCRT were explored using the Wilcoxon signed rank test.

(2) Redundancy analysis for the variables with a flexible parametric additive model investigating how well each variable could be predicted from the others. All continuous variables were expanded using restricted cubic splines (RCS) with three knots.

(3) Evaluation of a full model which all continuous variables were expanded with RCS with three knots in order to evaluate the relationship between the log odds ratio and the covariate value. This relationship was evaluated using the analysis of variance test and graphically in order to determine which of the covariates fulfilled the assumption of linearity.

(4) Testing of prespecified interactions to evaluate if a model with interactions would give a better predictive ability.

(5) Bootstrap resampling (500 resamples) to check model discrimination and calibration. Model discrimination allows us to predict how well the given model will predict in other samples, while calibration checks the errors in the prediction across a range of predicted probabilities.

(6) Plotting of the nomogram for the final model.

Internal validation

First, this model was used for predicting the probabilities for requiring IMRT or 3DCRT in a population of 17 patients treated in 2018. This cohort of patients was not used in the model development process. The accuracy, sensitivity and specificity of the model were calculated for the predicted values. Model-predicted probabilities of >50% were categorized as IMRT as rest as 3DCRT.

Utility of model

The primary utility of this model lies in saving the time a dosimetrist would use, for creating a 3DCRT plan which would be found inadequate, before deciding to change the planning approach to IMRT. In order to estimate the time spent by dosimetrists in creating the complex 3DCRT plans, that were subsequently deemed unsatisfactory, we obtained planning time data for 15 patients with NSCLC (three patients with small cell cancers were excluded) in whom both complex 3DCRT and IMRT plans were done [13]. In these patients, both plans had been done as a part of a service development audit. The results from this audit which have been published previously demonstrated that IMRT resulted in improved target volume coverage as compared to complex, multi segment 3DCRT [13]. The time required for planning 3DCRT was obtained by reviewing the editing log available in the treatment planning system. All of these patients were a part of the model building data set and hence data of these patients were not used for the internal validation.

Results

Subject population

Table 2 shows the distribution of the model parameters in patients undergoing 3DCRT vs IMRT. As expected, patients requiring IMRT had larger tumor volumes and more centrally located tumors and all parameters were significantly different between the two groups at a p-value of <0.05.

Initial heuristic decision-making

In the initial round of the testing the heuristic decision-making, both the oncologist and the physicist accurately predicted the planning modality in 65% of the cases. There was a disagreement in three cases between the raters. The majority of disagreement and incorrect prediction occurred in tumors which were central in location but not closely abutting the spinal canal. An interview with the two raters after this exercise confirmed the choice for the

variables. Our choice of at least 80% accuracy was deemed to be reasonable after this round.

Table 2: Distribution of model parameters in patients undergoing 3DCRT versus IMRT. Mean and standard deviation are displayed. Difference calculated using the Wilcoxon test.

Parameter	3DCRT (n = 109)	IMRT (n = 93)	p value
PTV (cc)	690.54 (325.27)	865.63 (360.02)	< 0.01
PTV:TLV ratio	0.27 (0.16)	0.33 (0.16)	<0.01
Midline to Centroid Distance (cm)	5.10 (1.61)	4.33 (1.36)	< 0.01
Centroid Distance from Spinal Canal (cm)	4.14 (1.97)	3.51 (2.05)	0.01
PTV Craniocaudal extent (cm)	11.96 (2.59)	13.88 (3.62)	<0.01
Extent of PTV crossing the Midline (cm)	1.51 (1.93)	3.60 (1.86)	<0.01

Model results

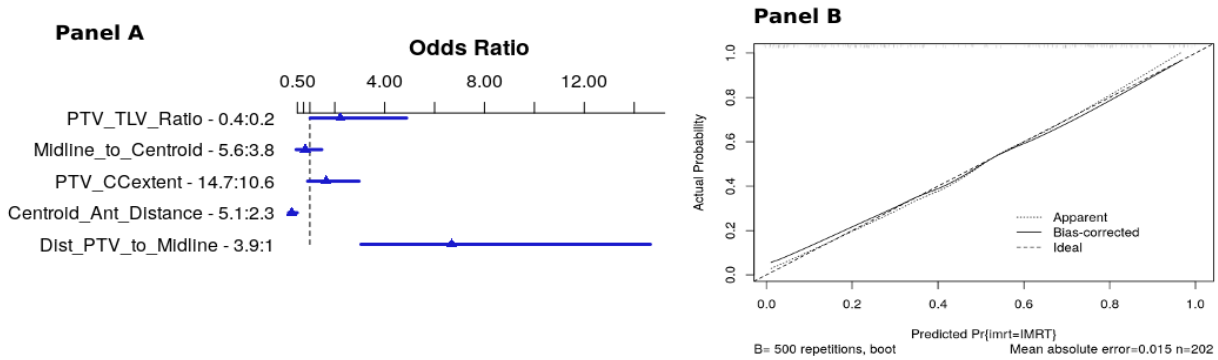
The initial model with all continuous terms expanded using RCS with three knots had a Harrell's C index of 0.867 and a Brier score of 0.147. Examination of the plots of the log odds ratio against the values of the individual variables showed that PTV:TLV ratio, PTV centroid to spinal canal distance, and craniocaudal PTV extent had a non-linear relationship. The results of the analysis of variance test confirmed the graphical findings. Hence, the decision was made to expand these three variables with RCS. The reduced model had a C-index of 0.866 and a Brier score of 0.148 indicating that the predictive accuracy would be maintained (Supplementary Material 1 for the details of the models and the analysis).

Redundancy analysis showed that PTV volume could be considered as a redundant variable at a threshold R2 of 0.7. Hence, a further model reduction was made where PTV was dropped from the model and ratio was retained.

This final reduced model with 8 degrees of freedom had a C-index of 0.867 and a brier score of 0.148 (Figure 2, panel A). The variables Dist_ PTV_to_midline and the Centroid_Ant_Distance influenced the model significantly with p-values of < 0.05. Cross-validation of the model discrimination showed that the model C-index was maintained at 0.843. The calibration curve shown in Figure 3, panel B shows that the model maintained good predictive accuracy across the range of predictions with a mean absolute error of 0.015.

The nomogram of the final model is shown in Figure 3 numerical summary of the model is further presented in Appendix A to ease calculations.

Figure 2: Panel A Shows the summary of the logistic regression model represented as the odds ratio. For each continuous variable comparisons are made between the values corresponding to the 1st and the 3rd quartile. Solid blue lines represent the 95% confidence intervals of the estimate of the odds ratio. Panel B: Represents the calibration plot for the model with the dark line being the bias corrected line obtained from 500 bootstrap resamples.



Internal validation

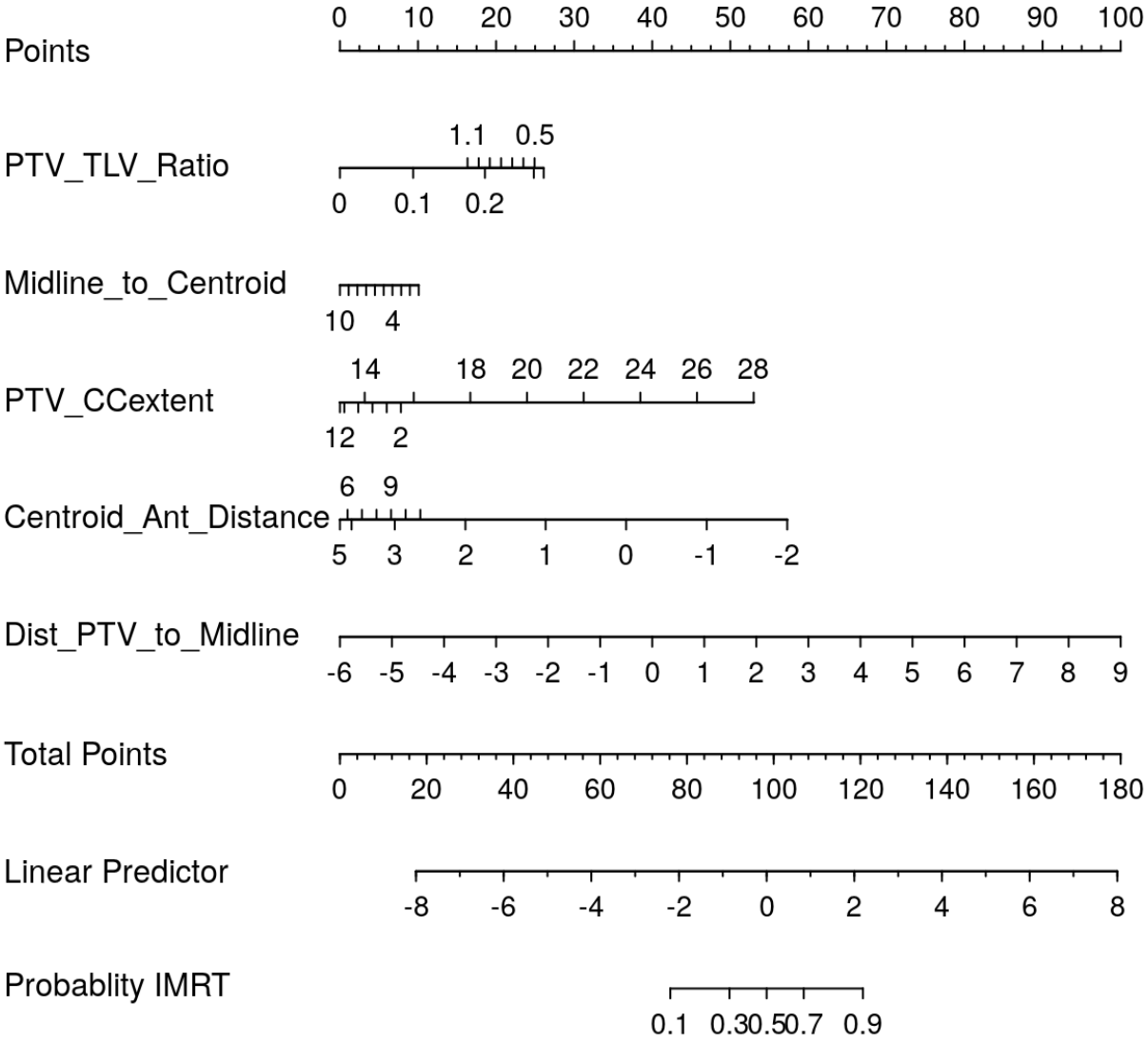
Internal validation of the model in a discreet data set not used for model development showed that the accuracy of the model in predicting that a patient would need IMRT was 94.12% (95% confidence intervals: 71.3–99.9%). The

positive predictive value was 91.7% and the negative predictive value was 100%.

Utility

In the sample of 15 patients chosen for analysis of utility, the nomogram correctly predicted the use of IMRT in 12 patients (accuracy of 80%). There were three patients where there was a discrepancy in the nomogram prediction and the actual planning modality chosen. These cases were analyzed retrospectively, and of the three patients, one had a deliverable 3DCRT plan but IMRT had been used. In another patient, IMRT was used as two separate PTV volumes were present and use of 3DCRT would have necessitated a dual isocentre plan which would be more complex. However, a dual isocentre 3DCRT plan was feasible for that patient. Finally, in the third patient, the choice of IMRT was dictated by the proximity to the heart and consequently higher doses to the heart. The median total time spent in obtaining an acceptable 3DCRT plan was 168 min (interquartile range: 82.5– 399.0 min). Using this nomogram would have saved a median time of 2 h 48 min of a planner's time for each patient, in this situation.

Figure 3: Nomogram showing the probability of the patient requiring IMRT. PTV_TLV_ratio = PTV to TLV ratio, Midline_to_centroid = Distance between PTV centroid to midline, PTV_CC_extent = Craniocaudal extent of the PTV, Centroid_Ant_Distance = Distance between the PTV centroid and the anterior spinal canal, Dist_PTV_to_Midline = Distance of the PTV across the midline. Total points of > 98 would indicate that the patient has a > 50% probability of needing IMRT.



Discussion

Radiotherapy treatment planning for lung cancer is complex and often involves trade-offs between target volume coverage and sparing of the organs at risk (OARs). Critical organs with a serial architecture like spinal cord are significant impediments as the nodal target volume often overlaps with the cord. Lateral fields expose the opposite lung to significant radiation doses, which increase the risk of radiation-induced pneumonitis.

IMRT for lung cancer enables better coverage of large or complex-shaped target volumes, while allowing adequate sparing of the OARs [2,13,15]. It allows the simultaneous treatment of multiple discrete targets, using a single isocentre [6]. However, a steep dose gradient renders the plan susceptible to motion interplay and necessitates robust image guidance. While the use of IMRT is being explored in isotoxic dose-escalation [16,17], the routine clinical use of IMRT is often limited in NSCLC [2,13,15].

The advantages of 3DCRT include no contouring of control structures, simpler forward planning and plan assessment, and no requirement for patient-specific quality assurance [6]. For many patients, IMRT does not confer any clinically significant dosimetric advantage, and 3DCRT meets all the planning criteria [2,4].

It stands to reason that it would be an advantage if the dosimetrist can predict if a complex 3DCRT plan would meet the dosimetric acceptance criteria, before spending several hours on planning. Planning complex 3DCRT is often time-consuming, as shown in the current study. This estimate of time has been obtained from the editing logs of the TPS and is likely to be an underestimate as the log does not record time spent in adjusting weights or multileaf collimators.

Use of this model allows the dosimetrist to predict the probability that a patient would need IMRT to ensure appropriate PTV coverage. Any patient with greater than 50% model predicted probability should be planned with IMRT upfront. This prediction is a function of the target volume, topography, and proximity to the spinal canal. The strongest predictor is the extent by which the

PTV crosses the midline. However, additional variables are needed, as complex 3DCRT may be used for PTV which are sufficiently ventral to the spinal canal.

While deciding on the list of variables, we opted for the variables that would be simple to measure and be reproducible. Astute dosimetrists would know that IMRT is needed when the PTV has a concave surface in proximity to the spinal canal. However, this concavity is difficult to measure reproducibly. While an angle of contact metric may be used (as is used to determine inoperability) [18], the measurement will be more variable.

Our model does not incorporate variables which are related to the doses to the OARs directly, but the variables like the ratio of the PTV to the total lung volume, midline_to_centroid distance and volume of PTV are all surrogates for doses to these structures. The choice of the variables was intentional as we wanted to develop the model using data which would be available to the planner before the first plan is generated. The model was developed in clinically approved plans in which doses of the critical structures met the acceptable standards and thus the use of this model allows the planner to choose the modality for planning (viz. 3DCRT or IMRT) with a greater degree of confidence.

In one of the patients, the model showed that an acceptable 3DCRT would be achievable, but the final choice for IMRT plan was made to reduce heart dose [1,19]. Dose constraints for the heart are poorly defined for NSCLC, though emerging evidence suggests a need to reduce the dose [20]. In the current model, there is no variable which accounts for the proximity to the heart. A variable which determines the extent of contact or overlap with cardiac contour may be used but would increase the complexity of collecting data significantly.

Data-driven decision-making is an emerging field in radiation oncology [21]. Existing TPS allows knowledge-based planning to inform the planner regarding the achievable doses with IMRT [22,23]. The current tool enables the planner to choose the planning modality viz. 3DCRT or IMRT, with a good degree of confidence. To our knowledge, none of the commercial knowledge-based planning tools provide this information. Our model does not inform about

the possible doses to the OARs and this could be an area of active research in the future.

Another limitation of the nomogram is the lack of external validation in a cohort of patients treated outside our hospital (Tata Medical Center) and we are actively exploring avenues to validate this nomogram in this manner. Part of the model performance may be related to the similarity in the target volume delineation practice and disease burden in our centre. The heuristic decision-making process employed at the beginning of the model development process is not ideal as heuristic decision-making incorporates the inherent bias that accompanies decision making by humans. The ideal way to get around this problem would have been using automatic planning for 3DCRT and IMRT but none of the commercially available planning systems allow this. We are planning an external validation study and will also be exploring the real-world gains in treatment planning time reduction achieved by the use of this planning technique.

Conclusion

A model that predicts the need to use IMRT for lung cancer with a high degree of accuracy was developed and validated. We expect that the use of this model can significantly reduce the time taken in the treatment planning for complex, locoregionally advanced NSCLC patients. A dynamic nomogram of this model is being used in clinical practice at our institute.

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Supplementary Material 1

Appendix A

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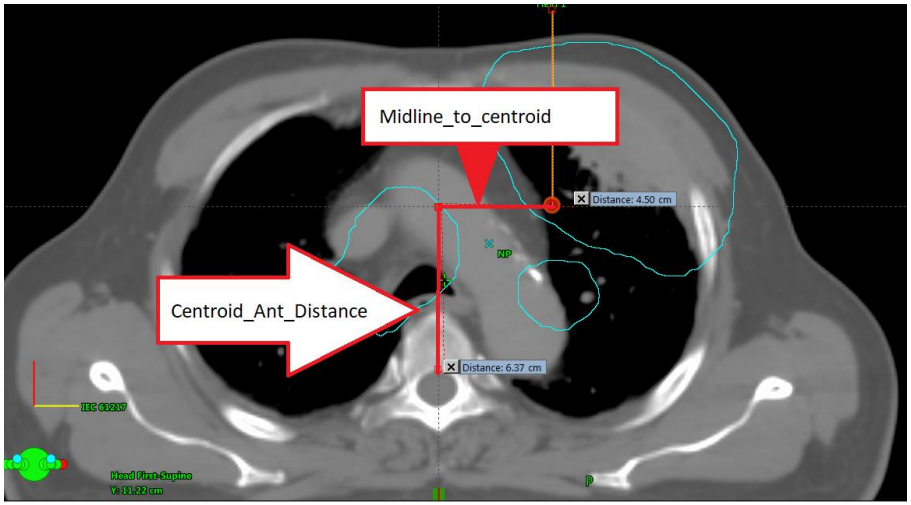
<td> 
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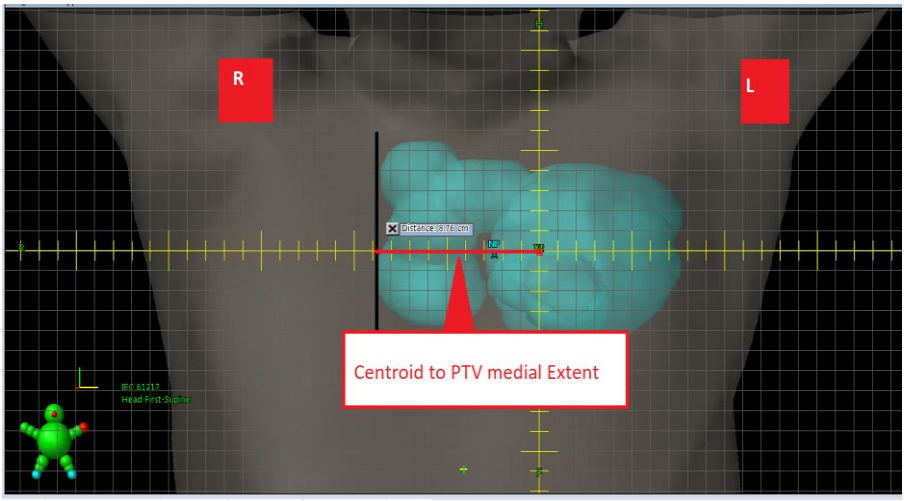
<td> 
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<td>Measurements on axial slice at level of Centroid
3. Centroid_Ant_Distance = Distance from mid of anterior spinal canal to the centroid of PTV along midline
4. Midline_to_Centroid = Distance from midline to the PTV Centroid</td>
<td>Measurement on the frontal Beam’s Eye View
2. Centroid to PTV medial extent: Distance measured between the centroid to the medial most extent of the PTV. In this patient the primary tumor is in the left side so measurement is towards the right side.</td>
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Dist_PTV_to_midline = Centroid to PTV medial extent - Midline_to_Centroid

This measures the extent PTV crosses midline. This value will be negative if PTV does not cross the midline.

PTV_CC_Extent: Can be measured either on the frontal BEV projection of PTV or from the superior and inferior most extent of PTV on the axial slices on the Planning CT

Nomogram for predicting probability of needing IMRT in NSCLC patients

Instructions: Note down the points for each variable based on the value recorded from the planning CT in the right hand most column. Add them to get the total of points. Check the probability of requiring IMRT from the table below that. If the predicted probability is more than 50% then proceed with IMRT.

Variable	**Variable Values and Points**																**Points Received**
PTV_TLV_Ratio	**0**	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1**	**1.1**					
Points	*0*	*9*	*19*	*25*	*26*	*25*	*23*	*22*	*21*	*19*	*18*	*16*					
Midline_to_Centroid (cm)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**							
Points	*10*	*9*	*8*	*7*	*6*	*4*	*3*	*2*	*1*	*0*							
PTV_CC_Extent (cm)	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**			
Points	*8*	*6*	*4*	*2*	*1*	*0*	*3*	*9*	*17*	*24*	*31*	*38*	*46*	*53*			
Centroid_Ant_Distance (cm)	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Points	*57*	*47*	*37*	*26*	*16*	*7*	*1*	*0*	*1*	*3*	*5*	*7*	*8*	*10*			
Dist_PTV_to_Midline (cm)	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Points	*0*	*7*	*13*	*20*	*27*	*33*	*40*	*47*	*53*	*60*	*67*	*73*	*80*	*87*	*93*	*100*	
																Total of Points	

Total of Points	**76**	**84**	**90**	**94**	**98**	**102**	**107**	**112**	**121**
Probability of requiring IMRT	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9

Appendix 6

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

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Abstract

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 radio-therapy. 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 chemo-radiotherapy (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.

Materials and Methods

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 chemo-radiotherapy (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 2Gy per fraction (usually 60Gy in 30 fractions), whereas SCRT was often delivered using either accelerated hypofractionated radiation (55Gy in 20 fractions, at 2.75Gy per fraction) or conventional fractionation [14]. Most radiotherapy-alone (RT-alone) treatments were either accelerated hypofractionated radiotherapy or continuous hyperfractionated accelerated radiation therapy using 1.5Gy 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 chemo-therapy 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 (450cc) 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.

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 (Chi-square) test for categorical variables.

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 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

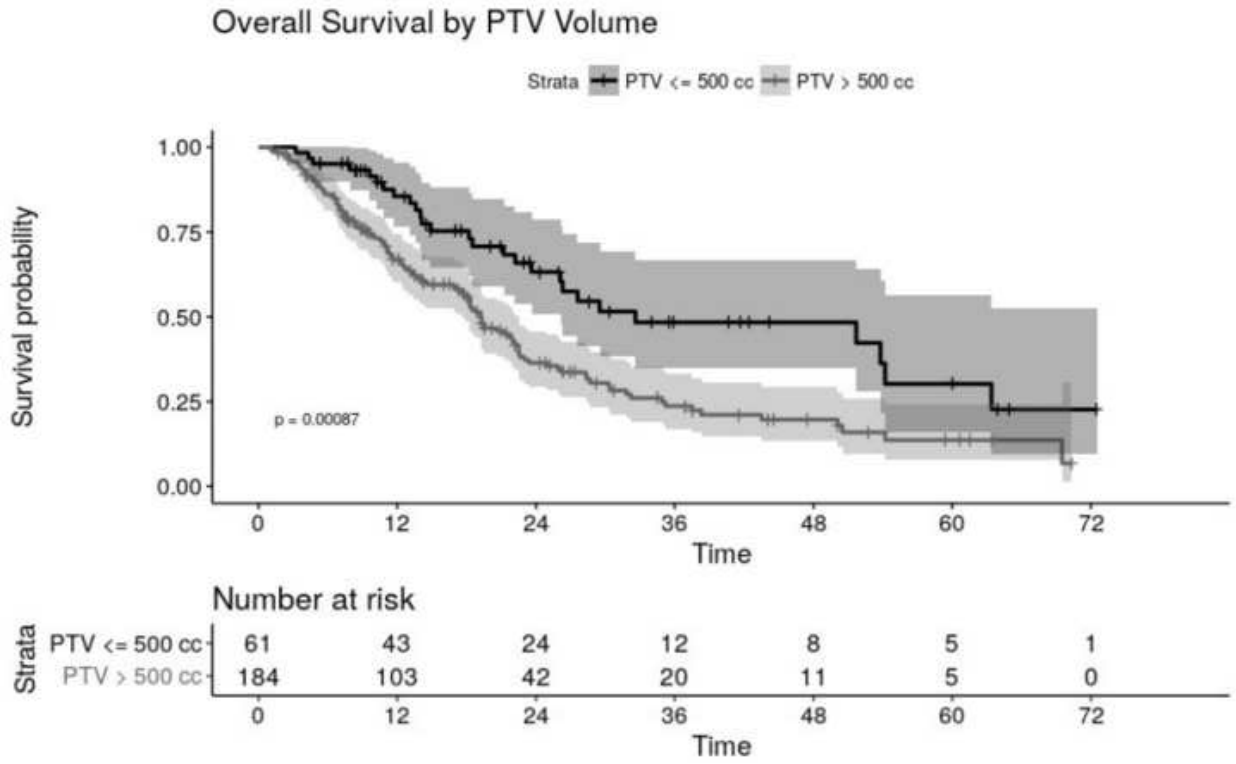
Adeno: adenocarcinoma; CCRT: concurrent chemoradiation; CI: confidence interval; 3DCRT: three-dimensional conformal radiotherapy; ECOG PS: European Cooperative Oncology Group performance status; IMRT: intensity modulated radiotherapy; Non-adeno: Non adenocarcinoma; PTV: planning target volume; RA: radiotherapy alone; SCRT: sequential chemoradiation. Variables marked with * were significant at *p* value < 0.05.

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 radio-therapy alone. The baseline variables for this cohort (Appendix A, Table 2in 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).

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—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.

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.

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

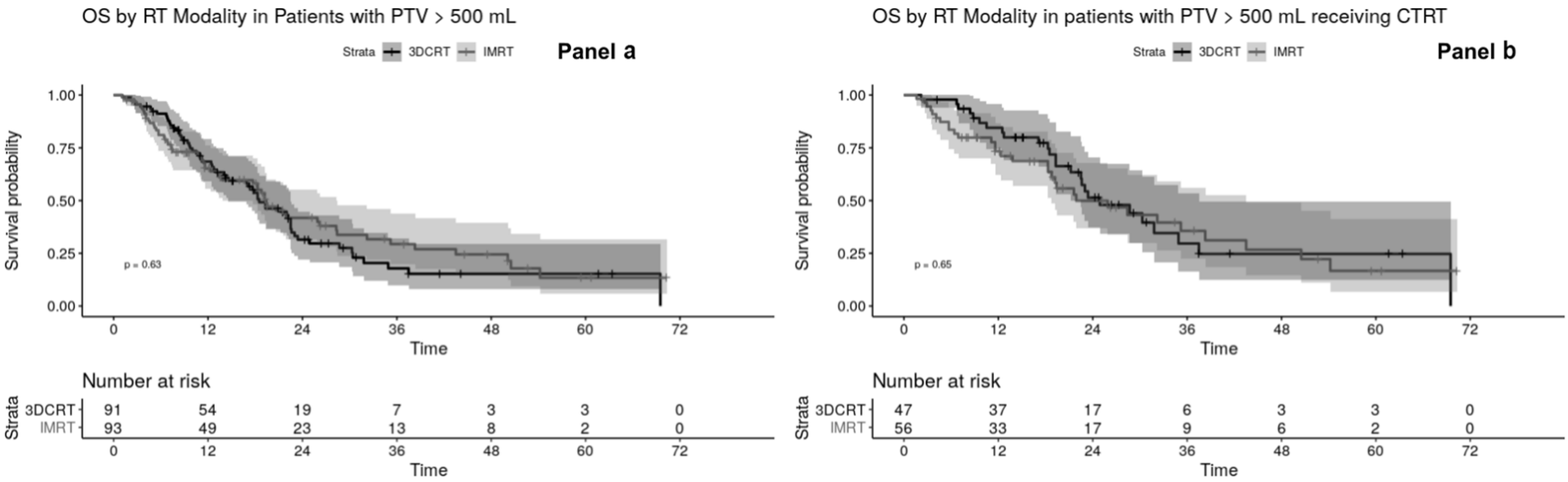
safely deliverable, despite larger volumes and higher stage distribution in this cohort.

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 >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.

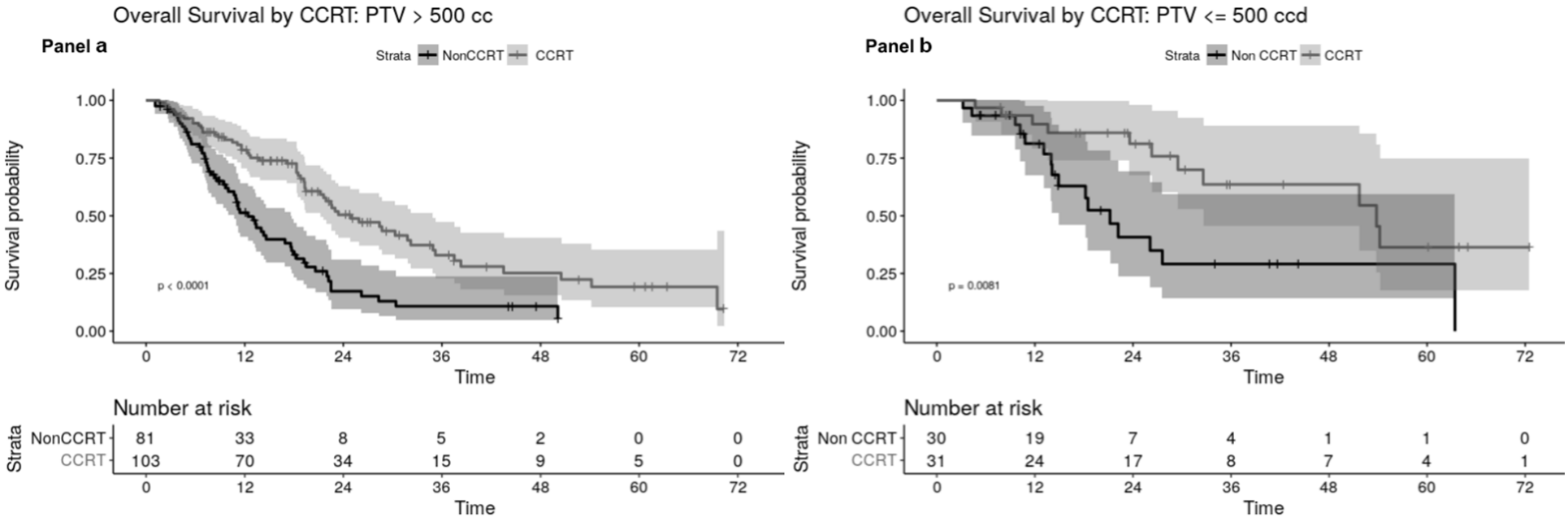
Figure 2: Kaplan–Meier plot of overall survival (using IMRT vs 3DCRT) in all patients with PTV >500 cc (Panel A) and those patients with PTV >500 cc who received CCRT (Panel B).



p-value calculated using the log rank test.

3DCRT: three-dimensional conformal radiotherapy; CCRT: concurrent chemoradiation; IMRT: intensity modulated radiotherapy; PTV: planning target volume.

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.

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 T3 and T4 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.

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 advance 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 700cc 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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APPENDIX A

Table 1: Institutional plan evaluation criteria

Volume	Metric	Criteria	Priority
PTV	D95	≥ 95%	1
	D107	< 1cc	2
	Dmax	<110%	2
Lung-PTV	V20	< 35%	2
	V10	< 50%	2
	V5	<70%	2
	Mean	<18 Gy	2
Spinal Cord	Dmax	< 48 Gy (Conventional fractionation) < 44 Gy (Accelerated radiotherapy)	1
Heart	Mean	< 26 Gy	3
	V30	< 46%	3
Oesophagus	Dmax	≤ Prescribed dose	4

Table 2: Depicts the results of the cox regression model for patients with large volume PTV.

Variable	Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI
Age	58:70	1.10	0.80	1.50
Gender	Female: Male	0.76	0.40	1.50
Histology	Adeno: Non-adeno	0.92	0.60	1.40
ECOG PS	2-3:0-1	0.97	0.57	1.60
Stage	I-IIA: IIIA	1.00	0.50	2.10
	IIIB: IIIA	1.40	0.94	2.20
	IV: IIIA	1.30	0.37	4.40
Treatment*	RT: CCRT	2.40	1.40	4.10
	SCRT: CCRT	2.80	1.50	5.20
PTV Volume	510: 900	1.50	0.81	3.00
Radiation Modality	IMRT:3DCRT	0.79	0.53	1.20

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

PTV = Planning Target volume, IMRT = Intensity Modulated Radiotherapy, Adeno = Adenocarcinoma, Non-adeno= Non adenocarcinoma, 3DCRT = 3-Dimensional Conformal Radiotherapy, ECOG PS = European Cooperative Oncology Group Performance Status, RT = Radiotherapy alone, SCRT = Sequential chemoradiation, CCRT = Concurrent Chemoradiation.

Table 3: Showing the distribution of the baseline disease and treatment related parameters among patients with PTV volume > 500 cc in 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	36 (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%)	

Brief Curriculum Vitae

Current role: Consultant Clinical Oncologist, Arden Cancer Centre, based within the University Hospitals Coventry and Warwickshire NHS Trust

My primary area of interest is non-surgical management for Lung cancer and other thoracic cancers (thymoma and mesothelioma). I have a very keen interest in using **technically advanced radiotherapy,** for patient care. My areas of expertise include IMRT, cone beam scan based IGRT and SBRT (SABR) for mobile tumours using 4DCT for target definition.

Previous experience

After completing my higher specialist training in Clinical Oncology (Jan 2005 - March 2010) at the Beatson Cancer Centre at Glasgow, I moved to Manchester to take up the role of **Post-CCT Research Fellow** under Professor Corinne Faivre-Finn**.** This post was created to help develop and set-up **lung SABR** using **4D scanning** & **on-line cone beam** verification. During this post, I also played my role with helping develop the practice of IMRT for locally advanced lung cancer. The first clinical series on IMRT for locally-advanced NSCLC, resulted as oral presentations at both the BTOG (British Thoracic Oncology Group) and the UKRO (UK Radiation Oncology) conferences in 2011 [1,2]. This post helped me obtain excellent training and experience with Technological Advances in Radiotherapy, including SBRT, IGRT and IMRT for thoracic tumours and tumours that move with breathing.

After working as a consultant at Aberdeen for 2 years, where I led the development of concurrent chemoradiation for NSCLC, I moved to Kolkata, India and took up a post at a philanthropic hospital (Tata Medical Center, Kolkata) where I had led the commissioning and development of VMAT service for locally-advanced lung cancers and subsequently 4D-CT based planning and lung SABR. I believe that my specialist training at Glasgow and the

experience I gained during my research fellowship under Professor Faivre-Finn helped laid the foundations of my service development work (2013-18) at Kolkata, India.

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