A COMPARISON OF VOLUMETRIC MODULATED ARC THERAPY (VMAT), INTENSITY MODULATED RADIATION THERAPY (IMRT) AND 3-DIMENSIONAL CONFORMAL RADIATION THERAPY (3DCRT) FOR STEREOTACTIC ABLATIVE RADIATION THERAPY (SABR) FOR EARLY STAGE LUNG CANCER.

SHORT NAME: LITESABR

Rhys Fitzgerald
BAppSc, Medical Radiation Technology, QUT

Dr Andrew Fielding, Dr Rebecca Owen and Tamara Barry

Submitted in fulfilment of the requirements for the degree of

Master of Applied Science (Research)

Science and Engineering Faculty

Queensland University of Technology

2016

Keywords

3-Dimensional conformal radiation therapy (3DCRT)
Dosimetry
Intensity modulated radiation therapy (IMRT)
Non-small cell lung cancer
Radiation therapy
Treatment planning
Volumetric modulated radiation therapy (VMAT)

Abstract

The aim of this study was to investigate three different radiation therapy treatment techniques; 3-Dimensional conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) for the delivery of stereotactic ablative radiation therapy (SABR) for peripheral early stage non-small cell lung cancer (NSCLC).

Twenty patients that met the eligibility criteria for SABR had their computed tomography scans de-identified and transferred to Pinnacle^3 ™ radiation therapy treatment planning system. All patients had completed their course of radiation therapy before this study so results had no clinical impact. Structures including the planning target volume, and critical structures such as the spinal cord and heart were contoured. Treatment plans were created for each of the three different techniques for the twenty patients. Radiation therapy dose metrics such as high and intermediate radiation dose constraints, dose to the tumour, dose to critical structures and treatment delivery time were assessed. Plan metrics were critiqued against the radiation therapy oncology group (RTOG) protocol number 1021, with either no deviation, acceptable deviation or unacceptable deviations to protocol.

Mean tumour coverage was found to be 95.6%, 95.7% and 95.6% for the 3DCRT, IMRT and VMAT techniques respectively. No deviations to the intermediate dose constraints were found in 65%, 65% and 85% of the patients for the 3DCRT, IMRT and VMAT plans respectively. All plans adhered to the high dose constraints. Mean treatment times were 20.0 minutes (16.4 – 21.5 minutes), 25.2 minutes (22.1 – 27.9 minutes) and 11.7 (8.0 – 15.2 minutes) minutes respectively for 3DCRT, IMRT and VMAT.

The VMAT technique was found to better adhere to the intermediate dose constraints stipulated by the RTOG 1021 protocol. Tumour coverage was comparable between all three techniques with no statistically significant difference found. Additionally, VMAT was found to reduce the treatment times of SABR delivery for peripheral lung tumours. However, both 3DCRT and IMRT are viable and safe treatment options for the delivery of SABR for peripheral early stage NSCLC.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

3DCRT	3-Dimensional conformal radiation therapy
4DCT	4-Dimensional computed tomography
ABC©	Active breathing Control
AJCC	American Joint Committee on Cancer
ASTRO	American society for radiation oncology
BED	Biologically equivalent dose
CBCT	Cone beam computed tomography
CI	Conformity Index
CRT	Chemo-radiation
CT	Computed tomography
CTV	Clinical target volume
CW	Chest wall
D_{2cm}	Dose at any point 2cm from the PTV
EBRT	External beam radiation therapy
EQD_2	Equivalent dose in 2 Gy per fraction
ESTRO	European society for therapeutic oncology
GTV	Gross tumour volume
Gy	Gray
HI	Homogeneity Index
IMRT	Intensity modulated radiation therapy
ITV	Internal target volume
IVC	Inferior vena cava
LD	Limited disease
MLC	Multi-leaf collimator
MU	Monitor units
MV	Megavoltage
NSCLC	Non-small cell lung cancer
OAR	Organ(s) at risk
PBT	Proximal bronchial tree
PCI	Prophylactic cranial irradiation
PTV	Planning target volume
$R_{50\%}$	Ratio of the volume of half the prescription dose to the volume of the PTV
ROI	Region of interest
RTOG	Radiation therapy oncology group

SABR	Stereotactic ablative radiation therapy
SBRT	Stereotactic body radiation therapy
SCLC	Small cell lung cancer
SRS	Stereotactic radiosurgery
SVC	Superior vena cava
TROG	Trans-Tasman radiation oncology group
VATS	Video-assisted thoracic surgery
VMAT	Volumetric modulated arc therapy

Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signature: QUT Verified Signature

Date: October, 2016

Acknowledgments

I would like to take this opportunity to thank my supervisory team. Without your leadership and guidance I would not have made it through this research journey. Dr Andrew Fielding, your knowledge and expertise strengthened the context and underlying functionality of this project. It was invaluable and contributed to the overall potency of the project. Your guidance through the research process was, instrumental and for this I thank you immensely.

Dr Rebecca Owen, your understanding and patient during this research journey has been fantastic. Your attitude toward research was fantastic and this project would not have been as detailed and in depth without your input. Your guidance and support was unremarkable. Thank you very much for all your help, it wouldn't have been possible without it.

Mrs Tamara Barry, thank you for your help with the technicalities of the project. Your experience led to improving current practices.

To my family, the most important people during this project. My wife Jade, without your support and understanding this project would not have been possible. The many late nights, weekend work, stress and emotions you had to deal with during this project is understated. Without your support I would not have been able to produce such a formidable project.

And to everyone else not part of my supervisory team, I thank you for your input and guidance, be it small or large. It all contributed to making this project that best that it could be.

Chapter 1: Introduction

1.1 BACKGROUND

1.1.1 Lung Cancer in Australia

Lung cancer is the fifth most common cancer in Australia but the most common cause of cancer related deaths [1] . Currently there are more than 11,000 new cases diagnosed each year, which is expected to increase by 16% in 2020 [2]. In 2010, the risk of developing lung cancer before the age of 85 was 1 in 16, and in 2011 the risk of death was 1 in 21 [3]. Presently, survival rates for patients diagnosed with lung cancer, although poor are improving due to advancements in treatment options. From 2006 -2010 the five year relative survival rate for Australians diagnosed with lung cancer was 14.1%, an increase from 8.1% since 1982-1987 [2] . Lung cancer is believed to be the leading cause of cancer related burden of disease for men, and second highest for women [2] .

1.1.2 Anatomy

The lungs are the organ that allow for the exchange of carbon dioxide and oxygen into the blood stream. The lungs are contained on either side of the mediastinum in the thorax, surrounded by pleura protected by the rib cage. The lungs are compartmental in structure and compromised of lobes, with the right lung consisting of an upper, middle and lower and the left lung consisting of an upper and lower lobe. The lower lobes rest directly adjacent to the muscle known as the diaphragm, which is used to control breathing. Therefore, the lower lobes are more prone to large amount of movement when compared to the middle or upper lobes.

The trachea is the organ which transports air from the larynx and pharynx inferiorly to the lungs. The trachea bifurcates at the carina into the right and left primary bronchus. The bronchus continues to divide once inside the respective lung into smaller bronchi, eventually splitting into bronchioles. These bronchioles end in clusters of microscopic air sacs known as alveolus (plural: alveoli). These pulmonary alveoli protrude from either alveolar sacs or ducts, and are the sites of gas exchange with the blood [4] .

The lungs are known as parallel functioning organs, meaning that they comprise of parenchymal tissues of which subdivisions are performing a similar, independent function (in parallel). For example the left lung is performing the same function as the right lung, acting in some ways, as a reserve function. This allows for destruction or removal of part of the organ without obvious clinical toxicity [5].

1.1.3 Aetiology, Histology and Staging

Lung cancer is a malignant tumour that usually forms in the airways contained within the lungs. Carcinomas predominantly arise from alveolar lining cells of the pulmonary parenchyma or from the mucosa of the tracheobronchial tree [6]. There are two main subtypes of lung cancer; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [7, 8]. NSCLC is a generic term to describe a subset of lung cancers including but not limited to adenocarcinoma and large cell carcinoma [9]. NSCLC is the more common of the two, accounting for 85% of all lung cancers [10]. Of the 15% of patients diagnosed with SCLC, 30% of these present with limited disease (LD), which is disease that is limited to one lung and nearby lymph nodes [11, 12]. Furthermore, only 5-15% of LD-SCLC patients present with disease contained within the lung, without regional or nodal involvement [13].

SCLC, due to it's predisposition to metastasize before diagnosis, is usually classified as either limited stage, or extensive stage [14]. NSCLC is typically staged using the TNM staging system. This system as described by American Joint Committee on Cancer (AJCC) [6] uses T to describe the size of the tumour, N to describe the nodal involvement and M to describe the metastatic state of the disease. Table 1.1 lists the TNM scale for staging lung cancer as given by the AJCC [6].

Table 1.1 - TNM staging for lung cancer

Primary Tumour (T)	
TX	Primary tumour can not be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour 3cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not the main bronchus)[1]
T1a	Tumour 2cm or less in greatest dimension
T1b	Tumour more than 2cm but less than 3cm in greatest dimension
T2	Tumour more than 3cm but less than 7cm or less or tumour with the following features (T2 tumours with these features are classified as T2a if 5cm or less): involves main bronchus, 2cm more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour more than 3cm but less than 5cm in greatest dimension
T2b	Tumour more than 5cm but less than 7cm in greatest dimension
T3	Tumour more than 7cm or one that directly invades any of the following; parietal pleural (PL3), chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or the tumour in the main bronchus is less than 2cm distal to the carina[1] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe

T4	Tumour of any size that invades any of the following; mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, separate tumour nodule(s) in a different ipsilateral lobe
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary lymph nodes, including involvement by direct extension
N2	Metastases in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
Distant Metastases (M)	
M0	No distant metastases
M1	Distant Metastases
M1a	Separate tumour nodule(s) in contralateral lobe, tumour with pleural nodes or malignant (or pericardial) effusion[2]
M1b	Distant Metastases (in extrathoracic organs)

[1]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.
[2]Most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathological examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is nonblood and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

In conjunction with the TNM scale there is also an Anatomic stage/prognostic group (table 2.2) [6] which summarizes the staging of the tumour using a combination of the TNM score for each individual diagnoses.

Table 1.2 - Anatomic Stage/Prognostic factors			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0

	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Table 1.2 gives an overview of how a tumour can be small in size, but due to its nodal involvement has the same prognosis as a larger tumour that doesn't have nodal involvement. Likewise, any tumour regardless of size, that has metastasized, is classified as stage IV.

1.2 TREATMENT OF LUNG CANCER

1.2.1 Prelude

The treatment of lung cancer depends on the location of the primary tumour, extent of the disease (staging) and other medical co-morbidities [6]. Only a small cohort of patients present with early or limited stage SCLC (LD-SCLC), making it rarely suitable for radiation alone. Typical treatment for LD-SCLC includes concurrent chemo-radiation (CRT) followed by prophylactic cranial irradiation (PCI) [15]. NSCLC on the other hand, presents with either localized or locally advanced disease at the time of staging, making surgery the typical treatment option [14]. For patients diagnosed with early stage NSCLC, either IA or IB (T1a/b, T2a, N0, M0), lobectomy is common practice due to high local control rates and regarded as the most oncologically sound surgical resection [16-18]. However, 25 % of NSCLC patients are unfit for surgery due to other medical co-morbidities and external beam radiation therapy (EBRT) is the primary treatment option for these cases [16, 19].

1.2.2 Surgery

Surgical intervention is the most common approach to remove early stage lung cancer. Surgery is characteristically reserved for early stage disease and not for more advanced disease that has already metastasized. There are three main surgical operations that can be performed;

- Pneumonectomy: an entire lung is removed
- Lobectomy: an entire lobe is removed
- Wedge Resection (or Segmentectomy): part of a lobe is removed.

The technique used depends on location and size of the tumour, along with lung function. Typically, if a patient has good lung function, more normal lung tissue is removed as this increases the chance

of a disease free survival. With all techniques, an incision is made in between adjacent ribs to access the lung tissue. This incision is known as a thoractomy.

A recent advancement in early stage lung cancer surgery is the video-assisted thoracic surgery (VATS). VATS is a technique used to treat small, peripheral lung tumours. This technique only requires a few small incisions that create a passage for a camera and surgical equipment into the patient's chest, rather than performing the surgery through the larger thoractomy incision. Due to the less invasive nature of this technique, it is associated with less pain and a shorter hospital admission.

As with any medical procedure, there are possible risks associated with surgery. Serious long term effects from surgery include excess bleeding, infections and pneumonia. Furthermore, there is also the rare, but possible chance of postoperative mortality which is age related and occurring in 3-5% of all lobectomy operations.[20]

1.2.3 External Beam Radiation Therapy (EBRT)

Conventionally, due to technology restrictions, curative dose regimes were limited to 60-66 Gray (Gy) in 30-33 fractions [21, 22]. However, this conventional fraction of 2 Gy per day results in 50% local failure rates and only 10-30% 5 year survival rates [23-27]. Compare this to surgery with only 5-20% failure rates, and it's clear why conventionally fractionated radiation therapy is not the primary treatment option for medically operable patients. To improve local control rates to above 50% with EBRT, doses would need to exceed 85 Gy [28].

However, historical field arrangements consisted of not only coverage of the primary tumour, but also regional lymphatics in the ipsilateral hilum and mediastinum. The implications of such large fields are that they are potentially poorly tolerated by this cohort of patients (usually presenting with co-morbidities) due to their limited pulmonary reserve [29]. Therefore a hypofractionated (increased daily dose of radiation) regime with a historical standard beam and field arrangement is unacceptable, due to the increased amount of non-cancerous tissue receiving highly ablative doses of radiation. Retrospective studies examined primary tumour fields compared to primary tumour and prophylactic nodal irradiation fields and found similar survival rates, demonstrating there was no advantage in treating nodes prophylactically [30-33]. Due to this reduction of field size when treating just the primary tumour, less normal tissue will be exposed to radiation and therefore hypofractionation is a potential treatment option. Similarly stage IIB to IV define large tumour sizes (>7cm) or nodal involvement and therefore include too much normal tissue for hypofractionation.

Consequently, only early stage (IA, IB or some IIA) NSCLC are suitable for hypofractionated, stereotactic ablative radiation therapy (SABR) [15].

Chapter 2: Literature Review

2.1 HISTORY OF SABR

Stereotactic ablative radiation therapy (SABR) derives from stereotactic radiosurgery (SRS), first described by Lars Leksell as a method for safely delivering high daily doses of radiation to intracranial neoplasms [34]. Over 4000 publications have demonstrated the clinical value of SRS in the treatment of not only benign and malignant diseases, but also functional disorders [35]. As described, radiobiologically, the justification for using SABR is similar to SRS in that delivering a large dose, over a few short fractions (hypofractionation) results in a more potent biological effect [35, 36]. The ability to deliver the desired dose over a single or few (usually 1-5) fractions of ionizing radiation with improved targeting accuracy and dosimetry that requires steep dose gradients provide the foundations of SABR [37]. Furthermore, SABR has compared favourably for both primary and metastatic disease when compared to surgery in regards to disease control rates [35].

The first published data on SABR outcomes was in 1995 by Blomgren et al, where they reported on 31 patients, with 42 tumours located in the liver, lung or retroperitoneal space. They observed local control of 80% with no disease progression during their follow up period of 1.5-38 months post treatment. Furthermore, 51% of tumours decreased in size or disappeared [38]. Since then, there have been numerous reports on the outcomes of SABR for the treatment of lung, liver and spinal tumours. Initial investigations began in Germany where lung and liver treatments and retrospective publications reporting on the safety and accuracy of SABR were emerging, which then eventually lead to prospective Phase I/II trials [39-49]. More recently, published data has emerged for the treatment of spinal lesions using SABR [50-55].

SABR has transformed the role of radiation therapy for numerous cancer sites, particularly for those patients diagnosed with NSCLC. It offers the patient a treatment that has fewer appointments and offers the medical community the ability to achieve low normal tissue toxicities and high local control rates comparable to surgery [56].

2.2 HYPOFRACTIONATION

Hypofractionation is the process of increasing the dose given to the tumour per fraction and reducing the number of fractions. Hypofractionation is not a new theory, nor is it applicable to every type of cancer or situation.

Hypofractionation was the initial fractionation schedule used for the delivery of radiation therapy. Treatments were basic, dose was delivered mostly to the skin rather than deep seated tumours and treatment was given in single sessions. However, this delivery of radiation was abandoned quite quickly due to the emergence of late effects. Late effects, as implied by the name, are side effects from the radiation that appear months or even years after the treatment is finished. Unlike early effects which are usually associated with damage to mucosa or epithelial lining, late effects usually involve the damage of vascular tissue [36]. These experiences led to the introduction of fractionated radiation therapy treatments. In 1928 and 1930 Coutard reported results from his experience of treating head and neck cancer where the choice of fractionation should depend on the size of the tumour and that the final dose to the tumour should depend on an ongoing response to treatment, for example mucositis [34, 36]. Excitement was generated over the better than expected results and was credited to the protracted-fractionation method. The majority of radiation oncologists therefore stepped away from using hypofractionation until the 1950's, when neurosurgeon Lars Leksell investigated the use of hypofractionated radiation to treat the radio-resistant central nervous system [34, 36]. Historically, large single doses were intolerable by the patient due to the aforementioned late effects, however, Leksell challenged conventional approaches by the use of technology, that allowed for rigid immobilisation, which altered the manner (daily dose) in which the radiation was delivered [36].

Conventionally, treatment fields were larger than the tumour and included a significant volume of the surrounding normal tissue [29, 36]. Conversely, Leksell endeavoured to make sure that large amounts of normal tissue surrounding the tumour, received as little dose as possible. The only normal tissue that was then damaged was tissue directly adjacent to the tumour or tissue that was treated due to poor dosimetry. Leksell observed that if this area of normal tissue receiving dose was small enough, then the patient did not suffer symptomatic clinical toxicity, even as a late effect [36]. This resulted in SRS, an effective and convenient treatment for patients with intracranial disease, and as discussed earlier, lead to the application of SABR for extracranial sites. There are two main issues associated with radiation delivery, acute and late affects.

2.3 RADIOBIOLOGY

The linear quadratic model describes how the tumour and normal tissue repairs itself after being damaged by radiation. Post-irradiation cell survival (SF) is given by the relationship:

$$SF = e^{-n} = e^{-\alpha D - \beta D^{\wedge}2}$$

where $n = (\alpha D + \beta D^2)$ = number of radio-induced lethal injuries; D = radiation dose administered; α, β = dose-effect co-efficients of lethal injury and α/β = dose at which the effect of α is equal to the effect of β. Furthermore, α represents the lethal single impact injury and β represents lethal injury due to repetitive sub-lethal damage. The linear component of the survival curve (αD) was ignored completely from the model, until 1973, when its importance in 2 Gy per day schemes was reported. However, it is now considered impossible to achieve tumour control by means of radiation without taking into account the single hit factor of irreparable cell injury[57]. Therefore, because damage caused by the β dose co-efficient is partially reparable, when a tumour and normal late responding tissue are irradiated together at 2 Gy per day, the radio-induced effect is greater in the tumour, than in the normal tissue. This is how conventional fractionation works and the main method of delivering lethal doses of radiation to the tumour, but still allowing the normal tissue time to repair itself [57]. Furthermore, malignant tumour biological behaviour is less homogenous than normal tissue. A downfall of the genetic make up of a tumour is their accelerated growth in response to the cytocidal (killing or tending to kill individual cells) action of radiation, which then means that longer treatment times have a negative effect on tumour control, a further reason for why hypofractionation is used for SABR [57].

Taking then the; a) α dose co-efficient and b) β co-efficient we get the α/β ratio. This is the dose where the late effects equal the early effects. Each different tissue has a different ratio depending on the genetic make up. There are two types for normal tissue;

- Rapidly proliferating tissues – Bone marrow, intestinal epithelium, skin, oropharyngeal mucosa, seminiferous tubule epithelium etc
- Non-proliferating tissues – Central and peripheral nervous system, liver, lung, kidneys, connective tissue, cartilage, bone vessels

For proliferating tissues functional impairment arises from the damage to stem cells, where as non-proliferating tissues are damaged by the loss of function in a number of mature, well-differentiated cells that make up the tissues' structure. Due to the nature of proliferation, early or acute radiation effects are noticed in proliferating tissues, and late effects are noticed in non-proliferating tissues. Malignant tumours act more like early-responding tissues [57].

As previously mentioned, hypofractionation was and still is, largely avoided due to complications arising from late effects. To describe and mathematically explain this phenomenon, the isoeffect equation of the linear quadratic model was derived;

$$D_2 = D_1 (d_1 + \alpha/\beta) / (d_2 + \alpha/\beta)$$

where D_2 = total equivalent dose, D_1 = total reference dose, d_1 = the original dose per fraction (typically 2 Gy), d_2 = the new dose per fraction and α/β equals the ratio for the corresponding tissue. Take for example a standard fractionation schedule for lung cancer treatment; 66 Gy over 33 fractions. Therefore, using an α/β of 3 for normal lung tissue;

$$D_2 = 66\ (2 + 3) / (3 + 3)$$
$$D_2 = 66 \text{ x } (.83)$$

which gives a total equivalent dose of 55 Gy for normal tissues. Then using an α/β of 10 for tumour, we get a total equivalent dose for the tumour of 60.9 Gy.

$$D_2 = 66\ (2 + 10) / (3 + 10)$$
$$D_2 = 66 \text{ x } (.92)$$

Therefore, if we choose to use this fractionation to reduce the late affects, then the tumour is only receiving 90% (.83/.92 = .9) of the reference dose. Likewise, if we aimed to produce the same percentage of tumour control, then doses to late responding tissues would increase by 11 % (.92/0.83). However, as reported by Lars Leksell, if this normal tissue receiving high dose is kept to a minimum, then this area of tissue did not receive symptomatic clinical toxicity, even as a late effect [36]. This is why when using SABR for lung cancer, patient's inclusion criteria stipulate that the tumour must be staged either IA or IB, meaning that it is 5cm or less in dimension. We know however, from reports, that 66 Gy does not produce the biologically effective dose to have comparable tumour control rates to surgery [58].

The biologically effective dose (BED) is the biological dose that is delivered to the patient and is calculated using the combination of dose per fraction, total dose and the specific α/β of the tissue. The equation for BED is;

$$BED = nd\ (1 + d/(\alpha/\beta))$$

where, n is the number of fractions, d is the dose delivered per fraction and α/β is the ratio of the specific tissue [59]. Therefore, when using a total dose of 66 Gy over 33 fractions, the total BED is only 67.2 Gy. However, a Japanese study reported inferior local control if the BED <100 Gy [58]. The Radiation Therapy and Oncology Group (RTOG) RTOG 0236 trial, a phase II trial of SABR, treating using 54 Gy in 3 fractions treated 55 patients. Primary tumour failure was only 2% at three years and three year estimated overall survival was 56%. There are however, reports that suggest the

linear quadratic model is unreliable when high daily doses are given. [60] Treating NSCLC with 54 Gy in 3 fractions, results in a BED of 151.2 Gy. Furthermore, the equivalent dose in 2 Gy per fraction (EQD2) can be calculated. This formula is;

$$EQD2 = BED / (1 + 2/\alpha/\beta)$$

where BED is the BED calculated in the previous formula, and α/β is the ratio of the specific tissue [61]. The EQD_2 equation is a rephrasing of the D_2 equation previously investigated. Taking for example a BED of 54 Gy in 3 fractions, if it was then to be treated in 2 Gy per fraction, it would be equivalent to 126 Gy. This means that to have the same biological cell kill, the patient would require 63 x 2 Gy fractions. This is unreasonable for both the patient and department.

As demonstrated, hypofractionation can increase the biologically effective dose to the tumour. This allows for patients that were deemed medically inoperable, to be given a treatment that is comparable to surgery in regard to local control. However, it was also demonstrated that doses to normal tissues also increase and therefore the radiation treatment fields must be kept as small as possible. Similarly, if the treatment times are excessive the patient is more likely to move, creating intra-fraction motion. This intra-fraction motion is enough for the tumour to move out of the treatment field and a larger amount of normal tissue to get a higher dose. This would then violate one of the key principles of SRS and SABR. To aid in the reduction of intra-fraction motion and random error, the use of sophisticated tumour delineation and immobilization equipment is also a necessary part of a SABR treatment.

2.4 SABR FOR NSCLC

Due to poor local control rates, external beam radiation therapy has typically been reserved for those patients unfit for surgery [22]. For the inoperable patient, RTOG 0236 produced results that show SABR has emerged as a viable treatment option for inoperable NSCLC. Reported control rates of 98% at three years and a three-year overall survival of 56% with toxicity in the order of 16%, justify SABR as a standard of care for inoperable patients [62]. Of importance is the differentiation between peripheral lung tumours and central lung tumours as this definition plays an important role in deciding if SABR is a clinically appropriate treatment option. Until recently, lung SABR has been restricted to peripheral tumours as dose to the central normal tissues has caused significant toxicity. RTOG defines peripheral lung tumours as a tumour (GTV) that is >2 cm away from the proximal bronchial tree. To aid in visualization, RTOG 0236 has a defined “no fly zone”.

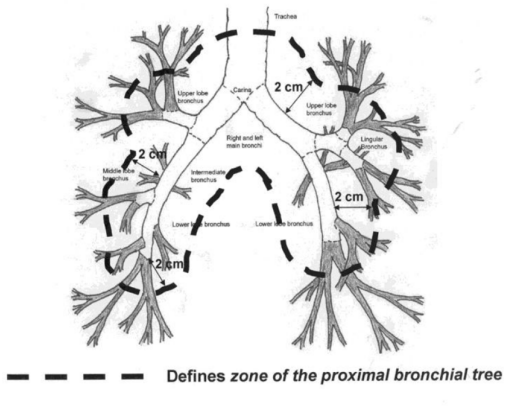

Figure 2.1 - No Fly Zone for peripheral lung SABR

2.5 MOTION, TUMOUR DELINEATION AND IMMOBILIZATION

Treatment fields and tumour volumes need to be relatively small for the patient to be a suitable candidate for SABR. Historically, a computed tomography (CT) scan was acquired to delineate the tumour. This CT scan is quite fast and can capture the tumour at any given point during the breathing cycle, be it inspiration, expiration or somewhere in between. As defined by ICRU 50, there are three levels of voluming/contouring for any cancer patient [63];

- Gross tumour volume (GTV) – tumour that is physically visible, palatable or visible on imaging
- Clinical tumour volume (CTV) – is an expansion around the GTV that accounts for any micro/macroscopic disease that isn't visible
- Planned target volume (PTV) – an expansion around the CTV that accounts for daily setup error and patient/organ movement.

With any radiation therapy plan the aim is to always deliver the prescribed dose to the PTV. However, generally the expansion from CTV to PTV for lung cancers is over determined to account for tumour motion, in order not to under dose it. Until recently, a CT scan of the patient for planning could result in an image which represents any part of the breathing cycle. Due to the uncertainty surrounding the actual extents of the tumour motion, generous PTV margins were added to the CTV. This resulted in large PTVs and excess amounts of normal tissue receiving damaging doses.

Tumour delineation is the process of defining the tumour for treatment. Conventional fractionation requires contouring of a GTV, followed by an expansion to create the CTV, accounting for micro/macroscopic disease and then finally an expansion for the PTV. However, with SABR, the GTV is directly expanded to the PTV. 4-dimensional computed tomography (4DCT) allows for accurate representation the GTV over the entire breathing cycle. When each of the individual GTVs

are contoured, they are combined to create an internal target volume (ITV). The ITV therefore, represents the entire range of motion during the patients breathing cycle [64]. A PTV is then created from the ITV to account for systematic and random errors. The reason the GTV can be expanded straight to the PTV with SABR is the thought that they dose directly outside the PTV would still likely be high enough to destroy any microscopic disease. [65, 66]. Typically the ITV is expanded 5 mm isotropically to create a PTV [67]. An expansion of up to 10 mm cranio-caudally can be justified if tumour motion is excessive [42]. Recent advancements in technology have led to the implementation of 4DCT that makes contouring the ITV possible [65].

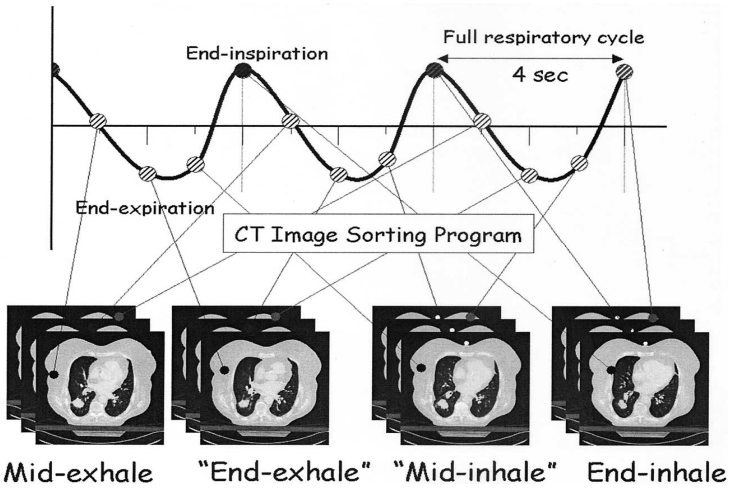

Figure 2.2 - Example of 4DCT "binning" process

4DCT uses amplitude or phase based methods of monitoring breathing motion. During a 4DCT scan, a marker or belt is placed on the patient's surface that measures the extent of the patient's diaphragmatic movement. During the scan each acquired projection can be correlated with a point in the patient respiratory cycle. The reconstruction software is then able to associate a particular slice, with a particular point in the breathing cycle and reconstruct multiple CT datasets for different parts of the respiratory cycle, i.e. 0%, 10% - 90% [68]. Figure 2.2 [69] displays how the software, in this instance has "binned" this 4DCT into 4 different respiratory phases.

The method of accounting for tumour motion is described as either motion assessment or motion management. Motion assessment is the act of taking into account tumour movement due to respiration, but does not reduce the effects of the motion. Motion control is the act of intervening and modifying the breathing pattern of the patient to reduce tumour motion. Motion control is recommended if the tumour motion exceeds 5mm [70]. Different devices allow for motion control including an abdominal compression plate, or Active Breathing Control © (ABC©) Reducing the

motion allows for a more stationary GTV, therefore a smaller ITV and PTV, which will result in less normal tissue receiving ablative doses. Additionally there is the problem of interplay, where a modulated beam is calculated to deliver dose to a stationary GTV in lung tissue on a stationary CT dataset, yet will be delivered to a moving GTV on the treatment machine [71]. This can be described as intra-fraction organ motion. This motion, during treatment, needs to be as low as possible to replicate the desired dose distribution calculated at planning.

To aid in the safe and accurate delivery of SABR, intra- and inter- fraction motion needs to be minimized. This can be achieved with the use of specific patient immobilization devices. Devices such as evacuated cushions and chest boards are two methods of patient immobilization [72]. Grills et al [73] investigated the use of a stereotactic body frame (SBF) or an alpha cradle for immobilization in lung SABR and found that both were suitable for immobilization. However, these two devices alone were not optimal for lung SABR treatment and required the use of daily treatment verification images, known as image guided radiation therapy (IGRT).

2.6 TREATMENT PLANNING

While treatment modality plays an important role in SABR planning, there are particular plan characteristics and constraints that are required, independent of treatment technique. The crux of SABR is to deliver ablative doses to the tumour, while having a steep isotropic dose fall off, reducing doses to normal tissues. There are certain plan aspects which vary from conventional planning methods that allow for suitable plan delivery. This section explores plan criteria required for safe delivery and then explores the techniques in which it can be achieved.

All treatment planning was carried out using Pinnacle v9.4 with a collapsed cone convolution algorithm. The CCC algorithm is classified as a type B algorithm and is more rigorous in accounting for changes in lateral electron transport and is a nessicity in modern day lung SABR treatment planning. Only 6MV was used for all planning techniques as the use 10MV for lung radiation therapy should be avoided as the pitfalls of the dose calculation algorithms are further enhanced with higher energies.

IMRT and VMAT plan specific quality assurance (QA) performed in which planned fluences were measured against actual delivered fluences for each field and arc of the IMRT and VMAT plans only, using a gamma analysis acceptance criteria of 3%/3mm [74]

2.6.1 Prescription dose

The prescription dose is the dose that is prescribed to the tumour volume, and planning involves making sure this dose totally encapsulates the tumour. The earliest reported Phase 1 trial for prescription doses was the Indiana University Experience which demonstrated the safety of a 3 fraction treatment regime [75]. Subsequently, an RTOG study (0236) was designed to determine if radiation therapy involving high biological doses with limited treatment volume (using SABR techniques) achieves acceptable local control (> 80%) in frail patients with medically inoperable early stage non-small cell lung cancer. RTOG 0236 reported that for 54 Gy in 3 fractions, primary tumour control failure at three years was only 2%. Furthermore, three-year estimated overall survival was 56% with grade 3 and 4 toxicity occurring in only 16% of patients [62]. Studies using lower doses report not only increased primary tumour control failure, but also increased local and regional failure. A regularly cited Japanese study demonstrated that >100 Gy BED resulted in superior local control. Overall local recurrence occurred in 20% of patients who had <100 Gy, but reduced to 6.5% when >100 Gy was administered [76]. Survival curve review expresses 1 and 2 year survivals of 90% and 75% for patients treated with >100 Gy, and 85% and 65% for patients treated with <100 Gy. The 54 Gy in 3 fractions approached has been widely adopted by North American centres. Japanese centres are more commonly prescribing 48 Gy in 4 fractions [77, 78]. Using the BED equation ($BED = nd\,(1 + d/(\alpha/\beta))$) , 54 Gy in 3 fractions will deliver a 151.2 Gy biologically effective dose, and 48 Gy in 4 fractions will be 105.6 Gy.

2.6.2 Prescription Isodose

The prescription isodose or covering isodose refers to the isodose value, which is intended to cover the PTV. The prescription isodose is independent of the prescription dose, which is the absolute dose prescribed to the PTV. Conventional planning involves prescribing a dose to the 100% isodose line, and then covering the PTV with the 95% isodose line [63]. For example, conventional lung planning would prescribe 66 Gy to the 100% isodose. This would then require 100% of the PTV to receive 62.7 Gy (95% of 66Gy). This would ensure that plan maximum doses stayed below 107% (ideally) of the 66 Gy to reduce normal tissue toxicity. However, with SABR, due to the small target volumes, PTV coverage is prescribed differently.

Firstly, the maximum dose in the plan is defined as the 100% isodose, so there can be no dose higher than this in the plan. Secondly, the PTV is planned to receive 100% of the prescription dose, i.e. for a prescription of 54 Gy, >95% of the PTV should receive 54 Gy, this negates the need for a CTV. Furthermore when prescribing conventionally to the 100% isodose line, the 95% isodose line would be the prescription isodose for the PTV. This would in turn relate to 88% of the maximum dose if it

was kept to 107%. However, with SABR, the 54 Gy dose will require a prescription isodose to be somewhere in the range of 59% to 90% [79], relative to the maximum dose in the plan. This means that the 54 Gy isodose will be in the beam penumbra. Penumbra is the region between the 20-80% isodose [80] at the edge of the beam where rapid dose fall off occurs. Figure 2.3 shows the isodose distribution for a 10x10 cm^2, 6 megavoltage (MV) beam prescribed at maximum dose depth in water (1.5 cm). It demonstrates the distance between the 100% line and 95% line, and why it is challenging to achieve steep dose fall off if prescribing to these higher isodoses. The broad-field penumbra collimated to the central axis for a single field represents the limit of dose gradient that can be achieved. In contrast, it displays how tight the distance is between the lower isodoses and how prescribing to these allow for a steep dose fall off adjacent to the PTV. Normal tissue just outside the PTV is going to receive ablative doses, but if this can be kept to a minimum, no acute side effects are noted. Furthermore, this process of prescribing SABR treatments causes a very high maximum dose in the tumour, which for conventional fractionation of 2 Gy a day is unacceptable, but for stereotactic ablative radiation therapy, is ideal.

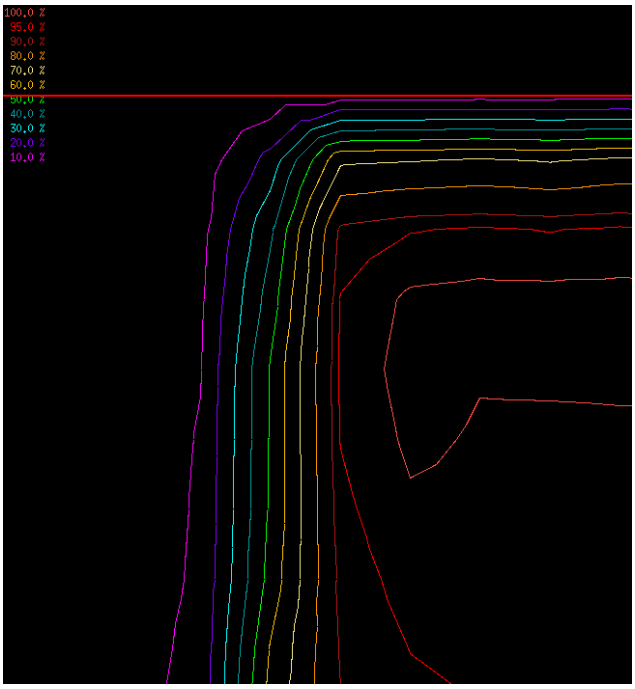

Figure 2.3 - Isodose distribution for a 10x10 cm^2, cm 6 MV photon field

Prescribing so that the 95% isodose line covers the PTV means that there is a distance before the beam penumbra, and therefore, a distance until steep dose fall off occurs. Thus, allowing for a higher maximum dose in the PTV results in the prescription isodose falling somewhere in the 80-20% isodose regions, where dose fall off is the steepest. For example, if the maximum dose in the

plan is 85 Gy, then the 54 Gy covering isodose will be 63% of the maximum dose. While the 20-80% region of penumbra is defined as the steepest, for dosimetry purposes, a prescription isodose lower than 50% creates a large amount of heterogeneity within the PTV and isn't recommended [79]. This is why a value of between 59% and 90% is recommended. Additionally, a report by Ding et al [79] reports that if the prescription isodose gets too low (<50%) , then the high dose region in the plan (conformity index) and intermediate doses ($R_{50\%}$, and D_{2cm}) begin to worsen, and don't meet RTOG guidelines, negating the effect.

As the penumbra of the beam is at the edge of the field, then this requires planning which deviates from conventional methods. Typically, because of penumbra, a margin has to be added to the shielding of the beam to allow coverage of the PTV with the 95% isodose. However, because SABR requires the prescription isodose to be within the penumbra, then there is no margin, or sometimes a negative margin for shielding. The reason for having a lower prescription isodose is to lower the amount of normal tissue receiving intermediate doses. If the dose fall off is steep around the PTV then less normal tissue is going to receive high doses. A number of techniques can be used to achieve this sharp dose fall off. A typical margin is minus 2mm anterior, posterior, left and right and then plus 2mm superior and inferior. The 2mm negative margin forces the covering isodose to be in the penumbra. The expansion superiorly and inferiorly is due to a loss of lateral equilibrium superiorly and inferiorly because there is no direct superior or inferior beam. These values are generally recommended but will change based on tumour location and prescription isodose requirements. Figure 2.4 shows the difference in MLC margins for conventional versus SABR planning.

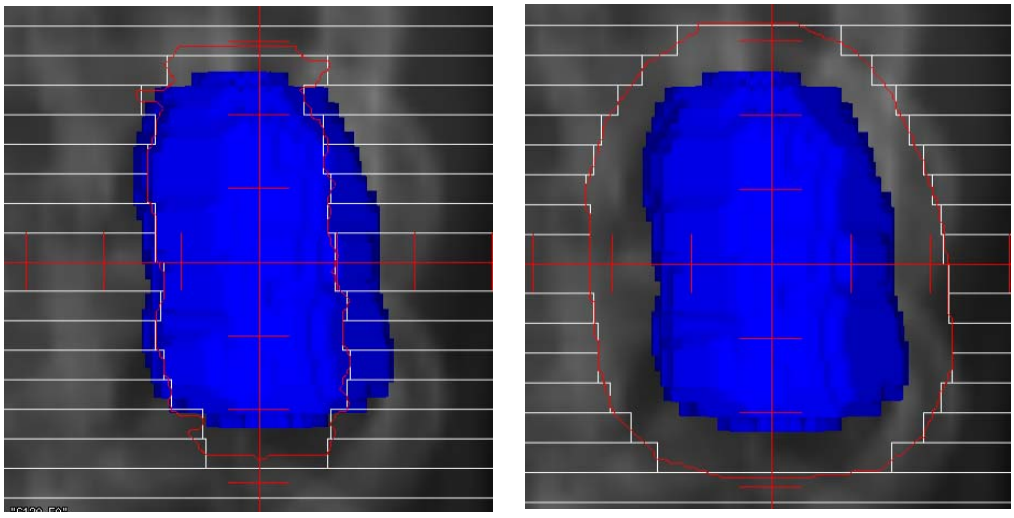

Figure 2.4 – Comparison of a negative block margin typically used for SABR (left) and conventional block margin (right) typically used for conventionally fractionated treatments

2.6.3 High and Intermediate Dose Constraints

As previously described, SABR is largely based on the work reported by Leksell, treating SRS using a GammaKnife [34]. In order to replicate the physical principles (i.e. conformal and steep dose fall off) achievable with GammaKnife, there are certain objectives [81] that need to be achieved with a linear accelerator;

1) The shape of the iso-surface defined by the prescription dose conforms to the outline of the target and highest doses delivered outside the tumour are confined to regions that spread uniformly on the outer boundary of the target volume

2) Rapid fall off of dose from the tumour volume to healthy tissue isotropically in all directions

3) Non-uniform dose distribution throughout the volume of the tumour, with the highest dose delivered to the central portion of the tumour where the hypoxic cells potentially reside.

In section 2.6.2 it was explained that a prescription isodose in the penumbra of the beam is used to lower the prescription isodose, which in turn reduces the normal tissue receiving certain doses and contributes to objective 2 and 3 being achieved. These objectives have later been given specific values which need to be adhered to in numerous RTOG protocols [82-84]. These are as follows;

High dose spillage

- Conformality or conformity index (CI) of the PTV coverage will be judged such that the ratio of the volume of the prescription isodose to the volume of the PTV is >0.75. The conformity index[85] (CI) will be calculated using the formula;

$$\frac{(TV_{PTV})^2}{TV * PIV}$$

where TV_{PTV} is the total volume of PTV covered by the covering isodose (54Gy), TV is the total volume of the PTV and PIV is the total volume of the covering isodose in the patient.

Intermediate dose spillage

- The maximum total dose over all fractions in Gray (Gy) to any point 2cm or greater away from the PTV in any direction must be no greater than D_{2cm} where D_{2cm} is given in Table 2.1

- The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than $R_{50\%}$ where $R_{50\%}$ is given in Table 2.1

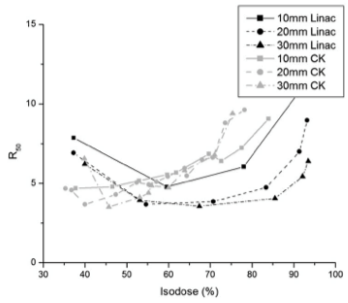

Figure 2.5a - Graph displaying how the change in prescription isodose (x) effects the $R_{50\%}$ (y) value [79]

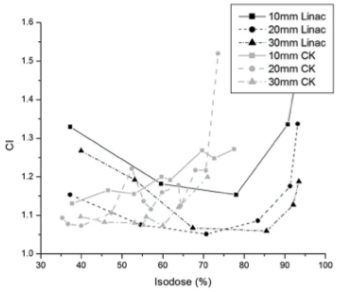

Figure 2.6b - Graph displaying how the change in prescription isodose (x) effects the CI (y) value [79]

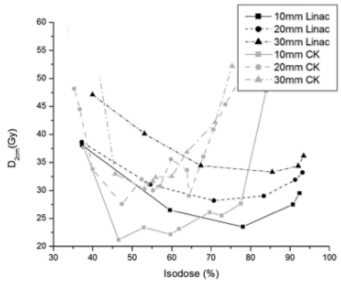

Figure 2.7c - Graph displaying how the change in prescription isodose (x) effects the D_{2cm} (y) value [79]

PTV Volume (cm^3)	Ratio of 27 Gy Isodose volume to the PTV, $R_{50\%}$		Maximum dose at 2 cm away from the PTV in any direction as % of the prescription dose. D_{2cm} = % x 54 Gy		Ratio of Prescription Isodose Volume to the PTV (CI)	
	None	Minor	None	Minor	None	Minor
1.8	<5.9	<7.5	<50.0	<57.0	>.75	>.65

3.8	<5.5	<6.5	<50.0	<57.0	>.75	>.65
5.6	<5.3	<6.25	<50.0	<57.0	>.75	>.65
7.4	<5.1	<6.0	<50.0	<58.0	>.75	>.65
10.3	<4.9	<5.9	<50.0	<58.0	>.75	>.65
17.6	<4.6	<5.6	<53.0	<60.5	>.75	>.65
22	<4.5	<5.5	<54.0	<63.0	>.75	>.65
28	<4.4	<5.4	<56.0	<65.5	>.75	>.65
34	<4.3	<5.3	<58.0	<68.0	>.75	>.65
50	<4.0	<5.0	<62.0	<77.0	>.75	>.65
70	<3.5	<4.8	<66.0	<86.0	>.75	>.65
95	<3.3	<4.4	<70.0	<89.0	>.75	>.65
126	<3.1	<4.0	<73.0	<91.0	>.75	>.65

Table 2.1 – Acceptable High and Intermediate Dose Spillage Guidelines [86]

These planning objectives/constraints inherently make the planner conform both the high and intermediate dose as tightly and isotropically around the PTV as possible. Without these objectives, more normal tissue than necessary will be receiving high doses of radiation. One method of achieving these values is with the use of a large number of, and in many situations non-coplanar, beams. The use of such a large number of beams results in an increased treatment time for patients.

2.6.4 Normal Tissue Constraints

Normal tissue refers to the tissue that is not the tumour. For the purpose of lung SABR, the tumour is defined as the ITV which accounts for all tumour motion during treatment. Since the tumour position, without respiratory gating, cannot be accurately accounted for at any given point in time, the ITV represents the worst case scenario and is therefore getting the full prescription dose and is not included in normal tissue constraints. The PTV however, does include normal tissue in its margins. Therefore some of the constraints will still require portions of the PTV to be included as normal tissue. Normal tissues are sensitive to radiation and the chances of acute or late side effects occurring are dependent on the dose that is given to the tissue. Different tissues respond to different ways to radiation damage, depending on their genetic makeup, capacity for oxygenation and their cell cycle. The normal tissues tolerances from RTOG 1021, [86] are listed in table 2.2.

OAR	Volume (cm^2)	Volume Max (Gy)	Max Point Dose* (Gy)	Endpoint (≥Grade 3)
Spinal Cord	<0.35	18.0	21.9	myelitis
	<1.2	12.3		
Oesophagus	<5	17.7	25.2	Stenosis/fistula
Brachial Plexus	<3	22	26	neuropathy
Heart/Pericardium	<15	24	30	pericarditis
Great Vessels	<10	39	45	aneurysm
Trachea	<5	15	30	Stenosis/fistula
Rib	<5	40	50	Pain or fracture
Lung (Rt and Lt)	1500	10.5		Basic Lung Function
Lung (Rt and Lt)	1000	11.4		Pneumonitis
CW	30	30		Chest Wall Pain
Skin	<10	30	33	Ulceration

Table 2.2 – Normal tissue tolerances for 3 fraction SABR [86]
*Max point dose is defined as a volume of 0.035 cm^3.

2.6.5 **Planning Priorities**

Generally, attempts should be made to adhere to all constraints, including tumour coverage and normal tissues constraints. Due to the nature and delivery of lung SABR, the high daily doses required for tumour control may lead to normal tissue tolerances (table 2.1) being exceeded. For this reason, there are a set of guidelines [86] that list in order of priority which can constraints should be met;

1. Meet the spinal cord and brachial plexus dose constraints
2. Meet the "dose compactness" constraints including the high dose conformity constraint, D_{2cm} and $R_{50\%}$
3. Meet organ at risk constraints other than the spinal cord

These rules differ dramatically from those used in conventional planning. The organ at risk constraints are last in priority, other than the spinal cord and brachial plexus, because these values are the least validated from phase 1 trials. It is suggested that if both the OAR and dose compactness

constraints (D_{2cm} and $R_{50\%}$) can't be met, then the dose compactness constraints (without deviation) take priority, even at the expense of normal tissues (except spinal cord and brachial plexus) having acceptable deviations. One acceptable deviation is when normal tissue abutting the PTV is allowed a maximum dose of 105% of the prescription dose. However, the volume constraint must still be adhered to. For example, for a PTV overlapping or adjacent to a rib, then the rib is able to receive a maximum dose of 56.7 Gy, but no more than 40 Gy to 5 cm^3. Another example is where a minor violation of the intermediate dose constraints is allowed, if an abutting normal tissue constraint is over tolerance [86].

2.7 IMAGE GUIDED RADIATION THERAPY

Due to the delivery of highly ablative fractionation, the importance of the use of isocentre verification cannot be overstated. The use of in-room imaging, known as cone-beam computed tomography (CBCT) is an essential part of SABR. CBCT allows for better soft tissue contrast than other forms of in-room imaging such as MV electronic portal imaging. It has been reported that soft-tissue matching for CBCT is integral to safe delivery of SABR as the use of bony landmarks for treatment localization can result in erroneous results [87]. Such is the importance of CBCT, trials such as CHISEL [88] stipulate the use of 3 CBCTs per treatment in order to monitor intrafraction motion. These images are taken before treatment, mid-way through treatment and after treatment. Due to the large number of beams required for safe delivery of SABR, the treatment time can be quite extensive, which results in long treatment times. It is reported that >34 minutes on the treatment couch can result in intra-fractional shifts of >5mm [87]. This is why the use of 3 CBCTs during treatment has been employed.

2.8 TREATMENT DELIVERY TECHNIQUES

2.8.1 3DCRT

3-Dimensional conformal radiation therapy is the most commonly used treatment method used for RTOG trials [82-84, 86] to deliver lung SABR. For hypofractionated techniques the number of beams required dramatically increases due to the higher daily dose and the importance placed on daily dose to normal tissues [89]. It has been reported that coplanar and non-coplanar beam arrangements consisting of between 7-11 beams can be used to satisfy all dose constraints for hypofractionated lung treatments. However, the European Organisation for Research and Treatment of Cancer (EORTC) recommends the use of only coplanar beams, and only if dose constraints cannot be met then the use of non-coplanar beams is suitable. This is due to tumour motion during SABR, and increased treatment time results in the likelihood of greater intra-fraction motion [87, 90].

However, when investigating low doses, coplanar beams may increase "dose bathing" (increased volume of low and intermediate doses) and a non-coplanar beam approach can have fewer deviations from recommended protocols [91]. Lim et al [91] report that all beam arrangements with 5, 7, 9,11, 13 or 15 beams either coplanar or non-coplanar, satisfied high dose and organ at risk constraints, but non-coplanar beams were required to reach the low (intermediate) dose constraints. Similarly Fakiris et al [92] report on using 10 -12 non-coplanar, non-opposing beams to achieve SABR constraints. However, both these articles do not account for tissue heterogeneity in the planning dose calculation which Xiao et al [93] reported on the importance of.

Although it may increase the dose bathing, Richmond et al, propose using a 7 field technique with an equal beam spacing of 50°, in an effort to reduce the number of beams that overlap on the skin surface, and decrease the risk of erythema [94]. They report that a 7 field technique was suitable for 17 out of 19 patients with two or fewer high and intermediate dose constraint minor deviations per plan. However, the dose constraints used in this study were from the ROSEL protocol [95], which have a more generous approach to D_{2cm} (Gy) and $R_{50\%}$ (ratio) constraints. When these plans are critiqued against the RTOG protocol, then there would be more deviations from protocol. Richmond et al [94] detail that a direct comparison between their work and other work is misleading as earlier work [91] does not account for tissue heterogeneity, whereas the current study does. Furthermore, they state the difference between RTOG 0236 and their study changes the "goal posts". RTOG states a $R_{50\%}$ deviation of less than 3.4-4.4, whereas with ROSEL, the deviation constraint is 6-12 for the corresponding PTV size. However, Xiao et al [93] evaluate the changes observed when the heterogeneity correction was applied to RTOG 0236. Where a previous value of 3.4 would have been a deviation, it is changed to approximately 4.0, with heterogeneity correction due to the differences in secondary electron transport. This change in value is much different to the ROSEL study of 6.

Increasing the beam number to 9 or more static non-coplanar beams is reported to comply with organ at risk tolerances when delivering 60Gy in 8-10 fractions [96-99]. The Department of Radiation Oncology, Washington University School of Medicine describes a minimum of 7 non-coplanar, non-opposing beams as their protocol [100, 101] with another group reporting the use of up to 20 non-coplanar beams for treatment of NSCLC [102]. Brock et al [103] describes significant differences in recommended beam arrangements depending on to the tumour location.

Finally, the reasoning behind the use of a larger number of beams is due to the effect of congregating multiple beams at the isocentre. This creates a highly conformal dose distribution around the PTV with a steep dose gradient at the margin of the volume, thus reducing dose to normal tissue, in particular the lung and chest wall [99, 104]. Ding et al [79] report using 10 beams with 6 or more

non-coplanar. This beam arrangement is reported to satisfy dose conformity and constraints. Verbakel et al [80] describe that their 10 field non-coplanar technique is better at conforming the high doses to the PTV. Furthermore they reported reduced incidence of reduction in rib fractures compared to reported studies that only use 4 to 6 non-coplanar beams.

2.8.2 IMRT

Intensity modulated radiation therapy (IMRT) is the delivery of dose using a non-uniform radiation fluence [105]. The literature on IMRT for lung SABR is relatively scarce and not well defined. However, it is reported that IMRT, like 3DCRT, can utilize coplanar and non-coplanar beams for hypofractionated treatment of lung cancer. The Netherlands Cancer Institute, reports a predefined class solution of either 9 coplanar IMRT beams or 12 to 16 non-coplanar beams, attempting to minimize segment overlap on the skin. [106]. They reported on average, a better $R_{50\%}$ value for the non-coplanar IMRT when compared to coplanar IMRT. The Cleveland Clinical Foundation have also reported a SABR planning approach that uses an average of 7 non-coplanar, non-opposing inversely planned beams [107]. However, no clear reasoning or beam arrangement comparison was given.

Le et al [108] report using 6-8 non-coplanar IMRT beams for their lung SABR technique. No gantry angles were specified, the number of segments per beam was limited to 5, to reduce the interplay effect. Furthermore, Kim et al [109] report using on average 6.4 IMRT fields for lung SABR.

A reason for the lack of literature on IMRT for lung SBRT could be due to the concern of leaf interplay. The interplay effect, as described by Yu et al [71] is the combination of a dynamic intensity modulated beam, coupled with the internal organ motion of the patient. As the intensity modulated beam is planned using a single free breathing respiratory phase, the intensity modulation is planned on the GTV, and therefore a more dense tissue at a specific point in the lung tissue. The GTV is in the same spot for the entire calculation, whereas for treatment, the GTV will be moving due to respiration. This group reports that the mechanistic interplay of the GTV and the beam can cause large errors in the delivered dose, for clinical realistic organ motion. Wu et al [110] describe a difference of 20 % in calculated dose to delivered dose for liver SABR. Although they experienced these differences with liver SABR, the same principles could be applied for lung, especially those close to, or on the diaphragm. There are however, recent investigations that utilize volumetric modulated arc therapy (VMAT) [111-113] that refute any interplay effect for lung SABR. Furthermore, the lack of IMRT papers may also be due to the fact that 3DCRT is able to deliver the desired plan, in a timely manner compared with IMRT, and therefore would only be used to achieve

OAR tolerances in certain plans [80]. There are some suggestions from the Advanced Radiation Therapy Committee of the International Association for the Study of Lung Cancer, that IMRT is more beneficial in centrally located tumours, firstly due to the improved ability to spare adjacent normal tissues and secondly because central tumours tend to not move as much as peripheral tumours the concern over MLC interplay is negated.

2.8.3 VMAT

Volumetric Modulated Arc Therapy (VMAT) is similar to IMRT in that it is inversely planned, but instead of delivering the radiation using static fields, VMAT involves the continuous delivery of dose while the linear accelerator rotates around the patient. Furthermore there is the ability to vary dose rate and gantry speed during treatment [114].

An advantage that VMAT has over IMRT is that it is not a fixed angle technique, so the challenge of selecting optimal fixed gantry angles is somewhat eliminated [115]. However, caution needs to be applied, making sure normal tissues are not receiving unwanted, avoidable dose. To avoid overdosing normal tissue, one available option is partial arcs. For example, it is reported that 2 partial arcs are created with a 204° degree rotation [116]. The first rotation is counter-clockwise from gantry angle 179°-335°, then a second clockwise arc from 335°-179° was used to limit dose to the contralateral lung parenchyma. This beam arrangement is for a left sided lung tumour, but the arc angles are mirrored for a right sided tumour [116]. Although Chan et al [116] did not treat using SABR, the philosophies of reducing dose to the contra-lateral lung are the same. Similarly Le et al [108] use a 200° degree arc, using a gantry spacing of 4° between arc control points (segments). A control point or segment is the term of reference given to the positions of the MLCs during an IMRT or VMAT delivery. It defines how many times the MLCs have to move to produce a different shape for each IMRT beam or VMAT arc [115].

Other studies [103, 117] have described using full (>358°) arcs for treatment. Verbakel et al [80] also noted that due to the higher fractional dose, multiple deliveries of the same arc may be required, as their machine limitations required each arc to have less than 999 monitor units (MU) and in some cases they report using up to 5 full arcs. The William Beaumont Hospital, initially used an arc of 360°, however, after careful consideration and attempts to lower doses to the contra-lateral lung, changed to a partial arc protocol of 180°. The start and stop angles are manually chosen to maximize tumour coverage while reducing dose to the contra-lateral lung [118].

Holt et al [106] describe a dual partial arc technique for delivery of an 18 Gy per fraction lung SABR plan. Arc lengths of between 180°-264° are used to reduce dose to the contra-lateral lung.

Similarly to Le et al, this group also describe using a final gantry spacing of 4° as there was no appreciable improvement in the plan if the final resolution is less than 4°. The SmartArc algorithm in Pinnacle[3] (Stockholm, Sweden) separates an arc into separate control points, similar to those control points on a sliding window fixed gantry IMRT technique. This gantry spacing feature tells the planning system at what angular separation the control points are to be placed. Over a 360° arc, a gantry spacing of 4 degrees will give 91 control points (starting gantry angle also has a control point). The smaller the gantry spacing, the more control points per arc, and higher the degree of beam modulation. As SABR is delivered using high doses to generally, cylindrical structures, highly modulated beams are not a necessity.

Flattening filter free (FFF) techniques are becoming a much published area of interest with lung SABR. Conventionally, there is a tungsten flattening filter in the head of the machine to flatten and harden the beam, essentially flattening the dose profile. However, with new techniques such as IMRT and VMAT, the beam is being modulated and unflattened. Rather than flattening a beam, and then un-flattening, the FFF technique removes the filter from the beam, which consequently allows dose rates of up to 2400 Mu/min, decreasing treatment times for patients [119]. At the time of this study the Princess Alexandra Hospital was not currently equipped to deliver these treatment techniques, therefore they have not been included in this study.

2.9 TREATMENT TIMES

The extended treatment time for lung SABR is one of the main motivations for this thesis. The ability to reduce treatment times will mean less chance of intra-fraction motion. Purdie et al [87] reports that for treatment times >34 minutes the difference in mean tumour position increases from 2.2 mm to 5.3 mm. As the expansion on the PTV is only 5 mm, the tumour deviation caused by extended treatment times needs to be reduced. In regards to 3DCRT, Ong et al [97] report on average a treatment time of 11.6 minutes for a 10 field non-coplanar technique. They also report that for coplanar IMRT and full arc VMAT treatment times were 12 minutes and 10.5 respectively. However, their VMAT plans required, in some cases, multiple copies of the same beam due to limitations of 999 monitor units per arc. As 18 Gy is delivered per fraction, even with no shielding or compensation, the minimum number of monitor units would be 1800. McGrath et al [118] report that for 7 – 10 non-coplanar 3DCRT beams that a mean treatment time of 11 minutes, 56 seconds can be achieved for the delivery of 12 Gy per fraction. Conversely the treatment time for 180 degree partial VMAT arc was 6 minutes, 9 seconds. For the delivery of 7.5 Gy fraction, reported treatment times are 2 minutes and 8 seconds, 12 minutes and 40 seconds and 7 minutes and 45 seconds for VMAT, five field non-coplanar and seven field coplanar techniques respectively. Finally, Holt et al

[106] report that full arc VMAT can reduce treatment times for an 18 Gy fraction by up to 70% when compared to coplanar and non-coplanar IMRT.

Chapter 3: Research Question

3.1 AIM, OBJECTIVES AND RESEARCH QUESTIONS

This study aimed to determine if IMRT and VMAT give comparable tumour coverage and normal tissue sparing when compared to 3DCRT for patients who are diagnosed with early stage NSCLC. The hypothesis was that VMAT will give comparable tumour coverage to both IMRT and 3DCRT while reducing treatment times for patients. To achieve this aim, the following objectives were investigated;

- Identified the best treatment planning approach for lung SABR using 3DCRT, by examining different numbers of beams and arrangements
- Identified the best treatment planning approach for lung SABR using IMRT, by examining different numbers of beams and arrangements
- Identified the best treatment planning approach for lung SABR using VMAT, by examining different numbers of arcs and arrangements
- Identify the best treatment planning approach for lung SABR from the tested techniques
- Developed a standardized protocol for VMAT treatment planning of lung SABR

The study therefore answered the following questions related to the delivery of SABR for lung cancer patients;

- What is the best beam arrangement for lung SABR using 3DCRT, IMRT and VMAT?
- Can IMRT and VMAT achieve comparable or improved treatment plans when compared to 3DCRT for lung SABR?
- Can treatment times for patients be reduced with the use of either IMRT or VMAT for lung SABR?
- Can IMRT and/or VMAT replace 3DCRT as the standard treatment option for lung SABR?

3.2 RESEARCH METHOD

This study design is a prospective dosimetric comparison of 3DCRT, IMRT and VMAT for the treatment of early stage NSCLC patients deemed eligible for SABR.

Because best practice has not yet been established for either 3DCRT, IMRT or VMAT, this study was broken into two phases. Phase 1 compared different beam arrangements within each of the three techniques for the first 10 out of 20 patients. The results from Phase 1 will identified which

3DCRT, IMRT and VMAT beam arrangement best adhered to RTOG procotocls. Each of the 3DCRT and IMRT plans had six different beam arrangements to compare, and the VMAT had 3 different arc arrangements to compare (table 3.1). Determining the "gold standards" for each delivery technique gives assurance that the overall results from the study were obtained using the best possible plans. Phase 2 of the study then took the best beam arrangements of the nominated techniques and compares them against each other for the entire 20 patient dataset.

3.3 STATISTICAL METHODOLOGY

R statistical software (http://www.r-project.org) will be used to perform statistical analysis. The treatment plans will be compared using a repeated measures ANOVA (parametric test) for normally distributed data and the Friedman test (non-parametric test) for non-normally distributed data. The Shapiro-Wilk test will used to test the normality of the data. Post hoc tests (paired t-tests for normally distributed data or Wilcoxon signed-rank tests for non-normally distributed data) will be performed to confirm where the differences occurred between treatment plans when an overall significant difference between treatment plans was demonstrated. A Bonferroni correction will be used to adjust p-values for multiple comparisons. Statistical significance was defined as $p \leq 0.05$.

3.4 RESEARCH IMPORTANCE AND SIGNIFICANCE

This study aimed to provide a treatment technique for NSCLC patients that is suitable for lung SABR and that is an improvement on current conventional practice. Some departments due to technological limitations may not be able to deliver a desired technique; this study will also identify all possible treatment technique options, which may benefit a wide number of departments.
Theoretical – This study outlines the importance that is placed on SABR and how delivery is a complex process. It outlines the possible beam arrangements that can be achieved with either 3DCRT, IMRT and VMAT and allows radiation oncology departments to make informed decisions about best practice.
Practical – This study aims to provide the Princess Alexandra hospital with an evidence based protocol for delivering lung SABR. It will aim to provide the best possible treatment technique, either 3DCRT, IMRT or VMAT that can be delivered safely and effectively in the shortest amount of time. In summary this study will determine a method for treating lung SABR patients in an attempt to standardise current practice.

3.5 STRUCTURE OF THESIS

A review of the literature was performed to determine what current treatment techniques are being used to deliver lung SABR. Paper 1 (chapter 4) investigates the first phase of this project and compares 6 different 3DCRT beam arrangements for lung SABR for ten patients. The objective of this article is to determine the optimal 3DCRT beam arrangement for lung SABR to compare against the optimal IMRT and VMAT techniques. Chapter 5 is the comparison of the 6 different IMRT techniques for phase 1 of the project. It aims to determine which IMRT technique is the most optimal for lung SABR delivery. Paper 2 (chapter 6) investigates the first phase of this project and compares 3 different VMAT beam arrangements for lung SABR for ten patients. The objective of this article is to determine the optimal VMAT beam arrangement for lung SABR to compare against the optimal 3DCRT and IMRT techniques. Paper 3 (chapter 7) investigates the main aim of this thesis. It compares the best 3DCRT, IMRT and VMAT techniques against each other to determine the optimal delivery technique for lung SABR that can be delivered in the quickest treatment time. The discussion (chapter 8) brings together the entire project and pitches itself against current literature on lung SABR. The conclusion summarizes the main findings of the project and provides recommendations for implementing lung SABR in a clinical setting.

Table 3.1 – Layout of Study		
PHASE 1 (10 Patients)		
3DCRT	IMRT	VMAT
6 different beam arrangements	6 different beam arrangements	3 different arc arrangements
PHASE 2 (10 Patients)		
3DCRT	IMRT	VMAT
Best Beam Arrangement from Phase 1	Best Beam Arrangement from Phase 1	Best Arc Arrangement from Phase 1

Chapter 4: Paper 1 - The effect of beam arrangements and the impact of non-coplanar beams on the treatment planning of stereotactic ablative radiation therapy (SABR) for early stage lung cancer

All authors were responsible for manuscript revisions and provided changes and guidance on multiple occasions. For the project, author's contributions are as follows: Rhys Fitzgerald, the primary author was responsible for the project design, planning the SABR plans, analyzing the data and preparing the manuscript for author review. Dr Rebecca Owen was instrumental in the design of the project and data analyses and was a constant source of mentorship during the process. Tamara Barry and Cathy Hargrave provided planning consultation and reviewed all the plans for the project to ensure that they satisfied protocols as per the manuscript. Drs Pryor, Mai and Lehman provided a clinical perspective for the project design and data analyses. Anne Barnard provided statistical support for the project and aided in presenting the data provided. Dr Andrew Fielding played an important role in project design, data analysis and mentorship during the project.

Published: Journal of Medical Radiation Sciences - Article first published online: 14 JUL 2015, DOI: 10.1002/jmrs.118

Author names and affiliations.

Rhys Fitzgerald[ab*], Rebecca Owen[c], Tamara Barry[a], Cathy Hargrave[c], David Pryor[d], Anne Bernard[e], Margot Lehman[d], Tao Mai[d] and Andrew Fielding[b]

[a]*Division of Radiation Therapy, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[b]*Science and Engineering Faculty, Queensland University of Technology, Brisbane, Queensland, Australia*
[c]*Radiation Oncology Mater Centre, South Brisbane, Queensland, Australia*
[d]*Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[e]*QFAB Bioinformatics, The University of Queensland, Queensland Bioscience Precinct, Queensland, Australia*

Corresponding author.
*Rhys Fitzgerald Tel.: +61 7 3176 6509
E-mail address: rhys.fitzgerald@health.qld.gov.au

Address: Level G, Building 1, Princess Alexandra Hospital, Woolloongabba, QLD 4102

Abstract

Introduction: The aim of this study was to compare various coplanar and non-coplanar 3-dimensional conformal radiation therapy (3DCRT) beam arrangements for the delivery of stereotactic ablative radiation therapy (SABR) to patients with early stage lung cancer, based on the dosimetric criteria from the Radiation Therapy Oncology Group (RTOG) 1021 protocol.

Methods: Ten medically inoperable lung cancer patients eligible for SABR were re-planned using 3 different coplanar and 3 different non-coplanar beam arrangements. The plans were compared by assessing planning target volume (PTV) coverage, doses to normal tissues, the high dose conformity (conformity index) and intermediate dose spillage as defined by the D_{2cm}, (the dose at any point 2cm away from the PTV), and the $R_{50\%}$ (the ratio of the volume of half the prescription dose to the volume of the PTV).

Results: 60 plans in total were assessed. Mean PTV coverage with the prescription isodose was similar between coplanar (95.14%) and non-coplanar (95.26%) techniques (p=0.47). There was significant difference between all coplanar and all non-coplanar fields for the $R_{50\%}$ (p=<0.0001) but none for the D_{2cm} (p=0.19). The 7 and 9 field beam arrangements with 2 non-coplanar fields had less unacceptable protocol deviations (10 and 7) than the 7 and 9 field plans with only coplanar fields (13 and 8). The 13 field coplanar fields did not improve protocol compliance with 8 unacceptable deviations. The 10 field non-coplanar beam arrangement achieved best compliance with the RTOG 1021 dose criteria with only 1 unacceptable deviation (maximum rib dose).

Conclusion: A 3DCRT planning technique using 10 fields with ≥6 non-coplanar beams best satisfied high and intermediate dose constraints stipulated in the RTOG 1021 trial. Further investigations are required to determine if minor protocol deviations should be balanced against efficiency with the extended treatment times required to deliver non-coplanar fields and if treatment times can be improved using novel intensity modulated techniques.

Keywords:

Stereotactic Ablative Radiation Therapy (SABR)

Lung Cancer

3-Dimensional Conformal radiation therapy (3DCRT)

Dosimetry

Treatment Planning

Introduction:

Lung cancer is the fifth most common cancer in Australia but the most common cause of cancer related deaths.[1] The majority of patients diagnosed with early stage (I/IIa) non-small cell lung cancer (NSCLC) are able to undergo surgical resection. However, 33% of patients present with co-morbidities that make them unfit for surgery. [120] For these patients local failure following

conventionally fractionated external beam radiation therapy is in the order of 40% and treatment involves 20 to 30 attendances over 4 to 6 weeks.[22] Stereotactic ablative radiation therapy (SABR) has emerged as an alternative treatment option capable of delivering a higher biologically effective dose (BED) resulting in higher local control rates in excess of 85%. [99, 120-122] SABR involves the delivery of hypo-fractionated schedules of >7.5 Gy per day in 1-5 fractions, typically to a BED_{10} of >100 Gy.[48] SABR utilises advanced immobilisation, motion management and image guidance systems and utilises complex planning techniques to achieve highly conformal, ablative doses with rapid dose fall off outside the planning target volume (PTV).[35, 90, 123]

Dosimetric parameters such as high and intermediate dose constraints have been established in an attempt to quantitatively describe the quality of SABR plans in regards to dose fall off and conformity. The high dose constraint refers to the conformity of the prescription isodose to the PTV, measured using the conformity index (CI). The intermediate dose constraints refer to both the maximum dose to any point 2 cm from the edge of the PTV (D_{2cm}) and the ratio of the volume encompassed by the 50% isodose line (relative to the prescription dose) to the volume of the PTV ($R_{50\%}$). These planning quality metrics have been integrated into Radiation Therapy Oncology Group (RTOG) trial protocols evaluating lung SABR.[82-84] The high and intermediate dose constraints are important dose metrics as a rapid dose fall-off minimizes toxicity. [36]

Several groups have reported on their experiences with SABR beam arrangements that were required to meet the high and intermediate dose constraints.[91, 92, 94] Both Lim et al and Fakiris et al report on using multiple non-coplanar beams to achieve SABR constraints. [91, 92] However, Richmond et al report that in 17 out of 19 cases, 7 equidistant coplanar fields produced no more than 2 minor deviations. [94] This group however used high and intermediate dose constraints from the ROSEL study [95], which are more relaxed than those of RTOG. Furthermore, both Lim et al and Fakiris et al did not apply tissue heterogeneity corrections, which when reported by Xiao et al, is shown to change the value of an acceptable and unacceptable protocol deviation. [91], [92], [93] The present study was therefore designed to compare different beam arrangements (coplanar and non-coplanar) for lung SABR taking into account heterogeneity correction to determine which best satisfies RTOG 1021 dosimetric criteria.

Methods and Materials:

Patient selection

Institutional ethical approval was granted for ten patients that had previously received treatment for lung cancer at the Princess Alexandra Hospital and who met the SABR eligibility criteria to be randomly identified from our local radiation oncology information system database. Patient eligibility was defined as early stage (IA/B or IIA), with the planning target volume (PTV) <5cm in the largest dimension and the gross tumour volume (GTV) >2cm away from the proximal bronchial tree.

Simulation

All patients had been positioned in the supine position with their forearms above head in a Civco® (Iowa, USA) Vac-lok cushion. All patients had a 4-dimensional computed tomography (4DCT) scan with 10 respiratory phase bins created. A free breathing scan with a 2mm slice thickness was obtained with the length including the entire lung volume and exported and registered to the 4DCT in Pinnacle v9.4 (Philips Medical Systems, Stockholm, Sweden). The free breathing scan was nominated as the primary data set for planning purposes. The GTV was contoured on each of the respiratory phases and then combined to create an internal target volume (ITV). The PTV was created by expanding the ITV 5mm isotropically. In addition, the organs at risk (OAR) were contoured and their constraints are listed in table 1. The chest wall was defined as a 2 cm expansion anteriorly, posteriorly and laterally on the ipsilateral lung, excluding the mediastinum, vertebral body and sternum. A 2cm expansion of the PTV was used to create the D_{2cm}. All reported doses are to a minimum clinically relevant measurable volume of 0.03 cm^3.

Dose prescribing

Patients were planned to receive a prescription dose (PD) of 54 Gy in 3 fractions at the periphery of the PTV. Dose was prescribed so the covering (prescription) isodose fell between 59-90% of the absolute maximum dose in the plan as recommended by RTOG.[79, 82-84]. PTV coverage was required to be >95% for the prescription dose (PTV_{54Gy}), and >99% for 90% of the prescription dose ($PTV_{48.6Gy}$). All D_{2cm} and $R_{50\%}$ constraints (RTOG 1021) are relative to PTV size (table 2) and were interpolated as required for each patient. In this study, the CI was calculated using equation 1,

$$\frac{(TV_{PTV})^2}{TV * PIV}$$

where TV_{PTV} is defined as the total volume of PTV covered by the covering isodose (54Gy), TV is defined as the total volume of the PTV and PIV is defined as the total volume of the covering isodose in the patient [124]. A CI value of ≥0.75 was desirable, with ≥0.65 constituting an acceptable deviation and anything <0.65 was considered unacceptable.

Treatment planning

All plans were constructed by a single planner and calculated with Pinnacle v9.4 using the collapsed cone convolution (CCC) algorithm with a grid spacing of 0.25 cm^3. The CCC algorithm is a type B algorithm and accounts for changes in lateral electron transport and should therefore be used for lung tumour treatments. As large differences are noted in calculations, the dose prescription and spillage guidelines (table 2) that were calculated using a type A or water based algorithm (0236) should not be used when using a type B algorithm. [8, 19] As a consensus does not exist in the literature, beam arrangements were derived from multiple sources to

account for a wide range of recommendations. RTOG recommends the use of 7 beams as a minimum, where as a retrospective review of local departmental preference showed 9 beams, including 2 non-coplanar beams was typical. Furthermore, the use of 10 beams, with six being non-coplanar is recommended by Ding et al, while the European Organisation for the Research and Treatment of Cancer (EORTC) recommend against non-coplanar beams due to the associated increase in treatment times. [79, 90] Lastly a 13 field evenly spaced all coplanar arrangement was also investigated to assess if number of coplanar beams, or non-coplanar beams improves plan quality. Treatment plans investigated in this study therefore included: 7 coplanar beams (7C), 9 coplanar beams (9C), 13 coplanar beams (13C), 7 beams including 2 non-coplanar beams (7NC), 9 beams including 2 non-coplanar beams (9NC) and 10 beams with 6 or more non-coplanar beams (10NC). Starting beam angles for a right-sided tumour where G represents gantry and angle and F represents floor angle were; 7C technique, G180, G210, G240, G270, G300, G330 and G10, all with a floor of 0 (F0), the 9C technique, G180, G210, G240, G270, G300, G330 and G10, G40, G100 all with a floor of 0 (F0), the 7NC technique, G210F0, G330F90, G240F0, G270F0, G300, G330 and G30F90, the 9NC technique G210F0, G330F90, G240F0, G270F0, G300, G330 and G30F90, G40F0 and G100F0. The 10NC used beam angles as referenced by Ding et al [79] and the 13C technique used 13 evenly spaced beams around 360° with a floor of 0. Beam angles were adjusted as necessary to achieve protocol compliance. Angles were mirrored for a left sided tumour. All beam angles were checked for clearance on the treatment machine.

Every attempt was made to ensure the 7C field techniques used beam angles entering only through the ipsilateral lung to avoid unnecessary exposure of the contra-lateral lung to radiation. However, the 9C field technique required beams entering through the contra-lateral to avoid overlapping beams and consequently increasing the low and intermediate dose wash. Two coplanar beams in the 7C and 9C techniques were made non-coplanar for the 7NC and 9NC techniques. These were typically superior anterior and superior posterior oblique fields. The 10NC technique used 6 non-coplanar beams and only introduced more non-coplanar beams if the D_{2cm} or $R_{50\%}$ values were unachievable. Beam weights were manipulated by the planner to achieve isotropic dose fall off in accordance with criteria listed in table 2, apart from the 13C technique, where each beam was given equal weighting and only adjusted if OAR were over tolerance. PTV coverage below 95% was only allowed if the spinal cord or brachial plexus constraints could not be met.

A structure for creating a block margin was created by shrinking the PTV 2mm laterally, anteriorly and posteriorly and expanding 2mm superiorly and inferiorly. The multi-leaf collimator (MLC) shielding of each beam was then shaped to the structure. This structure was adjusted as necessary to achieve PTV coverage and a prescription isodose between 59-90%. The block margin structure results in the MLC shielding the periphery of the PTV such that the prescription isodose falls into the beam penumbra, allowing for a steep dose gradient beyond the PTV. An expansion superior and inferior to the block margin structure was needed to account for limitations of non-coplanar beams. Even though non-coplanar beams are used, most of the dose is still delivered across the transverse plane. Dose in all plans was normalized to the maximum dose in the plan which was generally located in the centre of the PTV.

Planning Priorities and Protocol Deviations

Planning priorities were first and foremost, to adhere to the spinal cord and brachial plexus constraint, secondly to meet the high and intermediate dose constraints and lastly to meet the remaining OAR constraints. [86] The RTOG 1021 protocol defines plan deviations as either being none or acceptable, with an unacceptable deviation for plans that exceeds the acceptable deviation. With all plans, every attempt was made to achieve the no deviation values (table 2). However, some situations resulted in unavoidable digression from the priorities. For instance, if an OAR is immediately adjacent to the PTV, then adhering to the maximum dose constraint could be challenging. In this instance the maximum dose to the adjacent OAR can be105% of the prescription dose and registering as an acceptable deviation. However, all volumetric dose constraints to the structure must still be respected. Furthermore, to avoid clinical toxicity due to overdosing OAR, the dose fall off may be weighted so it is not isotropic, but still falls within the acceptable deviation. Plans were considered clinically suitable if there were no unacceptable deviations from protocol.

To represent protocol deviations with respect to the D_{2cm} and $R_{50\%}$ constraints, a scoring system was devised. As intermediate dose constraints are dependant on PTV size, mean D_{2cm} and $R_{50\%}$ for each planning technique would not best represent the cohort. Therefore, the absolute difference (if any), from the no deviation constraint was calculated. For example, if the no deviation constraint for D_{2cm} was 30 Gy, and the technique achieved 32 Gy, then this would result in a value of 2. Conversely, if another technique achieved 29.5 Gy at D_{2cm}, this would give a value of -0.5. Therefore, a D_{2cm} or $R_{50\%}$ value of 0 represents compliance with a no deviation.

Statistical methodology

Statistical analyses was performed using R statistical software (http://www.r-project.org). To compare coplanar and non coplanar arrangements statistical tests for paired data were performed with the normality of the data tested using the Shapiro-Wilk test. The paired Student parametric test has been used for normally distributed data and Wilcoxon signed-rank non parametric test for non-normally distributed data. Statistical significance was defined as $p \leq 0.05$.

Results:

Median patient age was 76, with 70% being male. Median PTV size was 27.5cm^3 (22.8 - 79.1cm^3). In 50% of cases, the PTV was overlapping the chest wall (CW). There were between 6 and 8 non-coplanar beams for the 10NC technique. The 10NC beam arrangement was the only technique where the number of non-coplanar beams was varied and the resultant plans met the dosimetric criteria. Across all techniques, only 19 of the 60 plans had no more than 2 minor protocol deviations. Total mean monitor units (MU) for the 7C, 9C, 7NC, 9NC, 10NC and 13C were 2867.65, 3019.54, 2919.23, 2996.87, 3225.36 and 3088.51 respectively. The largest

difference in monitor units was between the 7C and 10NC with a total of 357.71 MU. Plans were delivered at 600 MU/min.

Protocol Deviations

A summary of the plan deviations, relative to RTOG 1021 (table 2) is presented in table 3. Overall, as the number of beams increased, there were fewer protocol deviations. Only on one occasion was the 10NC beam arrangement unable to produce an acceptable plan. In this case the PTV was overlapping the chest wall by 6.7 cm^3 and the maximum dose could not be lowered to 56.7 Gy (105%), while maintaining PTV coverage.

PTV Coverage

Table 5 reports the PTV coverage for all beam arrangements. No statistically significant difference was found between PTV coverage for coplanar versus non-coplanar techniques (p=0.47 and p=0.87 for PTV_{54Gy} and $PTV_{48.6Gy}$ respectively). The median prescription isodose, independent of technique was 68% (60.9%-87%). Median prescription isodoses values and ranges were 68.4% (63.8-85.7%), 67.9% (62.2-86.9%), 66.8% (63.2-85.8%), 68.2% (63.3-86.4%), 62.6% (60.9-87%) and 68.8% (63.3-87%) for the 7C, 9C, 7NC, 9NC, 10NC and 13C plans respectively. Across all techniques, median prescription isodoses were 65.8% for PTVs not overlapping the CW, and 74.6% for PTVs overlapping the CW.

High and Intermediate Constraints

The recorded D_{2cm} and $R_{50\%}$ deviations are reported in table 4. The D_{2cm} values for combined techniques were 1.14 and 0.66 for all coplanar and all non-coplanar arrangements respectively with a non-significant p value of 0.19. Combined techniques recorded a $R_{50\%}$ value of 1.06 for coplanar, and 0.62 for non-coplanar with a significant p value of <0.0001. CI values, different to D_{2cm} and $R_{50\%}$ constraints are independent of PTV size and can be reported as the actual value. The mean CI values are reported in table 5 with no statistically significant difference (p=.71).

Organs at Risk

Forty-three percent (n=26) of plans had OAR tolerance dose violations, independent of technique. The maximum rib dose was responsible for the majority of protocol deviations. Five patients had PTVs overlapping the chest wall, limiting the rib to a maximum dose of 56.7 Gy. For the 7C, 9C, 7NC, 9NC and 13C, the mean maximum rib dose was on average for these plans, 60.5 Gy, 60.4 Gy, 60.5 Gy, 59.7 Gy and 60.4 Gy respectively, all of which are over the allowed tolerance. When removing patient 8 from the mean, the values for the aforementioned techniques are 61.0 Gy, 60.7 Gy, 60.8 Gy, 60.0 Gy and 60.8 Gy respectively. The 10NC technique had a mean maximum rib dose of 56.7 Gy (excluding patient 8), the allowable tolerance of 105% of the prescription dose. There was however an increase in the lung volume receiving 10.5 Gy and 11.4 Gy for the 10NC compared to other techniques. The results in table 5 show there was no statistically significant difference in mean lung dose between the coplanar and non-coplanar techniques (p=0.68).

Discussion:

This study investigated dosimetric factors of various coplanar and non-coplanar beam arrangements for the treatment of patients eligible for lung SABR with heterogeneity corrections applied.

There were no significant differences in PTV coverage (PTV_{54Gy} or $PTV_{48.6Gy}$) between beam arrangements, given that they are compulsory protocol requirements and coverage beyond 95% was only improved if the D_{2cm} and $R_{50\%}$ constraints maintained a no deviation. The 10NC technique had the greatest PTV_{54Gy} coverage of 95.37%, which is on average 0.5% higher than any other technique.

The prescription isodoses for the plans were kept to between 59% and 90% as recommended by RTOG and Ding et al.[79, 82-84] The median prescription isodose value in this study was 68% (62.6%-68.7%), which is consistent with previous reports on optimal prescription isodoses for peripheral lung SABR. [79] There was a difference in prescription isodoses for plans where the PTV was overlapping the CW. For those plans where PTV was overlapping the CW the prescription isodose could be increased from a median value of 65.8% to 74.6%. This is due to the more dense soft tissue adjacent to one side of the PTV and the reduced secondary electron range in the tissue.

Furthermore, without comprehensive rib maximum and dose volume constraints, it is considered best practice to minimize the dose where possible. [125-129] Because plans are prescribed in a way so the maximum dose typically falls within the centre of the PTV, those patients whose PTV overlaps a rib could have a maximum dose that is well beyond the 105% of the PD. Only the 10NC technique was able to consistently achieve the maximum rib dose constraint while still achieving 95% coverage of the PTV (with the exception of patient 8). This is likely due to a greater ability to improve shielding of the rib by increasing the number of non-coplanar beams coupled with a higher prescription isodose attainable on the chest wall.

The dosimetric study by Lim et al performed without a tissue heterogeneity correction found that increasing the number of non-coplanar beams increased the possibility of achieving intermediate dose constraints. [91] Our study accounted for tissue heterogeneity and confirmed that an increase in non-coplanar beams resulted in less protocol deviations. The greatest protocol deviations were found for the 7 and 9 field all coplanar beam arrangements. There were 13 and 8 instances respectively, where these techniques had major protocol deviations (table 3). The 10NC was found to produce the best plan with only one protocol deviation for the maximum rib dose on patient 8 (59.1 Gy).

The dosimetric advantages of using non-coplanar beams has previously been reported, however, the results of the current study illustrate that non-coplanar beams are necessary to meet the intermediate and OAR dosimetric constraints for any single plan. [81] We demonstrated that there is a statistically significant difference in the volume of the 27 Gy isodose ($R_{50\%}$), for coplanar versus non-coplanar techniques. Furthermore, there was no case where any technique apart from the 10NC was able to produce a plan with no protocol deviations. Increasing the number of fields (13C) resulted in a slight improvement when compared to either of the coplanar and non-coplanar 7 and 9 field techniques with fewer protocol deviations in regards to the intermediate dose. However, it was not able to replicate the intermediate dose sparing achievable with the 10NC technique. Figure 1 demonstrates a dose wash of all 6 techniques through the isocentre highlighting the reduction in intermediate dose achievable with the 10NC technique. In theory, increasing the number of beams reduces the dose delivered through each

beam, spreading out the low dose and overlapping beams, resulting in a lower intermediate dose. This is the philosophy of SABR and allows for a steep isotropic fall off and is shown clearly in our study.

Our findings differ from those reported by Richmond et al where in 89.5% of cases a 7 field, all coplanar technique had 2 or less minor deviations. [94] They too accounted for heterogeneity correction, but used the less stringent intermediate dose constraints from the ROSEL trial.[95] The difference in intermediate dose constraints between RTOG 1021 and ROSEL significantly alters which beam arrangements are deemed acceptable. All the techniques tested in this study had intermediate doses that were acceptable following the ROSEL guidelines. However, following RTOG 1021 criteria we report that a 7 field technique, with beams entering through only the ipsilateral lung produced no plans with equal to, or less than 2 minor deviations. The difference in acceptable D_{2cm} and $R_{50\%}$ constraints is believed to be the main reason for disparity.

The EORTC recommend avoiding the use of non-coplanar beams as this increases the treatment time, and chance of intra-fraction motion [90]. Furthermore, Purdie et al suggest that for treatment times >34 minutes intra-fraction motion can increase by up to 5 mm. [87] The trade off between small gains in intermediate dose sparing versus increased treatment time and the potential for intra-fractional error with increasing non-coplanar beams should be critiqued on an individual patient basis.

Conclusion:

Increased use of non-coplanar beams for 3DCRT lung SABR allows for improved control of intermediate dose objectives and produces fewer protocol deviations when correcting for tissue heterogeneity and following RTOG 1021 guidelines.. A technique using 10 beams, six or more of which were non-coplanar provided the greatest compliance to high and intermediate dose constrains, while lowering doses to some critical structures. However, increased non-coplanar beams results in an increased treatment time that needs to evaluated for each individual patient. The ability to deliver adequate PTV coverage and acceptable intermediate doses using coplanar techniques may be possible with novel techniques such as intensity modulated radiation therapy or volumetric modulated arc therapy and will be the subject of future work.

Table 4.1 - Organ at risk dose constraint

Organ	Constraint(s)
Spinal Cord	18 Gy < 0.35 cm^3 12.3 Gy < 1.2 cm^3 MPD < 21.9 Gy
Brachial Plexus	20.4 Gy < 3 cm^3

	MPD < 24 Gy
IVC	39 Gy < 10 cm^3 MPD < 49 Gy
SVC	39 Gy < 10 cm^3 MPD < 49 Gy
Aorta	39 Gy < 10 cm^3 MPD < 49 Gy
Pericardium	24 Gy < 15 cm^3 MPD < 30 Gy
Trachea	15 Gy < 4 cm^3 MPD < 30Gy
Combined Lungs – ITV	11.4 Gy < 1000 cm^3 10.5 Gy < 1500 cm^3
Oesophagus	17.7 Gy < 5 cm^3 MPD < 25.2 Gy
Rib	40 Gy < 5 cm^3 MPD < 50 Gy
CW	30 Gy < 30 cm^3 (<70 cm^3 for tumours on the CW)
Skin	30 Gy < 10 cm^3 MPD < 33 Gy

Abbreviations IVC = inferior vena cava, SVC = superior vena cava, ITV = internal target volume, CW = chestwall, MPD = maximum point dose (defined as ≥0.03 cm^3)

Table 4.2 - Acceptable dose spillage guidelines from RTOG 1021

Ratio of Prescription Isodose Volume to the PTV		Ratio of 27 Gy Isodose Volume to the PTV $R_{50\%}$		Maximum Dose at 2 cm from PTV in any direction as % of Prescribed dose (PD). D_{2cm} (gy) = % x PD		Percent of lung receiving 20 Gy total of more V20 (%)		PTV Volume (cc)
Deviation		Deviation		Deviation		Deviation		
None	Acceptable	None	Acceptable	None	Acceptable	None	Acceptable	
<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15	1.8
<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15	3.8
<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15	7.4
<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15	13.2
<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15	22.0
<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15	34.0
<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15	50.0
<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15	70.0
<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15	95.0
<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	<10	<15	126.0
<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	<10	<15	163.0

Deviation values can be interpolated as required.

Table 4.3 - Beam arrangements and protocol deviations following RTOG 1021 criteria.

	7C	9C	13C	7NC	9NC	10NC
D_{2cm}						
None	1	2	6	2	4	10
Acceptable	6	8	4	6	6	0
Unacceptable	3	0	0	2	0	0
$R_{50\%}$						
None	0	1	1	1	1	5
Acceptable	5	6	6	6	7	5
Unacceptable	5	3	3	3	2	0
CI						
None	9	10	10	10	9	9
Acceptable	1	0	0	0	1	1
Unacceptable	0	0	0	0	0	0
OAR						
None	4	4	3	4	4	5
Acceptable	1	1	1	1	1	4
Unacceptable	5	5	5	5	5	1
Total Deviations						
None	14	17	20	17	18	29
Acceptable	13	15	12	13	15	10
Unacceptable	13	8	8	10	7	1
Clinically Suitable Plans	1	2	2	3	3	9

Abbreviations D_{2cm} = dose at any point 2cm from the PTV, $R_{50\%}$ = ratio of the volume of half the prescription dose to the volume of the PTV, CI = conformity index, OAR = organ(s) at risk

Table 4.4 - Mean dose statistics for each technique, categorized into coplanar and non-coplanar and mean values for all coplanar and non-coplanar techniques combined with associated P values.

	PTV_{54Gy} (%)	$PTV_{48.6Gy}$ (%)	Mean Lung Dose (Gy)	$R_{50\%}$ (Deviation)	D_{2cm} (Deviation)	CI
Coplanar						
7 Fields	95.2	99.48	3.91	1.22	3.12	0.79
9 Fields	95.12	99.59	4.12	1.05	1.16	0.80
13 Fields	95.09	99.63	4.26	0.91	-0.86	0.82
Non-Coplanar						
7 Fields	95.07	99.58	4.10	0.79	2.06	0.80
9 Fields	95.12	99.57	4.13	0.71	0.70	0.81
10 Fields	95.6	99.58	4.38	0.35	-0.76	0.81
Mean Values						
All Coplanar	95.14	99.57	4.01	1.10	1.14	0.80
All Non-Coplanar	95.26	99.58	4.12	.62	0.66	0.80
P value	0.47	0.87	0.09	<0.0001	0.19	0.71

Abbreviations PTV_{54Gy} = Percentage of the PTV receiving 54 Gy, $PTV_{48.6Gy}$ = Percentage of the PTV receiving 48.6 Gy, D_{2cm} = dose at any point 2cm from the PTV, $R_{50\%}$ = ratio of the volume of half the prescription dose to the volume of the PTV, CI = conformity index

Table 4.5 - Mean values for recorded OAR doses for selected OAR categorized by technique and all coplanar and all non-coplanar techniques combined.

	SC			Pericardium		Combined Lung - ITV		Ribs		CW	Oesophagus	
Technique/ Constraint (Aim)	18Gy (<0.35 cm^3)	12.3Gy (<1.2 cm^3)	MPD (<21.9 Gy)	24Gy (<5 cm^3)	30 Gy (<30 cm^3)	10.5Gy (<1500 cm^3)	11.4Gy (<1000 cm^3)	40Gy (<5 cm^3)	MPD (<50Gy)	30 Gy (<30 cm^3)	17.7 Gy (<5 cm^3)	MPD (<25.2 Gy)
Coplanar												
7 Fields	0	0.1	10.2	0.4	18.3	450.1	422.0	1.4	46.0	19.9	0.3	9.4
9 Fields	0	0.2	10.6	0.7	17.5	472.9	438.9	1.4	45.6	19.1	0.1	12.3
13 Fields	0	0.3	12.3	2.0	18.3	465.5	419.1	1.5	45.5	18.8	0.0	14.0
Non-Coplanar												
7 Fields	0	0.1	8.3	0.2	15.9	453.9	420.4	1.5	45.2	18.0	0.2	9.8
9 Fields	0	0.1	8.8	0.4	15.8	451.3	416.5	1.5	45.6	17.4	0.0	12.9
10 Fields	0	0.2	9.9	0.5	13.6	508.9	461.7	1.2	42.6	15.4	0.0	12.4
Mean Values												
All Coplanar	0	0.2	11.0	1.0	18	462.8	426.7	1.4	45.7	19.3	0.0	11.9
All Non-Coplanar	0	0.1	9.0	0.4	15.1	471.4	432.9	1.4	44.5	16.9	0.0	11.7

Abbreviations SC = Spinal canal, ITV = Internal target volume, CW = Chest wall, MPD = Maximum point dose

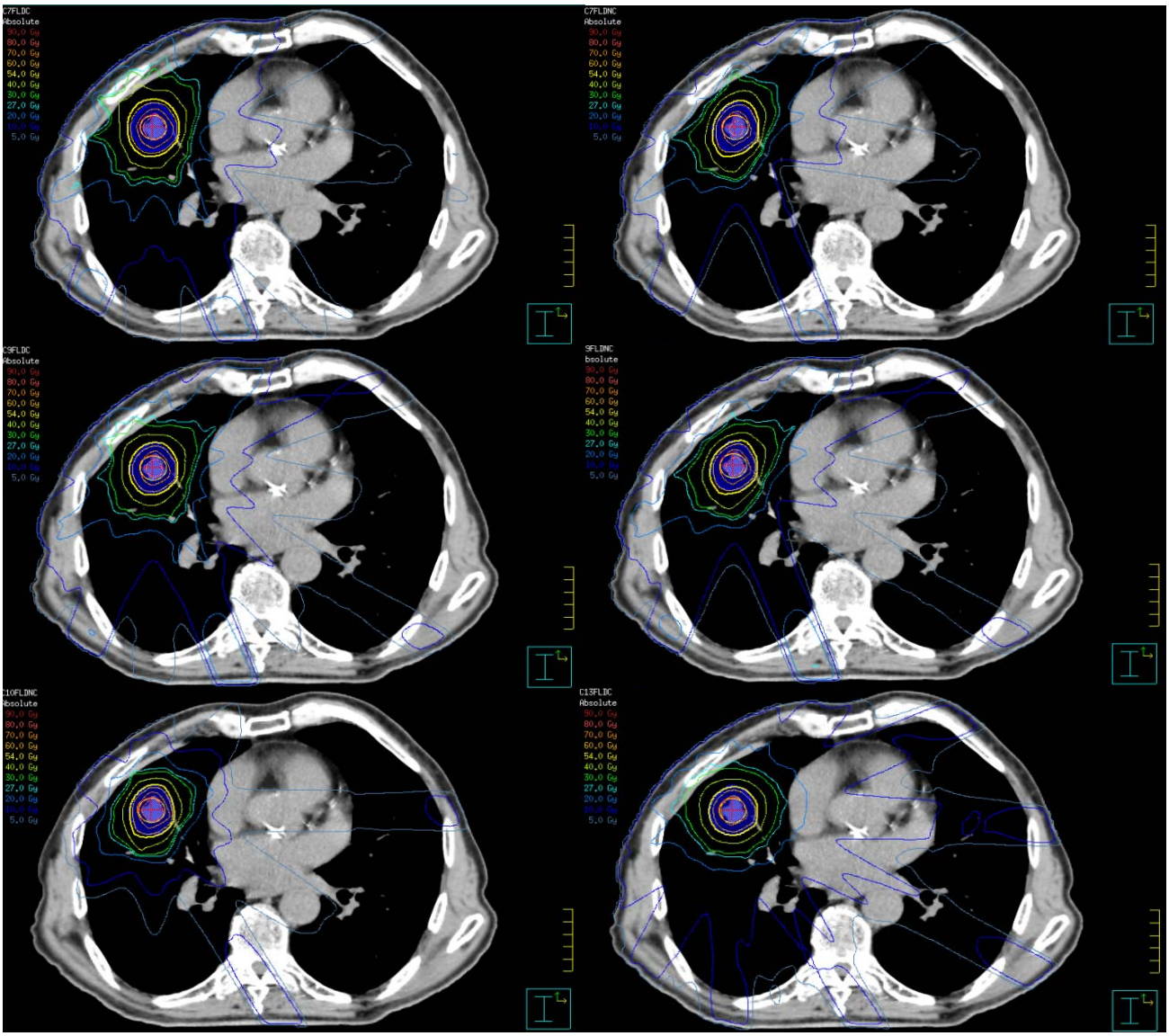

Figure 4.1 - Dose wash through a transverse slice for each of the six techniques. A, 7C. B, 7NC. C, 9C. D, 9NC. E, 10NC. F, 13C.

CHAPTER 5: Paper 2 - Intensity Modulated Radiation Therapy for peripheral lung stereotactic ablative radiation therapy: A comparison of 6 different beam arrangements

All authors were responsible for manuscript revisions and provided changes and guidance on multiple occasions. For the project, author's contributions are as follows: Rhys Fitzgerald, the primary author was responsible for the project design, planning the SABR plans, analyzing the data and preparing the manuscript for author review. Dr Rebecca Owen was instrumental in the design of the project and data analyses and was a constant source of mentorship during the process. Tamara Barry and Cathy Hargrave provided planning consultation and reviewed all the plans for the project to ensure that they satisfied protocols as per the manuscript. Drs Pryor, Mai and Lehman provided a clinical perspective for the project design and data analyses. Anne Barnard provided statistical support for the project and aided in presenting the data provided. Mr Venkatakrishnan Seshadri performed all necessary physics testing to make sure the plans were clinically deliverable. Dr Andrew Fielding played an important role in project design, data analysis and mentorship during the project.

Running Title: IMRT for peripheral lung SABR

Published: TBD

Author names and affiliations.
Rhys Fitzgerald[ab*] BAppSc (MRT), Rebecca Owen[bc] PhD, Catriona Hargrave[cd] MAppSc, David Pryor[e] MBBS FRANCR,Tamara Barry[c] BAppSc (MRT), Margot Lehman[e] MBBS FRANZCAR, , Anne Barnard[f] PhD, Tao Mai[e] MBBS FRANCZR, Venkatakrishnan Seshadri[g] PhD and Andrew Fielding[b] PhD

[a]*Radiation Oncology Centres, Mater Private Hospital, Springfield, Queensland, Australia*
[b]*Science and Engineering Faculty, Queensland University of Technology, Brisbane, Queensland, Australia*
[c]*Division of Radiation Therapy, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[d]*Radiation Oncology Mater Centre, South Brisbane, Queensland, Australia*
[e]*Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[f]*QFAB Bioinformatics, Institute for Molecular Bioscience, University of Queensland, Queensland, Australia*
[g]*Division of Radiation Physics, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*

Corresponding author.
*Rhys Fitzgerald Tel.: +6 1 7 3447 1900
Radiation Oncology Centres, Mater Private Hospital, Springfield, QLD, Australia, 4300
E-mail address: rhys.fitzgerald@roc.team

Conflicts of interest: None

Ethics: Institutional ethical clearance was granted for this study

Abstract

Purpose: The aim of this study was to investigate six different beam arrangements for the delivery of intensity modulated radiation therapy (IMRT) to peripheral lung tumours using stereotactic ablative radiation therapy (SABR).
Methods and Materials: Six new IMRT treatment plans were created for 10 patients who were deemed eligible for SABR. Plans consisted of between 7 and 10 beams, with 3 coplanar and 3 non-coplanar beam arrangements. These plans were critiqued against dosimetric parameters incorporated in the RTOG 1021 protocol including: planning target volume (PTV) coverage, dose to organs at risk (OAR), conformity index (CI) and intermediate dose constraints (D_{2cm} and $R_{50\%}$). For statistical calculations, the 3 coplanar and 3 non-coplanar techniques were group together.
Results: 60 plans (30 coplanar and 30 non-coplanar) were generated for comparison. Clinically acceptable plans (no unacceptable protocol deviations) were achieved in 10 out of 30 coplanar plans and 20 out of 30 non-coplanar plans. PTV coverage (V_{54Gy} and $V_{48.6Gy}$) was similar between the coplanar (95.2%, 99.97%), and non-coplanar techniques (95.35%, 99.99%) with no statistically significant difference found (p=0.64, 0.29). There was no difference in the CI between all coplanar and all non-coplanar techniques (p=0.9). Non-coplanar techniques provided better intermediate dose sparing with a statistically significant difference for the D_{2cm} (<0.01) and $R_{50\%}$ (<0.01) when compared to coplanar techniques.
Conclusion: Non-coplanar IMRT provided better compliance with RTOG 1021 protocol for intermediate dose sparing and OAR avoidance. Nine or more treatment fields (either coplanar or non-coplanar) are recommended for tumours adjacent to the chest wall.

Introduction:

Lung cancer has a high burden on the Australian population with 1 in 13 men, and 1 in 23 women expected be diagnosed in their lifetime[130]. Surgical resection is the current standard treatment option for the majority of patients. However, for those patients that are medically inoperable or refuse surgery, external beam radiation therapy (EBRT) is a practical alternative. EBRT for early stage peripheral lung cancer is more commonly being delivered in the form of stereotactic ablative radiation therapy (SABR). SABR is the delivery of ≥10 Gy per fraction in ≤5 fractions. This highly ablative dose regime requires advanced radiation therapy treatment planning techniques, which generally involve a high number of non-coplanar beams[131]. Numerous groups have previously reported on the use of 3-dimensional conformal radiation therapy (3DCRT) for the delivery of lung SABR.[91, 94, 131-133]

Intensity modulated radiation therapy (IMRT) is now a well established practice for many tumour sites due to its ability to better conform the dose to the tumour, resulting in reduced doses to critical structures adjacent to the tumour [134]. However, its use in lung SABR has been rarely reported on. In 2010, Videtic et al [107] report that there were no published reports on outcomes of lung SABR treated with IMRT. Both Ong et al [97] and Holt et al [106] have reported on dosimetric indices IMRT for peripheral lung SABR against other delivery

techniques. Ong et al [97] compared dynamic conformal arc therapy with coplanar 3DCRT and only used IMRT for those patients whose tumours where adjacent to the chest wall (CW). Holt et al [106] compared coplanar and non-coplanar IMRT against VMAT. To the best of the authors' knowledge, there is no previous study comparing different beam arrangements for lung SABR using IMRT. This study therefore explores six different beam arrangements for the delivery of peripheral lung SABR using IMRT.

Material and methods:

Ten patients whose tumours were early stage disease (Ia/b or IIa) measuring <5cm in the largest dimension and were >2cm away from the proximal bronchial tree were identified from our radiation oncology information system database. The inclusion criteria was as per RTOG 1021[86].

Patients underwent planning simulation as previously reported.[131] Both a 4 dimensional computed tomography (4DCT) and a free breathing CT scan were exported to Pinnacle v9.6 (Philips Medical Systems, Stockholm, Sweden) for treatment planning. An internal target volume (ITV) was created by contouring the gross tumour volume on each respiratory phase of the 4DCT. A 5mm isotropic expansion was used to generate the planning target volume (PTV) from the ITV. All OAR (table 1) contouring and treatment planning was done using the free breathing CT scan.

For each plan, 54 Gy in 3 fractions was prescribed to the periphery of the PTV. Planning aims were to achieve >95 % coverage of the PTV with the prescription dose (PTV_{54Gy}) and 99% coverage of the PTV with 90% of the prescription dose ($PTV_{48.6Gy}$). Maximum doses in the plan were allowed not allowed to exceed 90.5 Gy, but were expected to be relatively high (75-85 Gy) to achieve a steep dose gradient. OAR tolerances used were those reported in RTOG 1021 (table 1). The D_{2cm}, (the dose at any point 2cm from the PTV), and $R_{50\%}$ (the ratio of the volume of half the prescription dose to the volume of the PTV) were used to measure intermediate dose spillage and protocol deviations (RTOG 1021) and are shown in table 2. To quantify the conformity of the prescription dose to the PTV, the conformity index (CI) was used[131],

$$\frac{(TV_{PTV})^2}{TV * PIV}$$

where TV_{PTV} was defined as the total volume of PTV covered by the prescription dose, TV was defined as the total volume of the PTV and PIV was defined as the total volume of the prescription dose in the patient . A CI value of ≥0.75 was no deviation, ≥0.65 was an acceptable deviation and <0.65 was considered an unacceptable deviation, based on translating the RTOG 1021 CI constraints (table 2) to this formula.

Each plan was created using the initial set of objectives (table 3) as reported by the authors [131] and other non-target tissue objectives (heart, spinal cord etc.) were contoured and given an objective as clinically necessary on a patient by patient basis. The rationale for beam arrangements was derived from previously published reports by Ding et al [79] and Fitzgerald et al [131]. Treatment plans investigated in this study included: 7 coplanar beams (7C), 9

coplanar beams (9C), 13 coplanar beams (13C), 7 beams including 2 non-coplanar beams (7NC), 9 beams including 2 non-coplanar beams (9NC) and 10 beams with 6 or more non-coplanar beams (10NC). Starting beam angles used were as per Fitzgerald et al [131]. Beam angles were adjusted by the treatment planner to achieve target coverage and OAR sparing as per protocol. All beam angles were checked for clearance on the treatment machine. Standard IMRT based physics QA was performed in which planned dose distributions (fluence) were measured against actual delivered distributions (fluence) for each field using a gamma analysis acceptance criteria of 3%/3mm[74].

Intermediate doses were limited by two different control structures. Primarily, a structure which consisted of the patient's body contour minus a PTV expansion of 2cm was used to control the dose at D_{2cm} and given a maximum dose objective as per table 2 (27 Gy Ring). If this structure wasn't able to achieve the $R_{50\%}$ constraint (table 2) as well, then another dose limiting structure was created. This structure was typically a 1 cm isotropic expansion of the PTV removed from the patient's body contour, but was altered on an individual patient basis as needed. A 54 Gy ring, a 0.1cm expansion on the PTV, minus the PTV was used to control the prescription dose and improve conformity. Maximum doses in OAR directly adjacent to the PTV were allowed to receive up to 105% of the prescription dose. Planning priorities, in order, were to firstly respect the spinal cord constraint, secondly, cover the PTV with 95% of the prescription dose, thirdly, adhere to intermediate (D_{2cm} and $R_{50\%}$) dose constraints while generating a steep isotropic dose fall off, and lastly to meet non-spinal cord OAR constraints. The number of segments was limited to 70 for all 10 beams using the direct machine parameter optimization (DMPO) algorithm. The collapsed cone convolution (CCC) algorithm was used for calculations, with a minimum field size of $4cm^{2,}$ and a grid size of 0.3 cm^2.

The R statistical software (http://www.r-project.org) was used to perform statistical analysis. The six IMRT treatment plans were compared using a repeated measures ANOVA (parametric test) for normally distributed data and the Friedman test (non-parametric test) for non-normally distributed data. The Shapiro-Wilk test was used to test the normality of the data. Post hoc tests (paired t-tests for normally distributed data or Wilcoxon signed-rank tests for non-normally distributed data) were performed to confirm where the differences occurred between treatment plans when an overall significant difference between treatment plans was demonstrated. A Bonferroni correction was used to adjust p-values for multiple comparisons. Statistical significance was defined as $p \leq 0.05$.

Results:

Deviations to protocol (RTOG 1021 (table 2)) in regards to D_{2cm}, $R_{50\%}$, CI and OAR are reported in table 4. Acceptable plans which were defined as having no major protocol deviations were achievable in 2, 3, 5, 3, 7 and 10 of the 10 plans for the 7C, 9C, 13C, 7NC, 9NC and 10NC techniques respectively. Specific dosimetry metrics are reported in table 5. There was no statistically significant difference between the individual plans for PTV_{54Gy} or $PTV_{48.6Gy}$ coverage (table 5). There was no statistical difference between all coplanar techniques, when compared to all non-coplanar techniques for PTV coverage. The CI was similar among techniques, and for coplanar versus non-coplanar.

A previously used scoring system for measuring the absolute difference of the D_{2cm} and $R_{50\%}$ was used to evaluate the deviations from an acceptable value (no deviation) [131]. This method was used as the intermediate dose constraints are dependent on PTV size and therefore, mean $R_{50\%}$ and D_{2cm} for the entire cohort could be misleading. A value of zero would indicate compliance, >0 would be a deviation and <0 would mean no deviation. The mean absolute difference from the $R_{50\%}$ no deviation value (table 2) was 1.42, 0.98 and 0.99 for the 7C, 9C and 13C techniques respectively. Mean differences for the non-coplanar techniques were 1.1, 0.90 and 0.30 respectively for 7NC, 9NC and 10NC. Additionally, combined coplanar and non-coplanar techniques had a mean $R_{50\%}$ difference from no deviation of 1.13 and 0.60 respectively. D_{2cm} absolute mean differences from no deviation were, -0.67, -2.46, -3.82, -1.67, -2.62 and -3.92 for the 7C, 9C, 13C, 7NC, 9NC and 10NC techniques respectively. Furthermore, combined coplanar and combined non-coplanar had mean D_{2cm} differences from no deviation of -1.84 and -2.74 respectively.

OAR sparing was similar among techniques (table 6). Spinal cord maximum doses were lower with the non-coplanar techniques (table 6). Maximum rib doses were achievable in 7, 8, 9, 7, 10 and 10 of the 10 plans respectively for the 7C, 9C, 13C, 7NC, 9NC and 10NC techniques. Additionally, there was one patient where the 7C and 7NC techniques couldn't achieve 40 Gy < 5 cm^3 of the rib. Other acceptable OAR deviations were recorded for the skin maximum dose (two patients), heart maximum dose (two patients) and greater than 30 cm^3 of CW receiving above 30 Gy (3 patients). Median prescription isodose values were 65.4 % (60.8 – 79.4 %), 63.6 % (59.9 – 79.4 %), 63.5 (59.8 – 77.5 %), 65.2 % (59.8 – 78.6 %), 62.9 % (59 – 78.5 %) and 61.6 % (59.8 – 77.4 %) for the 7C, 9C, 13C, 7NC, 9NC and 10NC techniques respectively. Mean monitor units for each of techniques were 3112.8, 3328.9, 3475.0, 3113.8, 3372.4 and 3622.2 for the 7C, 9C, 13C, 7NC, 9NC and 10NC respectively.

Discussion:

This study investigates the use of six different beam arrangements for the use of IMRT in the delivery of SABR to peripheral lung tumours. Non-coplanar IMRT, similar to findings using 3DCRT[131] provides better compliance with the RTOG 1021 protocol than purely coplanar techniques.

The 10NC technique produced the highest quality plan, with less deviation to the RTOG 1021 protocol than the other techniques. The $R_{50\%}$ dose constraint was the main protocol deviation for the 7C, 9C, 13C, 7NC and 9NC techniques, with an increase in beam number reducing the protocol deviations. This finding suggests that regardless of technique, either 3DCRT or IMRT, a larger amount of beam numbers provides greater distribution of the intermediate dose allowing for $R_{50\%}$ constrains to be met. Including non-coplanar beams further reduces the intermediate dose wash. This finding is aligned with that of Holt et al [106] where they also report improved intermediate dose wash with non-coplanar IMRT.

As beam number increased, the amount of unacceptable OAR deviations decreased. Similarly to Holt et al [106], spinal cord sparing was improved using non-coplanar techniques. The mean reduction in spinal cord maximum dose was 2.5 Gy. Only the 13C technique registered a (mean) volume of the spinal cord getting above 12.3 Gy. Although the 13C technique angles

were altered (from evenly spaced) to avoid the spinal cord in some patients, it still marginally increased this dose metric. This is similar to findings comparing full arc volumetric modulated arc therapy (VMAT) to partial arc (VMAT) for lung SABR[135]. The V_{30Gy} received by the chest wall was not improved with increasing number of beams (coplanar or non-coplanar) except for one patient where the volume was reduced 17.8 cm^3 with the 10NC, compared to the mean value of all other techniques. OAR sparing was similar for all other OAR (table 6).

The interplay effect was taken into consideration when designing this study. The effect that the breathing motion has on the resultant dosimetry when treatment is delivered has been previously investigated, mainly for VMAT treatments [111-113, 136]. Studies have shown that for conventionally fractionated treatments the interplay effect is less than 1-2%. Additionally, due to the increased treatment times and increased monitor units associated with SABR, the interplay effect for hypofractionated treatments (>1 fraction) is negligible [134].

The authors acknowledge that a potential limitation of the study is the mixture of tumours adjacent to the chest wall, and those entirely surrounded by lung parenchyma. As the planning objectives of achieving PTV coverage and meeting intermediate dose constraints (with isotropic dose fall off) were prioritized higher than non-spinal cord OAR constraints, then there is some bias that the non-coplanar beam arrangements will always be superior to coplanar arrangement. This is due to the fact that isotropic fall off will be more achievable with non-coplanar beams[81], therefore allowing non-coplanar beam arrangements to place higher weightings on rib tolerances with the IMRT optimisation parameters. However, this study has demonstrated that rib tolerances can be achieved in 63.3 % of cases regardless of technique tested. Of the plans where rib maximum doses were unachievable, only four plans (two 7C and two 7NC) had an $R_{50\%}$ that failed to reach an acceptable deviation. This highlights that maximum rib dose constrains only impact intermediate dose objectives if 7 (coplanar on non-coplanar) or less fields are used. Therefore, from the beam arrangements tested, >9 fields (either coplanar or non-coplanar) are required for tumours adjacent to the chest wall in order to meet both intermediate and OAR dose constraints.

Conclusion:

An IMRT beam arrangement consisting of 10 beams, with ≥6 non-coplanar beams provided best compliance with the dose constraints in the RTOG 1021 protocol. The 10NC provided improved intermediate dose sparing and a reduction in doses to OAR when compared to the other techniques. The 9NC achieved clinically acceptable plans in 70 % of cases and may be a viable alternative in select patient's if treatment times are required to be shorter. Nine or more treatment fields are recommended for tumours adjacent to the chest wall.

Table 5.1 - Organ at risk dose constraints

Organ	Constraint(s)
Spinal Cord	18 Gy < 0.35 cm^3 12.3 Gy < 1.2 cm^3 MPD < 21.9 Gy
Brachial Plexus	20.4 Gy < 3 cm^3 MPD < 24 Gy
Aorta, SVC and IVC	39 Gy < 10 cm^3 MPD < 49 Gy
Pericardium	24 Gy < 15 cm^3 MPD < 30 Gy
Trachea	15 Gy < 4 cm^3 MPD < 30Gy
Combined Lungs – ITV	11.4 Gy < 1000 cm^3 10.5 Gy < 1500 cm^3
Oesophagus	17.7 Gy < 5 cm^3 MPD < 25.2 Gy
Rib	40 Gy < 5 cm^3 MPD < 50 Gy
CW	30 Gy < 30 cm^3 (<70 cm^3 for tumours on the CW)
Skin	30 Gy < 10 cm^3 MPD < 33 Gy

Abbreviations IVC = inferior vena cava, SVC = superior vena cava, ITV = internal target volume, CW = chestwall, MPD = maximum point dose (defined as ≥0.03 cm^3)

Table 5.2 - Acceptable dose spillage guidelines from RTOG 1021

Ratio of Prescription Isodose Volume to the PTV		Ratio of 27 Gy Isodose Volume to the PTV $R_{50\%}$		Maximum Dose at 2 cm from PTV in any direction as % of Prescribed dose (PD). D_{2cm} (gy) = % x PD		PTV Volume (cc)
Deviation		Deviation		Deviation		
None	Acceptable	None	Acceptable	None	Acceptable	
<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	1.8
<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	3.8
<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	7.4
<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	13.2
<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	22.0
<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	34.0
<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	50.0
<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	70.0
<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	95.0
<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	126.0
<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	163.0

PTV = planning target volume

Table 5.3- List of starting objectives for all techniques

ROI	Objective Type	Target Dose (Gy)	Volume (%)*	Weight
PTV	Minimum DVH	54	100	5
ITV	Minimum Dose	60		1
ITV	Maximum Dose	91.5		5
D_{2cm}	Maximum Dose	Table 3		5
27 Gy Ring	Maximum Dose	27		5
54 Gy Ring	Maximum Dose	54		1

Abbreviations: ROI = Region of interest, DVH = Dose volume histogram, PTV = planning target volume, ITV = internal target volume

* Only applicable for Maximum or Minimum DVH objective types

	7C	9C	13C	7NC	9NC	10NC
D_{2cm}						
None	5	8	10	8	8	10
Acceptable	5	2	0	2	2	0
Unacceptable	0	0	0	0	0	0
$R_{50\%}$						
None	1	0	0	2	1	3
Acceptable	3	5	6	3	6	7
Unacceptable	6	5	4	5	3	0
CI						
None	10	10	10	10	10	10
Acceptable	0	0	0	0	0	0
Unacceptable	0	0	0	0	0	0
OAR						
None	3	3	3	4	4	5
Acceptable	3	5	6	2	6	5
Unacceptable	4	2	1	4	0	0
Total Deviations						
None	19	21	23	24	23	28
Acceptable	11	12	12	7	14	12
Unacceptable	10	7	5	9	3	0
Clinically Suitable Plans	2	3	5	3	7	10

Table 5.4 - Beam arrangements and protocol deviations following RTOG 1021 criteria.

CI = conformity index

Table 5.5 - Mean dose statistics for each technique, categorized into coplanar and non-coplanar and mean values for all coplanar and non-coplanar techniques combined with associated P values.

	PTV_{54Gy} (%)	$PTV_{48.6Gy}$ (%)	$R_{50\%}$ (Deviation)	D_{2cm} (Deviation)	CI
Coplanar					
7 Fields	95.18	99.98	1.42	-0.67	0.86
9 Fields	95.14	99.97	0.98	-2.46	0.88
13 Fields	95.19	99.97	0.99	-2.4	0.87
Non-Coplanar					
7 Fields	95.10	99.98	1.09	-1.67	0.86
9 Fields	95.13	99.98	0.90	-2.62	0.87
10 Fields	95.83	100.00	0.30	-3.92	0.88
Mean Values					
All Coplanar	95.17	99.97	1.13	-1.84	0.87
All Non-Coplanar	95.35	99.99	.60	-2.74	0.87
P value	0.64	0.29	<0.01	<0.01	0.9

PTV = Planned targe volume, CI = conformity index, OAR = organs at risk

Table 5.6 - Mean values for recorded OAR doses for selected OAR categorized by technique and all coplanar and all non-coplanar techniques combined.

	SC			Pericardium		Combined Lung - ITV		Ribs		CW
Technique/ Constraint (Aim)	18Gy (<0.35 cm^3)	12.3Gy (<1.2 cm^3)	MPD (<21.9 Gy)	24Gy (<5 cm^3)	MPD (30 Gy)	10.5Gy (<1500 cm^3)	11.4Gy (<1000 cm^3)	40Gy (<5 cm^3)	MPD (<50Gy)	30 Gy (<30 cm^3)
Coplanar										
7 Fields	0	0.0	10.4	0.6	19.8	460.4	429.5	1.8	43.2	22.4
9 Fields	0	0.0	10.3	1.1	21.9	458.3	424.6	1.8	43.6	21.3
13 Fields	0	0.3	12.6	1.2	20.5	458.1	420.0	1.7	41.7	20.4
Non-Coplanar										
7 Fields	0	0.0	8.1	0.5	19.3	451.5	412.1	1.9	42.9	22.4
9 Fields	0	0.0	8.5	0.6	22.5	461.0	422.9	1.8	42.5	20.9
10 Fields	0	0.0	9.2	0.3	19.2	457.5	408.9	1.7	42.5	18.9
Mean Values										
All Coplanar	0	0.0	11.1	0.9	20.7	458.9	424.7	1.7	42.8	21.4
All Non-Coplanar	0	0.0	8.6	0.5	20.3	456.7	414.6	1.8	42.6	20.8

*Adjusted p value of post hoc tests. MPD = Maximum point dose, CW = chest wall, SC = spinal cord, ITV = Internal target volume

Chapter 6: Paper 3 - A comparison of three different VMAT techniques for the delivery of lung stereotactic ablative radiation therapy

All authors were responsible for manuscript revisions and provided changes and guidance on multiple occasions. For the project, author's contributions are as follows: Rhys Fitzgerald, the primary author was responsible for the project design, planning the SABR plans, analysing the data and preparing the manuscript for author review. Dr Rebecca Owen was instrumental in the design of the project and data analyses and was a constant source of mentorship during the process. Tamara Barry and Cathy Hargrave provided planning consultation and reviewed all the plans for the project to ensure that they satisfied protocols as per the manuscript. Drs Pryor, Mai and Lehman provided a clinical perspective for the project design and data analyses. Anne Barnard provided statistical support for the project and aided in presenting the data provided. Mr Venkatakrishnan Seshadri performed all necessary physics testing to make sure the plans were clinically deliverable. Dr Andrew Fielding played an important role in project design, data analysis and mentorship during the project.

Published: Journal of Medical Radiation Sciences

DOI: 10.1002/jmrs.156

Author names and affiliations.

Rhys Fitzgerald[ab*] BAppSc (MRT), Rebecca Owen[bc] PhD, Catriona Hargrave[cd] MAppSc, David Pryor[e] MBBS FRANCR,Tamara Barry[c] BAppSc (MRT), Margot Lehman[e] MBBS FRANZCAR, , Anne Bernard[f] PhD, Tao Mai[e] MBBS FRANCZR, Venkatakrishnan Seshadri[g] and Andrew Fielding[b] PhD

[a]*Radiation Oncology Centres, Mater Private Hospital, Springfield, Queensland, Australia*
[b]*Science and Engineering Faculty, Queensland University of Technology, Brisbane, Queensland, Australia*
[c]*Division of Radiation Therapy, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[d]*Radiation Oncology Mater Centre, South Brisbane, Queensland, Australia*
[e]*Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[f]*QFAB Bioinformatics, Institute for Molecular Bioscience, University of Queensland, Queens, land, Australia*
[g]*Division of Radiation Physics, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*

Corresponding author.

*Rhys Fitzgerald Tel.: +61 7 3447 1900
E-mail address: rhys.fitzgerald@roc.team
Address: Radiation Oncology Centres, 30 Health Care Dve, Mater Private Hospital, Springfield 4300

Acknowledgements:
Mr Rhys Fitzgerald would like to acknowledge that this study was undertaken at the Department of Radiation Oncology, Princess Alexandra Hospital between May 2012 and June 2015 and was employed by the institution during this time.

Abstract:

Introduction: The purpose of this study was to investigate coplanar and non-coplanar volumetric modulated arc therapy (VMAT) delivery techniques for stereotactic ablative radiation therapy (SABR) to the lung.
Methods: For ten patients who had already completed a course of radiation therapy for early stage lung cancer, 3 new SABR treatment plans were created using 1.) a coplanar full arc technique (FA), 2.) a coplanar partial arc technique (PA) and 3.) a non-coplanar technique utilising three partial arcs (NCA). These plans were evaluated using planning target volume (PTV) coverage, dose to organs at risk and high and intermediate dose constraints as incorporated by RTOG 1021.
Results: When the FA and PA techniques were compared to the NCA technique, on average the PTV coverage (V_{54Gy}) was similar (p=0.15); FA (95.1%), PA (95.11%) and NCA (95.71%). The NCA resulted in a better conformity index (CI) of the prescription dose (0.89) when compared to the FA technique (0.88, p = 0.23) and the PA technique (0.83, p=0.06). The NCA technique improved the intermediate dose constraints with a statistically significant difference for the D_{2cm} and $R_{50\%}$ when compared to the FA ($p < 0.03$ and < 0.0001) and PA ($p < 0.04$ and < 0.0001) techniques. The NCA technique reduced the maximum spinal cord dose by 2.72 Gy and 4.2 Gy when compared to the PA and FA techniques respectively. Mean lung doses were 4.09 Gy, 4.31 Gy and 3.98 Gy for the FA, PA and NCA techniques respectively.
Conclusion: The NCA VMAT technique provided the highest compliance to RTOG 1021 when compared to coplanar techniques for lung SABR. However, single full arc coplanar VMAT was suitable for 70 percent of patients when minor deviations to both the intermediate dose and OAR constraints were accepted.

Keywords:
Stereotactic Ablative Radiation Therapy (SABR)
Lung Cancer
Volumetric Modulated Arc Therapy (VMAT)
Dosimetry
Treatment Planning

Introduction:

Stereotactic ablative radiation therapy (SABR) is the delivery of a highly ablative radiation dose in a few fractions. It was originally introduced for early stage lung cancer patients who were deemed medically unfit for surgery. [5] SABR is commonly delivered using a high number of coplanar and non-coplanar 3 dimensional conformal radiation therapy (3DCRT) beams. In a previous single centre dosimetry comparison the authors demonstrated that a predominantly non-coplanar, 10 beam technique had the most favourable compliance with the RTOG 1021 protocol.[86, 131] A highly non-coplanar beam arrangement allowed for improved intermediate dose conformity and organ at risk (OAR) sparing. However, the engagement of a high number of couch rotations can extend the treatment times to potentially unfavourable lengths.[97] It has previously been reported that for treatment times extending over 34 minutes that a base line shift in tumour position of up to 5 mm can occur.[87] Delivery times for lung can SABR can vary depending on the equipment used, fractional dose, patient compliance and the delivery technique itself.

Volumetric modulated arc therapy (VMAT) is a novel technique that delivers the dose while the linear accelerator rotates continuously around the patient.[80, 115] The dose rate, gantry rotation speed and multileaf collimator (MLC) positions are all variables that can be altered while the machine is delivering the dose. Single coplanar arcs have already been shown to reduce treatment times for SABR to the lung when compared to 3DCRT, whilst achieving highly conformal dose distributions.[97] However, non-coplanar beam arrangements improve the intermediate dose conformity, which is one of the key dosimetry metrics for SABR. Therefore, this study was designed to quantify any benefits arising from non-coplanar VMAT when compared to coplanar VMAT for SABR to the lung.

Methods:

Institutional ethics approval was granted for this retrospective study. Ten patients who were eligible for SABR and had completed their course of radiation therapy were identified from our local radiation oncology information system. Inclusion criteria was limited to early stage disease (Ia/b or IIa) measuring <5cm in the largest dimension. Furthermore, the gross tumour volume (GTV) was required to be >2cm away from the proximal bronchial tree.

Patients were simulated as previously reported.[131] A 4 dimensional computed tomography (4DCT) scan was acquired at the time of simulation along with a free breathing CT scan. Both scans were exported to Pinnacle v9.4 (Philips Medical Systems, WI, USA) with the 4DCT used to generate an internal target volume (ITV). The PTV was created by expanding the ITV 5mm isotropically. The free breathing simulation CT scan was used for all OAR (table 1) contouring and treatment planning. All maximum doses reported were to a clinically significant and measurable volume of 0.03cm^3. The chest wall contour was defined as a 2 cm expansion on the ipsilateral lung, excluding the vertebral body, sternum and mediastinal structures. A structure was also created for reporting the maximum dose at any point 2cm from the PTV (D_{2cm}).

Treatment planning was carried out with Pinnacle v9.4 and the SmartArc™ algorithm. The final gantry spacing option in Pinnacle allows for the treatment planner to select the angular separation (in degrees) of the arc segments. It has previously been reported that a gantry spacing of 4° (new segment every 4°) is optimal, with no benefit in reducing the spacing any further.[106] In the present study, a full 360° arc will always have 91 segments with 0°, or the

starting angle, being included as a segment. The plans were computed using an Elekta Axesse beam model with the beam modulator collimator system with 4 mm MLC leaves. A dose grid resolution of 0.25 cm^3 was used for all plans. All plans were calculated using the collapsed cone convolution algorithm (CCC). The CCC algorithm is a type B algorithm and accounts for changes in lateral electron transport and should therefore be used for lung tumour treatments. Treatment planning was performed by a single planner and the machine quality assurance was performed by a medical physicist to ensure the plans were clinically deliverable with a gamma analysis passing rate of 3 mm/3%.

Unlike 3DCRT where the isocentre is placed in the centre of the PTV, the isocentre for the arc plans was placed on the patient's midline. This was to avoid any further complications that could cause a collision, such as when the bed is shifted laterally and is coupled with a rotating gantry and non-coplanar floor angles. The isocentre could have been placed in the PTV for the coplanar arcs but was left on the patient's midline to avoid any bias. All fields used 6 MV photons delivered with a collimator angle of zero.

The single full arc (FA) technique started at 181°, and travelled in a clockwise (CW) direction for 359° to stop at 180°. The partial arc (PA) technique started at either 181° or 180° and travelled an arc length of 180-200° around the ipsilateral side of the patient either in a CW or counter-clockwise (CCW) direction. The non-coplanar partial arc technique (NCA) used three partial arcs, one with a couch angle of 0° and two using non-coplanar couch angles. For left sided tumours the couch angles were 0°, 15° and 340° and for right sided tumours they were 0°, 20° and 345°. These angles were chosen as they were the greatest possible couch rotations away from zero (allowing for less overlapping of beams, and reducing the intermediate dose wash) without the gantry head and couch colliding. The arc angles for the NCA technique were the same as used for the PA technique. MLC speed was constrained to 0.46 cm/degree as per department protocol.

A total dose of 54 Gy in 3 fractions was prescribed to the periphery of the PTV ensuring that >95 % of the PTV received the prescription dose (PTV_{54Gy}) and that 99% of the PTV received 90% of the prescription dose ($PTV_{48.6Gy}$). The 54 Gy isodose (prescription isodose) was planned to fall between 59-90% of the maximum dose in the plan, resulting in a maximum dose of no more than 91.5 Gy. OAR tolerances used were those reported in RTOG 1021 (table 1). The constraints to limit the intermediate doses, D_{2cm}, the dose at any point 2cm from the PTV, and the ratio of the volume of half the prescription dose to the volume of the PTV ($R_{50\%}$) are also shown in table 2. To quantify the conformity of the prescription isodose the conformity index (CI) was used[131],

$$\frac{(TV_{PTV})^2}{TV * PIV}$$

where TV_{PTV} is defined as the total volume of PTV covered by the covering isodose (54Gy), TV is defined as the total volume of the PTV and PIV is defined as the total volume of the covering isodose in the patient . A CI value of ≥0.75 was no deviation, with ≥0.65 constituting an acceptable deviation and anything <0.65 was considered unacceptable. This CI formula was used instead of the RTOG formula as it is more robust and less prone to errors.

Each technique was created using the initial set of objectives outlined in table 3. Other objectives such as the maximum dose to the spinal cord, pericardium, chest wall, trachea and oesophagus were used on an individual patient basis as necessary. As the dose being delivered to the PTV is of an ablative nature, limiting the dose to surrounding tissues directly adjacent to the PTV is extremely important. Therefore, unlike conventional intensity modulation, no expansion was made to the PTV for dose optimization. The objective used on the PTV was a dose volume histogram (DVH) objective to cover a minimum of 100% of the PTV with 54 Gy. To promote a steep dose gradient, a minimum and maximum dose objective was used to control dose to the ITV. This would ensure that the maximum dose would be between 60 Gy and 91.5 Gy, and that the 54Gy isodose would fall within 59-90% of the maximum dose. To control the prescription dose, a ring with a 1mm gap to the PTV was created with a maximum dose objective equal to the prescription dose. This gave the optimisation algorithm a 1 mm gap to place the 54 Gy isodose, ensuring a tight and compact high dose region. To limit the intermediate dose, two different objective functions were used. Firstly, a structure constructed from the patients external contour minus the PTV plus a 2 cm expansion was used to control the dose at D_{2cm}. This ROI was given a maximum dose objective as per the relevant values in the no deviation column for D_{2cm} in table 2. Furthermore, to help meet the $R_{50\%}$ (the value of half the prescription dose divided by the volume of the PTV) constraint (table 2) a structure constructed from the patients external contour minus an expansion on the PTV was used to control the 27 Gy isodose. This expansion was typically a 1 cm isotropic expansion of the PTV based on the assumption that dose reduction of 5%/mm is achievable. The expansion on the PTV was reduced/increased but was altered on an individual patient basis as needed to better control the 27Gy isodose volume. The weights in the objective list were chosen to firstly cover the entire PTV with 54 Gy isodose, and then use the ring structures to control the intermediate dose to meet the dose conformity constraints. For PTVs adjacent to or overlapping the chest wall, the allowable maximum dose to the rib was increased to 105% of the prescription dose and recorded as an acceptable deviation.

Statistical analyses were performed using R statistical software (http://www.r-project.org). The three new SABR treatment plans were compared using a repeated measures ANOVA (parametric test) for normally distributed data and the Friedman test (non-parametric test) for non-normally distributed data. Normality of the data has been tested using the Shapiro-Wilk test. When an overall significant difference between treatment plans was demonstrated, post hoc tests (paired t-tests for normally distributed data or Wilcoxon signed-rank tests for non-normally distributed data) were performed to confirm where the differences occurred between treatment plans. The p-values have been adjusted for multiple comparisons using False Discovery Rate (FDR) correction to control the expected proportion of incorrectly rejected null hypotheses. The p-values obtained have been adjusted for
multiple comparisons with a Bonferroni correction. Statistical significance was defined as $p \leq 0.05$.

Results:

Mean planning target volume (PTV) size was 32.3 cm^3 with five of the ten patients having tumours adjacent to the chest wall. Patient characteristics are detailed in table 4. Acceptable plans, defined as having no major protocol deviations as outlined in RTOG 1021 (table 2) were obtained for 70 percent, 40 percent and 100 percent of the FA, PA and NCA techniques respectively. A summary of the dosimetry parameters for each technique are reported in table 5.

PTV_{54Gy} coverage was similar for the FA, PA and NCA techniques achieving 95.09%, 95.11% and 95.71% respectively. Coverage for the $PTV_{48.6Gy}$ objective was 99.97%, 99.92% and 99.99% for the FA, PA and NCA respectively with a statistically significant difference ($p=0.04$) between the PA and NCA. The NCA technique provided the best high dose conformity with a value of 0.89, when compared to the FA (0.88) and PA (0.82) techniques.

The NCA technique resulted in the highest compliance with the no deviation criteria in table 2. A previously used scoring system for measuring the absolute difference of the D_{2cm} and $R_{50\%}$ was used to evaluate the deviations from an acceptable value.[131] The mean absolute difference from the $R_{50\%}$ no deviation value (table 2) was 1.04, 0.52 and 0.12 for the PA, FA and NCA techniques respectively. The mean absolute difference from the D_{2cm} no deviation was of, -5.33, -3.71 and -0.46 for the NCA, FA and PA respectively. This resulted in a statistically significant difference of 0.03 when comparing the FA and PA, and $p=0.04$ when comparing the NCA and PA for the $R_{50\%}$ constraint and <0.0001 for the D_{2cm} between all techniques. Figure 1 plots the achieved $R_{50\%}$ values against the PTV size for each of the ten patients. OAR sparing was similar among techniques (table 5). For doses to the combined lung minus the ITV volume, the NCA reduced the 10.5 Gy wash by a mean volume of 44 cm^3 and 24 cm^3 for the PA and FA technique respectively, and the 11.4 Gy dose wash by a mean volume of 44 cm^3 and 25 cm^3 respectively. Spinal cord maximum doses were lower with the NCA technique (table 5). The FA had 1 plan and the PA technique had 3 plans where the maximum dose to the ribs could not be achieved. Conversely the NCA technique was able to achieve maximum rib doses for all 10 patients. The chest wall volume receiving 30 Gy (V_{30Gy}) ranged from 0-62.07 cm^3, 0-52.36 cm^3 and 0-53.30 cm^3 for the PA, FA and NCA techniques respectively for all ten patients. Where the PTV was overlapping the chest wall, the mean V_{30Gy} was 35.79 cm^3, 33.18 cm^3 and 32.46 cm^3 for the PA, FA and NCA techniques respectively.

Discussion:

This study presents an expansion on previous work where the effects of non-coplanar beam arrangements for lung SABR using 3DCRT were reported. Similar to those findings with 3DCRT, the non-coplanar VMAT technique tested in this current study also provides greater compliance with the RTOG 1021 protocol when compared to single arc coplanar techniques.

The NCA technique provided the most optimal plan with greater adherence to the RTOG 1021 guidelines than the other two techniques. All 10 of the NCA treatment plans adhered to RTOG 1021 protocol guidelines. The technique that had the least compliance with the planning objectives was the PA technique. Only 40 % of the plans were acceptable with a majority of the deviations being associated with the intermediate dose constraints. Having an arc only enter through a 180-200° sector did not allow for enough low dose spread throughout the normal tissue, resulting in higher than favourable intermediate doses. The FA technique had 7 out of 10 plans which were clinically acceptable. Of the three not acceptable, the $R_{50\%}$ was above an acceptable deviation in 2 plans and the rib maximum dose was over tolerance in the other.

Similarly to Holt et al we also report that the CI for the prescription isodose were within acceptable limits for all techniques.[106] Holt et al report a few exceptions to achieving an optimal CI for the prescription dose. In the present study we report no deviations to the CI regardless of delivery technique. This could be due to a number of different factors including

the different CI equations used, different treatment machine and contrasting intensity modulation objectives. Furthermore, there was also an improvement in the CI with the FA and NCA techniques, which is largely due to the greater number of segments, and therefore "individual beams" used with the FA and NCA techniques.

OAR sparing was similar between each technique. There was improved spinal cord sparing with the NCA and PA technique which is due to the fact that neither of these techniques had beams entering through the spinal cord, an unavoidable consequence of the FA technique. Furthermore, the NCA was able to improve both the maximum dose and specific volumetric dose constraint for all midline structures such as the aorta, trachea and oesophagus. The NCA technique was able to either achieve the constraint or limit the maximum rib dose to acceptable deviation for all 10 patients. Furthermore, the maximum V_{30Gy} (62.07 cm^3) to the chest wall for the PA technique was able to be reduced by almost 10 cm^3 (52.36 cm^3 and 53.33 cm^3 for the FA and NCA respectively) by the other two techniques. Although still within the 70 cm^3 constraint, this reduction in chest wall dose is likely to be clinically significant, as reported by both Ong et al and Dunlap et al, where a $V_{30Gy} < 30$ cm^3 could reduce the risk of toxicity, especially if SABR offers an improvement in long term survival. [97, 126] The improvement to OAR sparing could be due to the larger number of control points for the NCA and FA techniques, and therefore larger number of opportunities to shield out OAR.

A universal issue arising from arc based techniques is the increased dose wash to the lungs, especially the contra-lateral lung. Pre-established 3DCRT non-coplanar techniques enter through the contralateral lung, however they are generally only from one or two static angles. The FA technique used in this study enters through the entire contralateral lung, exposing more volume to a lower dose. The effect of this can be seen with the increase in the mean lung dose (MLD). Holt et al report a MLD of 4.2 Gy for single coplanar VMAT which is on par with our result of an average MLD of 4.3 Gy.[106] The reduction in MLD for the PA technique is because a smaller volume of lung is receiving low dose. Furthermore, dose is being deposited through non-coplanar angles with the NCA technique, further reducing the MLD. In a matched analysis study, Palma et al investigated radiobiological and clinical pneumonitis after both VMAT (RapidArc) and 3DCRT and concluded that there was no difference in the severity of clinical or radiobiological sequelae after treatment.[117] Figure 2 displays the reduced dose wash to the contra-lateral lung with both the PA and NCA techniques when compared to the full arc technique.

A general concern with intensity modulated treatments for lung cancer is the interplay effect, which is the potential difference in the planned dose to the delivered dose. This is caused by differences in the MLC movements to tumour motion when comparing the static respiratory phase the planning CT captured with the breathing cycle during treatment.[112] Several groups have investigated this phenomenon (VMAT or RapidArc) and report that for a single fraction split over two arcs, or >1 treatment fractions, the interplay effect is negligible and the actual delivered dose is within reasonable tolerance to the planned dose. [111, 112, 136]

Although the NCA provides improved plan quality, these small gains in intermediate dose reduction may be of little importance in the current clinical setting. With $R_{50\%}$ and D_{2cm} values achieved by the FA technique within acceptable protocol deviations, the advantage of a single coplanar arc may outweigh the improved performance of non-coplanar techniques. In a clinical setting where patients are generally from an older population and may not tolerate long

treatment times and a high emphasis is placed on departmental efficiency, the FA technique provides acceptable treatment plans in a majority of cases and can be delivered in a shorter treatment time. However, if the delivery of highly ablative doses is beneficial to a younger cohort of patients diagnosed with early stage lung cancer, increased reduction in intermediate doses available with the NCA may be of benefit. Furthermore, a coplanar arc technique may better lead to advanced treatment techniques such as dynamic MLC tracking or breath hold techniques where quicker treatment times are a necessity.

Conclusion:

The non-coplanar (NCA) VMAT technique utilizing three non-coplanar partial arcs produced optimal plans that demonstrated better compliance with the dose constraints in the RTOG 1021 protocol when compared to the single arc coplanar techniques. For those tumours entirely encapsulated in lung parenchyma, full single arc coplanar VMAT provided acceptable plans when accepting small deviations to the intermediate dose constraints. Single full arc coplanar VMAT is a suitable treatment option for lung SABR when intermediate and OAR doses are within acceptable limits.

Table 6.1 - Organ at risk dose constraints

Organ	Constraint(s)
Spinal Cord	18 Gy < 0.35 cm^3

	12.3 Gy < 1.2 cm^3 MPD < 21.9 Gy
Brachial Plexus	20.4 Gy < 3 cm^3 MPD < 24 Gy
Aorta, SVC and IVC	39 Gy < 10 cm^3 MPD < 49 Gy
Pericardium	24 Gy < 15 cm^3 MPD < 30 Gy
Trachea	15 Gy < 4 cm^3 MPD < 30Gy
Combined Lungs – ITV	11.4 Gy < 1000 cm^3 10.5 Gy < 1500 cm^3
Oesophagus	17.7 Gy < 5 cm^3 MPD < 25.2 Gy
Rib	40 Gy < 5 cm^3 MPD < 50 Gy
Chestwall	30 Gy < 30 cm^3 (<70 cm^3 for tumours on the CW)
Skin	30 Gy < 10 cm^3 MPD < 33 Gy

Abbreviations IVC = inferior vena cava, SVC = superior vena cava, ITV = internal target volume, MPD = maximum point dose (defined as ≥0.03 cm^3)

Table 6.2 - Acceptable dose spillage guidelines from RTOG 1021

Ratio of Prescription Isodose Volume to the PTV		Ratio of 27 Gy Isodose Volume to the PTV ($R_{50\%}$)		Maximum Dose at 2 cm from PTV in any direction as % of Prescribed dose (PD). D_{2cm} (Gy) = % x PD		PTV Volume (cc)
Deviation		Deviation		Deviation		
None	Acceptable	None	Acceptable	None	Acceptable	
<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	1.8
<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	3.8
<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	7.4
<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	13.2
<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	22.0
<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	34.0
<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	50.0
<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	70.0
<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	95.0
<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	126.0
<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	163.0

Table 6.3 - List of starting objectives for all techniques

ROI	Objective Type	Target Dose (Gy)	Volume (%)*	Weight
PTV	Minimum DVH	54	100	5
ITV	Minimum Dose	60		1
ITV	Maximum Dose	91.5		5
D_{2cm}	Maximum Dose	Table 3		5
27 Gy Ring	Maximum Dose	27		5
54 Gy Ring	Maximum Dose	54		1

Abbreviations: ROI = Region of interest, DVH = Dose volume histogram
* Only applicable for Maximum or Minimum DVH objective types

Table 6.4 - Patient characteristics

Gender (n)	
Male	7
Female	3
Age (y)	
Range	61 - 83
Median	76
Mean	74.8
Staging	
T1aN0M0	5
T1bN0M0	2
T1NOSN0M0	3
Location	
RUL	5
RML	1
RLL	2
LUL	1
LLL	1
Overlapping with CW (n)	
Yes	5
No	5
ITV Size (cm^3)	
Range	4.43 – 29.9
Median	8.3
Mean	10.4
PTV Size (cm^3)	
Range	22.8 – 79.12
Median	27.49
Mean	32.26

Abbreviations NOS = not specified, CW = chest wall, ITV = internal target volume, PTV = planned target volume
RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe; LUL = left upper lobe, LLL = left lower lobe

Table 6.5 - Mean dose statistics for each technique with associated P values.

Metric	Parameter	PA	FA	NCA	P value* (PA-NCA)	P Value* (FA-NCA)
PTV_{54Gy}	(%)	95.11	95.09	95.71	0.15	0.15
$PTV_{48.6Gy}$	(%)	99.92	99.97	99.99	0.04	
D_{2cm}	Absolute Difference	-0.46	-3.71	-5.33	<0.0001	<0.0001
$R_{50\%}$	Absolute Difference	1.04	0.52	0.12	0.04	0.03
CI		0.83	0.88	0.89	0.06	0.23
MLD	(Gy)	4.09	4.31	3.98	0.05	<0.0001
Spinal Cord	D_{max} (Gy)	9.52	11.0	6.80		
	V_{18Gy} (cm^3)	0.0	0.0	0.0		
	$V_{12.3Gy}$ (cm^3)	0.02	0.11	0.0		
Rib	D_{max} (Gy)	45.45	43.3	42.75		
	V_{40Gy} (cm^3)	1.55	1.40	1.47		
Chest Wall	V_{30Gy} (cm^3)	20.12	16.95	16.44		
Combined Lung - ITV	$V_{10.5Gy}$ (cm^3)	434.79	414.79	390.93		
	$V_{11.4Gy}$ (cm^3)	400.01	380.41	355.59		
Pericardium	D_{max} (Gy)	1.93	1.49	0.52		
	V_{24Gy} (cm^3)	19.53	19.91	18.46		
Skin	D_{max} (Gy)	0.50	0.49	0.49		
	V_{30Gy} (cm^3)	23.62	21.39	20.0		
Oesophagus	D_{max} (Gy)	9.82	12.47	6.64		
	$V_{17.7Gy}$ (cm^3)	0.0	0.0	0.0		
Aorta	D_{max} (Gy)	11.97	14.60	9.94		
	V_{39Gy} (cm^3)	0.0	0.0	0.0		
Trachea	D_{max} (Gy)	0.02	0.47	0.0		
	V_{15Gy} (cm^3)	6.05	7.2	5.6		

*Adjusted p value of post hoc tests.

Abbreviations

PA = coplanar partial arc technique; FA = coplanar full arc technique; NCA = non-coplanar technique utilising three partial arcs

ITV = internal target volume, PTV = planned target volume, MLD = mean lung dose, CI = conformity index

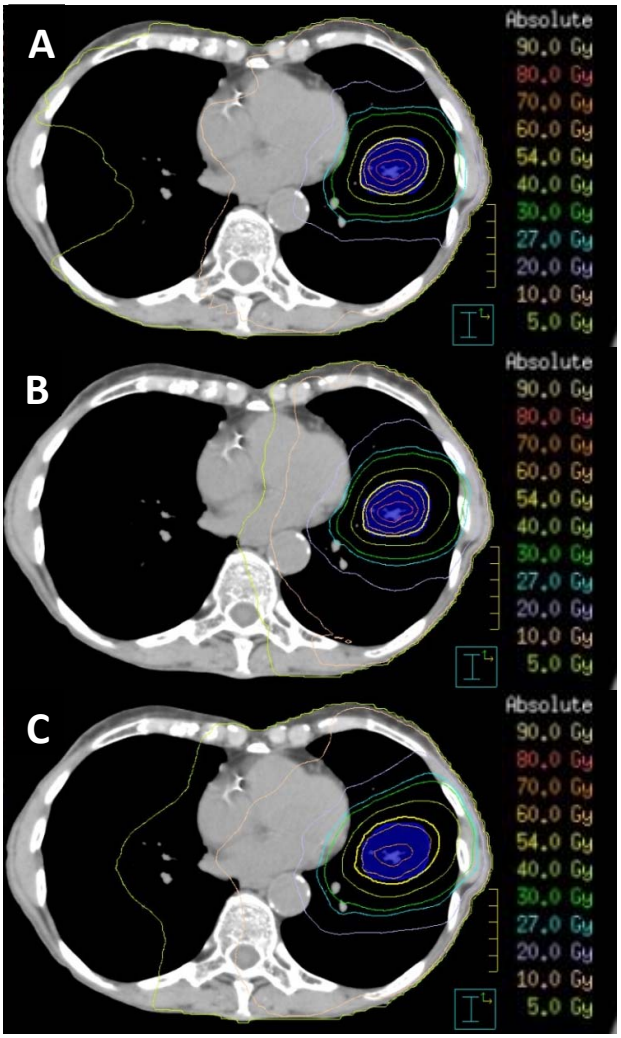

Figure 6.1 - Dose wash through a transverse slice for each of the three techniques. A, Full arc. B, Non-coplanar partial arc. C, Partial arc.

Chapter 7: Paper 4 - A comparison of three non-coplanar techniques for delivering stereotactic ablative radiation therapy (SABR) for early stage peripheral lung cancer

All authors were responsible for manuscript revisions and provided changes and guidance on multiple occasions. For the project, author's contributions are as follows: Rhys Fitzgerald, the primary author was responsible for the project design, planning the SABR plans, analyzing the data and preparing the manuscript for author review. Dr Rebecca Owen was instrumental in the design of the project and data analyses and was a constant source of mentorship during the process. Tamara Barry and Cathy Hargrave provided planning consultation and reviewed all the plans for the project to ensure that they satisfied protocols as per the manuscript. Drs Pryor, Mai and Lehman provided a clinical perspective for the project design and data analyses. Anne Barnard provided statistical support for the project and aided in presenting the data provided. Mr Venkatakrishnan Seshadri performed all necessary physics testing to make sure the plans were clinically deliverable. Dr Andrew Fielding played an important role in project design, data analysis and mentorship during the project.

Published: TBD

Author names and affiliations.

Rhys Fitzgerald[ab*] BAppSc (MRT), Rebecca Owen[bc] PhD, Catriona Hargrave[cd] MAppSc, David Pryor[e] MBBS FRANCR,Tamara Barry[c] BAppSc (MRT), Margot Lehman[e] MBBS FRANZCAR, , Anne Bernard[f] PhD, Tao Mai[e] MBBS FRANCZR, Venkatakrishnan Seshadri[g] PhD and Andrew Fielding[b] PhD

[a]*Radiation Oncology Centres, Mater Private Hospital, Springfield, Queensland, Australia*
[b]*Science and Engineering Faculty, Queensland University of Technology, Brisbane, Queensland, Australia*
[c]*Division of Radiation Therapy, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[d]*Radiation Oncology Mater Centre, South Brisbane, Queensland, Australia*
[e]*Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*
[f]*QFAB Bioinformatics, Institute for Molecular Bioscience, University of Queensland, Queens, land, Australia*
[g]*Division of Radiation Physics, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia*

Corresponding author.

*Rhys Fitzgerald Tel.: +61 7 3447 1900
E-mail address: rhys.fitzgerald@roc.team
Address: Radiation Oncology Centres, 30 Health Care Dve, Mater Private Hospital, Springfield 4300

Acknowledgements:
Mr Rhys Fitzgerald would like to acknowledge that this study was undertaken at the Department of Radiation Oncology, Princess Alexandra Hospital between May 2012 and June 2015 and was employed by the institution during this time.

Abstract

Aim: To compare three non-coplanar delivery techniques (3-dimensional conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT)) for the delivery of lung stereotactic ablative radiation therapy (SABR) to peripheral lung tumours.

Methods and Materials: Treatment plans for 3DCRT, IMRT and VMAT were generated for each of the twenty patients. The plans were compared by assessing the planning target volume (PTV) coverage, doses to organs at risk, high and intermediate dose constraints (D_{2cm} and $R_{50\%}$) and delivery times using ANOVA for repeated measurements or Friedman's test when appropriate.

Results: Mean PTV_{54Gy} coverage was found to be 95.6%, 95.7% and 95.6% for the 3DCRT, IMRT and VMAT techniques respectively. PTV48.6Gy coverage was increased for IMRT (99.99%) (p=<0.001) and VMAT (99.99%) (p=<0.001) when compared to 3DCRT (99.56%). No deviations to the intermediate dose constraints were found in 65%, 65% and 85% of the patients for the 3DCRT, IMRT and VMAT plans respectively. Mean treatment times were 20.0 minutes (16.4 – 21.5 minutes), 25.2 minutes (22.1 – 27.9 minutes) and 11.7 (8.0 – 15.2 minutes) minutes respectively for 3DCRT, IMRT and VMAT.

Conclusion: A non-coplanar VMAT technique was found to provide superior intermediate dose sparing with comparable prescription dose coverage when compared to non-coplanar 3DCRT or IMRT. Additionally, VMAT was found to reduce the treatment times of SABR delivery for peripheral lung tumours.

Introduction:

Stereotactic ablative radiation therapy (SABR) is currently emerging as the standard of care for medically inoperable patients diagnosed with early stage lung cancer or pulmonary oligometastases. The capability to deliver highly ablative doses with minimal clinical toxicity relies significantly on the ability to limit dose to normal tissues. 3 dimensional conformal radiation therapy (3DCRT) has traditionally been the delivery technique for lung SABR. Generally, a large number (>7) of beams with a non-coplanar contribution is required to reduce toxicities and satisfy intermediate dose constraints [79, 93]. The inclusion of non-coplanar beams is advantageous in the reduction of intermediate dose spillage and normal tissue sparing, however a longer treatment time is observed [80, 87]. Nevertheless, key dosimetric criteria

such as the prescription dose conformity, intermediate dose spillage and organ at risk (OAR) sparing should not, in principal, be significantly compromised in order to achieve reduced treatment times.

Treatment modalities, including 3DCRT, intensity modulated radiation therapy (IMRT), dynamic conformal arc (DCA), tomotherapy and volumetric modulated arc therapy (VMAT) have previously been investigated for lung SABR [76, 80, 91, 92, 94, 97, 106-109, 118, 131-133, 137-142]. Furthermore, various task groups have also reported on safe and effective delivery techniques for lung SABR, which address number of beams and direction (coplanar or non-coplanar) [35, 95, 143]. The consensus is that for 3DCRT and IMRT a large number of beams, the majority of which tend to be non-coplanar [131], are required to meet intermediate dose constraints (D_{2cm} and $R_{50\%}$) and improve OAR sparing. For VMAT, single or multiple full coplanar arcs have previously been compared to non-coplanar 3DCRT and IMRT. VMAT produced similar or improved treatment plan quality, in shorter treatment times. To extend on preceding reports, the authors have previously reported on the use of non-coplanar VMAT for the delivery of lung SABR [135]. It was found that non-coplanar VMAT produced superior plans than either single or partial arc coplanar VMAT. To further investigate this non-coplanar VMAT technique this current study was designed to compare three different non-coplanar techniques for the delivery of SABR to early stage peripheral lung tumours. Plans were critiqued using RTOG 1021[86] criteria to identify the most favourable technique in terms of both plan quality and efficiency.

Methods:

Institutional ethical clearance was granted to use the computed tomography (CT) data sets of twenty early stage lung cancer patients eligible for SABR. Patient eligibility was defined as early stage (IA/B or IIA), with the gross tumour volume (GTV) volume measuring <5cm in the largest dimension and >2cm away from the proximal bronchial tree.

Patients were simulated in the supine position with arms up, using a vac-lok cushion from above the head to below the torso and knee fix under knees to aid in rigid patient immobilization. A 10 phase 4 dimensional CT (4DCT) was captured at the time of simulation along with a free breathing scan for dose calculation. Both data sets were exported to Pinnacle v9.4 (Philips Medical Systems, Stockholm, Sweden) for contouring and planning. The internal target volume (ITV) was generated by contouring the different positions of the GTV during all phases of the breathing cycle.

A planned target volume (PTV) was created by an isotropic 5mm expansion on the ITV. Organs at risk listed in table 1 were contoured. A D_{2cm} structure to measure intermediate dose spillage was created by removing a 2cm isotropic expansion of the PTV from the body. A volume of 0.03 cm^3 was defined as the maximum point dose.
For all techniques, plans were prescribed to deliver 54 Gy to the periphery of the PTV in three fractions. The PTV was planned to receive >95% of the prescription dose (PTV_{54Gy}), and >99% coverage of the PTV with 90% of the prescription dose ($PTV_{48.6Gy}$). The 54 Gy isodose was optimized so that it fell somewhere between 59-90% of the maximum dose in the plan. Plans were assessed by PTV coverage, the conformity of the prescription isodose to the PTV, intermediate dose constraints (D_{2cm} and $R_{50\%}$), doses to OAR and treatment times. Criteria for intermediate dose spillage are listed in table 2. Conformity index (CI) was calculated using the formula [124];

$$\frac{(TV_{PTV})^2}{TV * PIV}$$

A CI value of ≥0.75 was no deviation, ≥0.65 was an acceptable deviation and <0.65 was an unacceptable deviation.

All treatment planning was carried out using Pinnacle v9.4 with a collapsed cone convolution algorithm. The CCC algorithm is classified as a type B algorithm and is more rigorous in accounting for changes in lateral electron transport and is a nessicity in modern day lung SABR treatment planning. The 3DCRT technique used 10 beams with a minimum of 6 non-coplanar angles. The initial beam angles were based on a previous report [131] by the authors and altered by the planner as needed to improve intermediate dose spillage or doses to OAR. Negative margins were used to shield the periphery of the PTV to ensure that the prescription isodose fell within the penumbra of the beam.

The IMRT technique replicated the beam angles from the 3DCRT technique to avoid any bias. IMRT planning was replicated from a previous study [131]. The IMRT plans were optimized using the set of objectives (table 3)[131] and other structures (spinal cord, oesophagus) were added to the optimization if required. Segments numbers were limited to a mean of 7 per beam and optimized using the direct machine parameter optimization (DMPO) algorithm.

The VMAT technique used three non-coplanar partial arcs, with gantry angles chosen by the planner to limit dose to the contra-lateral lung. Each arc started at 180° and rotated between 180-220° around the ipsilateral side. Couch angles of 15, 340 and 0 were used for right sided tumours, and angles of 20, 345 and 0 were used for left sided tumours to avoid collisions. A final gantry spacing of 4° was used which defines at how many degrees the control points for the arc occur. Quite simply, there is a control point or segment change every 4°, meaning 91 for a full 360° arc (as both) ° and 360° are define as a control point). VMAT dose objectives used were similar to IMRT (table 3) and adjusted as necessary to compensate for the difference in delivery techniques.

IMRT and VMAT used two different structures to limit intermediate dose spillage. Firstly, a D_{2cm} structure was created by expanding the PTV 2cm isotopically. This structure is then removed from the body contour, leaving a donut structure to control the dose at 2cm from the PTV. This structure was routinely able to also control the $R_{50\%}$ constraint, however if this wasn't possible, another donut like structure was created. This was generally a 1 cm uniform expansion from PTV but was expanded asymmetrically in order to control the $R_{50\%}$ as required. Planning objectives were prioritized as per Fitzgerald et al[131]. IMRT and VMAT plan specific quality assurance (QA) performed in which planned fluences were measured against actual delivered fluences for each field and arc of the IMRT and VMAT plans only, using a gamma analysis acceptance criteria of 3%/3mm [74].

The treatment plans were then delivered on a linear accelerator and treatment times were measured from the beam on time of the first beam/arc until the end of the last beam/arc and all associated treatment couch rotations in between. No patient setup or imaging times were included in the measurements

Results:

The mean PTV size was 35.7 cm^3 with 11 patients having PTVs that overlapped the chest wall. The mean volume of PTV overlapping the chest wall was 4.1 cm^3. Mean PTV_{54Gy} coverage was 95.59%, 95.71% and 95.63% for the 3DCRT, IMRT and VMAT techniques respectively. Furthermore, there was a statistically significant difference in $PTV_{48.6Gy}$ coverage for the 3DCRT (99.56%) to IMRT (99.99%) (p=<0.001) and 3DCRT to VMAT (99.99%) (p=<0.001).

Mean dose statistics from each of the techniques are represented in table 4. Protocol deviations for the D_{2cm}, $R_{50\%}$, CI and OAR doses are listed in table 5. Unacceptable deviations for each technique were only noted for OAR where either the maximum rib dose or volume constraint could not be met. The VMAT technique provided greatest compliance with intermediate dose constraints with no deviations from protocol in 85% of plans, compared with 65% for both the 3DCRT and IMRT plans respectively. A previously reported (reference) scoring system was used to evaluate individual deviations to D_{2cm} and $R_{50\%}$. The 3DCRT, IMRT and VMAT plans produced mean absolute difference $R_{50\%}$ values of 0.37, 0.25 and 0.08 away from the no deviation constraint in table 5. The mean D_{2cm} values were -0.86 Gy, -4.49 Gy and -5.72 Gy less than the no deviation constraint for the 3DCRT, IMRT and VMAT plans respectively. Overall the mean $R_{50\%}$ and D_{2cm} values were 4.64, 4.52 and 4.35 and 30.2, 26.6 and 25.3 for the 3DCRT, IMRT and VMAT techniques respectively. Furthermore, mean CI values for each technique were 0.80, 0.88 and 0.89 for the 3DCRT, IMRT and VMAT with a statistically significant difference for 3DCRT compared to VMAT (p = <0.001) and 3DCRT to IMRT (p <0.001).

As reported, the only unacceptable deviations were due to the maximum rib dose and volume of rib receiving 40 Gy. The maximum rib dose was violated by all techniques on patient 12, where 12.5 cm^3 of the PTV overlapped the chest wall. This also resulted in the rib volumetric constraint being violated. The maximum rib dose for this patient was 60 Gy, 58.3 Gy and 61.6 Gy for the 3DCRT, IMRT and VMAT plans respectively, with the volume receiving 40 Gy being 5.79 cm^3, 6.08 cm^3 and 6.03 cm^3 respectively. Furthermore all plans had a rib volume constraint violated for patient 18 with 5.24 cm^3, 6.95 cm^3 and 6.44 cm^3 receiving 40 Gy for the 3DCRT, IMRT and VMAT plans respectively. The 3DCRT technique also had a maximum rib dose violation for patient 8 (59.1 Gy). For the patients whose PTV overlapped the chest wall, mean maximum rib doses for 3DCRT, IMRT and VMAT were 56.9 Gy, 56.0 Gy and 56.2 Gy respectively.

For other OAR, VMAT showed preferential sparing. Spinal cord maximum doses for VMAT (7.5 Gy) were lower than both the 3DCRT (9.9 Gy) and IMRT (8.9 Gy) techniques. The volume of lung receiving 10.5 Gy and 11.4 Gy was also reduced using VMAT (table 4). Furthermore, there was a statistically significant difference in the mean lung dose (MLD) for VMAT when compared to 3DCRT (p = <0.001) and IMRT (p = < 0.001).

Mean prescription isodoses for each technique were 69.2%, 66.3% and 66.0% for 3DCRT, IMRT and VMAT respectively. For PTVs overlapping the chest wall mean prescription isodoses were 75.5% for 3DCRT, 70.8% for IMRT and 70.5% for VMAT. For PTVs completely surrounded by lower density lung tissue, prescription isodoses were 61.5%, 60.8% and 60.4% for 3DCRT, IMRT and VMAT respectively. Treatment times were recorded for the first ten plans per techinque and the mean times were, 20.0 minutes, 25.2 minutes and 11.7 minutes respectively for 3DCRT, IMRT and VMAT.

Discussion:

This study investigated the use of 3 different non-coplanar treatment techniques for the delivery of peripheral lung SABR. All three techniques demonstrated the ability to deliver clinically suitable plans in over 90% of cases. The only unacceptable deviations reported are maximum dose and volumetric deviations for the rib when the PTV is overlapping the chest wall. In a clinical setting, the treating oncologist would have to make a clinical judgement call to either overdose the rib, or compromise PTV coverage.

With respect to PTV coverage, IMRT showed preferential increases in the percentage of PTV receiving 48.6 Gy and 54 Gy when compared to 3DCRT ($p=<0.0001$ and $p=0.048$ respectively). However, the resultant increase in treatment time with IMRT may not outweigh the small gain in coverage. VMAT however, demonstrated superior 48.6 Gy coverage when compared to 3DCRT and had substantially reduced treatment times. Brock et al [103] compared several coplanar and non-coplanar 3DCRT techniques with VMAT for lung SABR delivery 60 Gy in 8 fractions, also finding an increase in the volume of PTV receiving 95% and 90% of the prescription dose.

All of the techniques generated plans that adhered to both the $R_{50\%}$ and D_{2cm} constraints, with no unacceptable deviations in any plan. However, the VMAT technique demonstrated the ability to produce a greater number of plans that had no deviation to either of the intermediate dose constraints. Both the IMRT and VMAT techniques showed a statistically significant improvement to the D_{2cm} constraint when compared to 3DCRT. Similarly to that of McGrath et al [118], our data also represents a statistically significant improvement of the $R_{50\%}$ for VMAT when compared to 3DCRT.

High dose conformity ensures that normal tissue directly adjacent to the PTV is not being unnecessarily exposed to the prescription dose or higher. This present study shows that both IMRT and VMAT significantly improve the conformity of the prescription isodose when compared to 3DCRT. The mean CI for 3DCRT was 0.81, with IMRT and VMAT producing mean CI values of 0.88 and 0.89 respectively, both with a statistically significant difference. For VMAT this is an increase of 9%, similar to the findings of Ong et al [97], who reported an increase in the CI of 7% when comparing VMAT to 3DCRT.

The essence of stereotactic planning is to create a steep and isotropic dose fall off. Therefore when planning used a fixed gantry angle technique such as 3DCRT or IMRT, beam arrangements are required to be spread out, minimizing the overlap of intermediate doses. This occasionally results in treatment beams entering through an OAR. VMAT, however, has the advantage of limiting the gantry arc from entering through OAR. The plans presented in this study started at 180°, and either moved clockwise or anti-clockwise 200-220°. This meant that the spinal cord only received exit dose from the arc. This resulted in a low mean maximum point dose to the spinal cord. On average VMAT was able to lower the maximum spinal cord dose by 2.4 Gy and 1.4 Gy compared to 3DCRT and IMRT techniques respectively. While still under tolerance it is advantageous to reduce dose to the spinal cord for a number of reasons, including but not limited to the possibility of future spinal metastases requiring irradiation. Furthermore, even though the VMAT technique technically delivered dose from more "individual beams", the low weighting through each segment resulted in a higher ablative dose in the PTV and less dose to the lungs, this is evident with a reduction in the 10.5 Gy and 11.4

Gy isodose volume. Furthermore, VMAT had a statistically significant lower mean lung dose than either the 3DCRT or IMRT techniques.

Decreasing the influence of intra-fraction motion associated with extended treatment times is important. Purdie et al [87] report for treatment times >34 minutes, intra-fractional shifts of up to 5mm can occur. As this present study was a retrospective analysis, the beam on times measured were purely only dose delivery, and any time associated with couch and gantry rotations. From these values alone, VMAT reduced the delivery time by 8.3 minutes (41.5%) and 13.5 minutes (53.4%), compared to 3DCRT and IMRT respectively. These results sit favourably with those reported by McGrath et al [118] who report on average 6.15 minutes to deliver a 180°, 12 Gy per fraction arc. Treatment times reported in this study are slightly extended due to delivering 18 Gy per fraction coupled with couch rotations. VMAT will be able to further reduce treatment times with the inclusion of flattening filter free (FFF) beams [119].

Conclusion:
A non-coplanar VMAT technique provides superior intermediate dose and OAR sparing with comparable prescription dose coverage when compared to non-coplanar 3DCRT or IMRT. Treatment times can be reduced with the use of VMAT. Future directions include the use of FFF treatment machine to reduce treatment times even further.

Table 7.1 -. Organ at risk dose constraints

Organ	Constraint(s)
Spinal Cord	18 Gy < 0.35 cm^3 12.3 Gy < 1.2 cm^3 MPD < 21.9 Gy
Brachial Plexus	20.4 Gy < 3 cm^3 MPD < 24 Gy
Aorta, SVC and IVC	39 Gy < 10 cm^3 MPD < 49 Gy
Pericardium	24 Gy < 15 cm^3 MPD < 30 Gy
Trachea	15 Gy < 4 cm^3 MPD < 30Gy
Combined Lungs – ITV	11.4 Gy < 1000 cm^3 10.5 Gy < 1500 cm^3
Oesophagus	17.7 Gy < 5 cm^3 MPD < 25.2 Gy
Rib	40 Gy < 5 cm^3 MPD < 50 Gy
CW	30 Gy < 30 cm^3 (<70 cm^3 for tumours on the CW)
Skin	30 Gy < 10 cm^3 MPD < 33 Gy

Abbreviations IVC = inferior vena cava, SVC = superior vena cava, ITV = internal target volume, CW = chestwall, MPD = maximum point dose (defined as ≥0.03 cm^3)

Table 7.2 - Acceptable dose spillage guidelines from RTOG 1021

Ratio of Prescription Isodose Volume to the PTV		Ratio of 27 Gy Isodose Volume to the PTV $R_{50\%}$		Maximum Dose at 2 cm from PTV in any direction as % of Prescribed dose (PD). D_{2cm} (gy) = % x PD		PTV Volume (cc)
Deviation		Deviation		Deviation		
None	Acceptable	None	Acceptable	None	Acceptable	
<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	1.8
<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	3.8
<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	7.4
<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	13.2
<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	22.0
<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	34.0
<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	50.0
<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	70.0
<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	95.0
<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	126.0
<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	163.0

PTV = planning target volume

Table 7.3 - List of starting objectives for all techniques

ROI	Objective Type	Target Dose (Gy)	Volume (%)*	Weight
PTV	Minimum DVH	54	100	5
ITV	Minimum Dose	60		1
ITV	Maximum Dose	91.5		5
D_{2cm}	Maximum Dose	Table 3		5
27 Gy Ring	Maximum Dose	27		5
54 Gy Ring	Maximum Dose	54		1

Abbreviations: ROI = Region of interest, DVH = Dose volume histogram, PTV = planning target volume, ITV = internal target volume

* Only applicable for Maximum or Minimum DVH objective types

Table 7.4 - Mean dose statistics for each technique with associated P values.

Metric	Parameter	3DCRT	IMRT	VMAT	P value* (3DCRT-VMAT)	P Value* (IMRT-VMAT)	P value* (3DCRT-IMRT)
PTV_{54Gy}	(%)	95.59	95.71	95.63			0.048
$PTV_{48.6Gy}$	(%)	99.56	99.99	99.99	<0.0001		<0.0001
D_{2cm}	Absolute Difference	-0.86	-4.485	-5.72	<0.0001	<0.0001	<0.0001
$R_{50\%}$	Absolute Difference	0.37	0.25	0.08	0.04	0.04	
CI		0.80	0.88	0.89	<0.0001		<0.0001
MLD	(Gy)	4.12	4.01	0.04	<0.0001	<0.0001	
Spinal Cord	D_{max} (Gy)	9.87	8.95	7.55			
	V_{18Gy} (cm^3)	0.00	0.00	0.00			
	$V_{12.3Gy}$ (cm^3)	0.22	0.07	0.00			
Rib	D_{max} (Gy)	44.10	43.5	43.87			
	V_{40Gy} (cm^3)	1.55	2.00	1.82			
Chest Wall	V_{30Gy} (cm^3)	20.22	20.69	19.71			
Combined Lung - ITV	$V_{10.5Gy}$ (cm^3)	447.94	450.44	369.60			
	$V_{11.4Gy}$ (cm^3)	440.16	404.01	338.09			
Pericardium	D_{max} (Gy)	22.34	21.02	19.74			
	V_{24Gy} (cm^3)	0.94	0.50	0.47			
Skin	D_{max} (Gy)	22.6	22.50	17.19			
	V_{30Gy} (cm^3)	0.19	0.30	0.25			
Oesophagus	D_{max} (Gy)	13.3	12.86	8.82			
	$V_{17.7Gy}$ (cm^3)	0.18	0.03	0.01			
Aorta	D_{max} (Gy)	16.3	15.63	11.03			
	V_{39Gy} (cm^3)	0.00	0.00	0.00			
Trachea	D_{max} (Gy)	9.44	9.1	7.68			
	V_{15Gy} (cm^3)	0.75	0.34	0.15			

*Adjusted p value of post hoc tests.

Abbreviations

PA = coplanar partial arc technique; FA = coplanar full arc technique; NCA = non-coplanar technique utilising three partial arcs

ITV = internal target volume, PTV = planned target volume, MLD = mean lung dose, CI = conformity index

Table 7.5 - Protocol deviations for each technique, categorized into coplanar and non-coplanar and mean values for all coplanar and non-coplanar techniques combined with associated P values.

	3DCRT	IMRT	VMAT
D_{2cm}			
None	18	20	20
Acceptable	2	0	0
Unacceptable	0	0	0
R50%			
None	8	6	14
Acceptable	12	14	6
Unacceptable	0	0	0
CI			
None	19	20	20
Acceptable	1	0	0
Unacceptable	0	0	0
OAR			
None	9	9	9
Acceptable	8	9	9
Unacceptable	3	2	2
Total Deviations			
None	35	21	43
Acceptable	22	12	15
Unacceptable	3	7	2
Clinically Suitable Plans	17	18	18

CI = conformity index, OAR = organs at risk

Chapter 8: Discussion

This project compared three different delivery techniques for the delivery of stereotactic ablative radiation therapy (SABR) to the lung to treat early stage lung cancer. The aim was to determine if lung SABR could be delivered in quicker treatment times with the use of VMAT, without a reduction in plan quality compared to both 3DCRT and IMRT. To answer this question, the project was separated into two main components, the first being a like-for-like comparison between differing 3DCRT, IMRT and VMAT techniques. This was an important step in the project as the "gold standard" for each technique needed to first be identified, before comparisons between the techniques could be made. The second component was to compare 3DCRT with IMRT and VMAT to reach the primary end point for this project which was to find the optimal delivery technique for lung SABR. This project used dose prescriptions, dose restraints to organs at risk and intermediate dose constraints that have been stated in RTOG protocols.[82-84, 86]

The first paper of this project explored the 3DCRT treatment technique where six different beam arrangements using 3DCRT for 10 different patients were compared. The dosimetric advantages of using non-coplanar beams has previously been reported, however, the results of the current study illustrate that non-coplanar beams are necessary to meet the intermediate and OAR dosimetric constraints for any single plan. [81] It was found that a 10 field technique that had a majority of non-coplanar beams (≥6) provided the most optimal plan and adhered to the constraints as prescribed by RTOG 1021. This finding was inline with another publication by Lim et al [91] that report that with an increasing number of non-coplanar beams, the intermediate doses, in particular the $R_{50\%}$ value can be reduced. This present study found that the $R_{50\%}$ and D_{2cm} values can be significantly reduced with the appropriate beam selection and adequate amount of non-coplanar beams. There was no case where any technique apart from the 10NC was able to produce a plan with no protocol deviations.

Increasing the number of fields (13C) resulted in a marginal improvement when compared to either of the coplanar and non-coplanar 7 and 9 field techniques, with fewer protocol deviations in regards to the intermediate dose. However, it was not able to replicate the intermediate dose sparing achievable with the 10NC technique. In theory, increasing the number of beams reduces the dose delivered with each beam, spreading out the low dose and overlapping beams, resulting in a lower intermediate dose. This is crucial with SABR and allows for a steep isotropic fall off in dose.

Our findings do however, differ from those reported by Richmond et al [94] where they report in 89.5% of cases a 7 coplanar field technique had 2 or less minor deviations to the ROSEL protocol [95]. The difference in intermediate dose constraints between RTOG 1021 and ROSEL significantly alters which beam arrangements are deemed acceptable. All the techniques tested in this study had intermediate doses that were acceptable following the ROSEL guidelines. The difference in acceptable D_{2cm} and $R_{50\%}$ constraints is believed to be the main reason for disparity. It is therefore important to take care in critiquing SABR results, and comparing studies as the starting protocol significantly influences the outcomes.

Paper two investigated IMRT for lung SABR re-iterated similar findings to that of 3DCRT, in which increasing the number of beams, especially the number of non-coplanar beams improved plan quality and better adhered to intermediate dose (D_{2cm} and $R_{50\%}$) constraints. This findings were consistent with those published by Holt et al [106] who also investigated non-coplanar IMRT for peripheral lung SABR. Non-coplanar IMRT also reduced the maximum dose to the spinal cord. This project demonstrated that rib tolerances can be achieved in 63.3 % of cases regardless of technique. Of the plans where rib maximum doses were unachievable, only four plans had an $R_{50\%}$ that failed to reach an acceptable deviation. This highlights that maximum rib dose constrains only impact intermediate dose objectives if 7 (coplanar on non-coplanar) or less fields are used. Therefore, from the beam arrangements tested, >9 fields (either coplanar or non-coplanar) are required for tumours adjacent to the chest wall in order to meet both intermediate and OAR dose constraints.

One potential limitation of both paper 1 and paper 2 is the mixture of location of the tumours. Of the 10 patients data sets used for each study, 50 % of tumours were adjacent to the chest wall, and 50 % were entirely surrounded by lung parenchyma. Planning priorities in order were first and foremost, to adhere to the spinal cord and brachial plexus constraint, secondly to meet the high and intermediate dose constraints and lastly to meet the remaining OAR constraints. Therefore, prioritizing intermediate doses before non-spinal cord OAR may in fact cause some bias as the non-coplanar beam arrangements will always be superior to a coplanar arrangements in meeting intermediate does. This is due to the fact that isotropic fall off will be more achievable with non-coplanar beams[81], therefore allowing the planner to concentrate more on rib tolerances with non-coplanar beam arrangements. While the 3DCRT technique demonstrated that the only beam arrangement able to achieve rib tolerance was the 10NC, it was difficult to reach any conclusion. However, with the IMRT techniques, the 9C, 9NC, 13C and 10NC techniques were able to achieve maximum rib dose constraints. This demonstrates that if IMRT is being used with ≥9 fields coplanar or non-coplanar then both intermediate and rib maximum doses are achievable, indicating no bias between coplanar and non-coplanar techniques.

Paper three compared three different VMAT delivery techniques across 10 patients as part of the first component of this project. Similarly to the first paper it also demonstrated that a non-coplanar aspect to treatment planning produced superior quality plans than to those that had beams entering through only a coplanar (single plane) element. Although, the single full arc coplanar VMAT plans were inferior to the non-coplanar plans, they did produce clinically suitable plans in 70 % of the patient cohort. As a single full arc coplanar treatment would be quicker than a non-coplanar treatment technique with multiple couch rotations, the small gains in intermediate dose reduction may not outweigh any gains in treatment times. However as treatment times were not measured, this theory can only by hypothesised for future work.

Regardless if the conventional or hypofractionated radiation is being administered, a general concern for arc based treatments to the lung is the increased low dose wash, especially to the contra-lateral lung. The effect of this low dose wash or “bathing” can be seen with the increase in the mean lung dose (MLD) of the full arc technique. Paper 3 reports a MLD dose of 4.3 Gy which is similar to that of Holt et al [106] (4.2 Gy) for single coplanar VMAT. The MLD for the NCA (3.98 Gy) and PA (4.09 Gy) techniques were lower than the full arc technique. In a matched analysis study, Palma et al investigated radiobiological and clinical pneumonitis after both VMAT (RapidArc) and 3DCRT and concluded that there was no difference in the severity of clinical or radiobiological sequelae after treatment [117].

Lastly, the fourth paper was the most important of this project. After identifying the optimal delivery technique for each of the three respective technologies, they were compared in a larger cohort of 20 patients. This compared 10 field non-coplanar 3DCRT, 10 field IMRT and 3 partial arc non-coplanar VMAT. This paper found that the VMAT technique had the most optimal plans when critiqued against RTOG 1021 protocol criteria. The intermediate dose wash and OAR sparing was increased with the VMAT technique while still producing higher doses to the tumour when compared to 3DCRT. However, both the 3DCRT and IMRT technique did produce clinically acceptable plans. While IMRT showed improved tumour coverage and OAR sparing, the treatment time was increased when compared to 3DCRT. As an increase in treatment time results in a baseline shift of tumour position, the small gains in a plan where OAR doses are under tolerance 3DCRT should be the treatment option of choice[87].

Decreasing the influence of intra-fraction motion associated with extended treatment times was a secondary objective for this project. Purdie et al [87] report for treatment times >34 minutes, intra-fractional shifts of up to 5mm can occur. VMAT reduced the delivery time by 8.3 minutes (41.5%) and 13.5 minutes (53.4%), compared to 3DCRT and IMRT respectively. These results sit favourably with those reported by McGrath et al [118] who report on average 6 minutes and nine seconds to deliver a 180°, 12 Gy per fraction arc. IMRT should therefore only be used if OAR, in particular the rib, pericardium and spinal cord maximum or volumetric doses could not be achieved with 3DCRT. Nonetheless, if VMAT is an available treatment option then it should be used over both 3DCRT and IMRT as treatment times are significantly reduced. As the interplay effect is still a subjective phenomenon, it is suggested the departments take due course in implementing VMAT without an understanding of the dosimetric implications between leaf speed and tumour motion. One other issue arising from IMRT and VMAT is the increased workload placed on physics within a deparmtnet. The patient specific QA that is required for IMRT and VMAT far outweighs the time required to do a point dose check of a 3DCRT plan. As 3DCRT demonstrates the ability to produce clinically acceptable, then intensity modulation may best be reserved for those tumour streams where is a necessity, i.e. head and neck and prostate cancer, especially in a department where resources are stretched thin.

A general concern with intensity modulated techniques investigated in this project is the interplay effect. The interplay effect is the potential difference in the planned dose to the delivered dose due to patient respiration. This is caused by differences in the MLC movements to tumour motion when comparing the static respiratory phase the planning CT captured with the breathing cycle during treatment [112]. Several groups have investigated this phenomenon (VMAT or RapidArc) and report that for a single fraction split over two arcs, or >1 treatment fractions, the interplay effect is negligible and the actual delivered dose is within reasonable tolerance to the planned dose. [111, 112, 136]

While finding the optimal delivery technique was the primary aim for this project, some other interesting data came out of the project which could also lead to more efficient planning of lung SABR. Ding et al [79] report that for linear accelerator based lung SABR, the optimal prescription isodose falls somewhere between the 59-69% isodose. However, this range is only a guide and does not give a specific value that is achievable or should be aimed for. And, as the results from papers 1, and 4 show, the value of the prescription isodose changes dramatically if the tumour is attached to the chest wall or completely surrounded by lung parenchyma. Therefore an investigation took place

into observing if any correlation between the final plan and the prescription isodose was noticeable. It was found that when the density of the PTV plus a 2cm isotropic margin was plotted against the prescription isodose for individual plans, there was an R^2 value of 0.88, signifying high correlation. This finding now allows for the prescription isodose to be calculated before beginning planning and removes the monotonous task of trial and error to find the optimal –prescription isodose for individual patients. This data is currently being collated to be submitted to a peer reviewed journal.

Chapter 9: Future work

Future work from this project could include looking into the use of FFF for the delivery of lung SABR. As iterated throughout this report, the main aim was to reduce the treatment times for patients. FFF will most likely be bale to do this for lung SABR. Although the MU can increase to 2400 MU/min, the limit will be the MLC leaf speed. If the VMAT plans are over modulated then the treatment delivery speed may not be much quicker, as the leaf speed is limiting the treatment and reducing treatment efficiency.

Another avenue is the validate and report on any interplay effect present with these plans. With the use of a 4D phantom, the MLC interplay could potentially be measured and the plans could be validated for delivery and the actual dose delivered to a moving target under a modulated beam.

Chapter 10: Conclusion and Recommendations

This project demonstrated that non-coplanar VMAT consisting of 3 partial arcs provided more optimal plans than either coplanar or non-coplanar 3DCRT, coplanar or non-coplanar IMRT and coplanar VMAT. The ability to modulate the dose while delivering non-coplanar arcs that are continuously delivering the dose not only provided increased tumour coverage, but reduced doses to organs at risk and treatment times. However, non-coplanar 3DCRT, non-coplanar IMRT and coplanar single full arc VMAT were still able to produce clinically acceptable plans in a majority of the cases and still meet RTOG criteria. IMRT demonstrated only small improvements to plan quality, and no clinically significant improvements when compared to 3DCRT and significantly increased the treatment time.

It is recommended that for patient comfort and treatment efficiency that the first technique that should be attempted for lung SABR is single full arc VMAT. Even though the plans were slightly inferior to non-coplanar VMAT, the plans still fell within RTOG criteria and are able to be treated in a quicker treatment time than a technique that requires two floor rotations. For those departments that do not have VMAT technology, then a 10 field 3DCRT technique with 6 or greater non-coplanar fields should be used. IMRT should only be used in specific cases instead of 3DCRT when specific OAR constraints (such as the rib maximum dose) can not be achieved with 3DCRT due to extended treatment times with IMRT.

Bibliography

1. AIHW and AACR, *Cancer in Australia: an overview 2012*. 2012: Canberra: AIHW.
2. Australia, C. *Lung Cancer Statistics*. 2015 [cited 2015 27th January]; Available from: http://canceraustralia.gov.au/affected-cancer/cancer-types/lung-cancer/lung-cancer-statistics.
3. AIHW, *Australian Cancer Incidence and Mortality (ACIM) Books - Lung cancer for Australia*. 2015.
4. Henson, J.E., et al., *The Branching Pattern of Airways and Air Spaces of a Single Human Terminal Bronchiole.* Journal of Applied Physiology, 1975. **38**(6): p. 983-989.
5. Timmerman, R.D., J. Herman, and L.C. Cho, *Emergence of Stereotactic Body Radiation Therapy and Its Impact on Current and Future Clinical Practice.* Journal of Clinical Oncology, 2014. **32**(26): p. 2847-2854.
6. AJCC, *Cancer Staging Manual*. 7th ed. 2009, Philadelphia, PA.: Springer.
7. Institute, N.C. *Lung Cancer*. 2009 [cited 2014 24th April]; Available from: http://www.cancer.gov/cancertopics/types/lung.
8. Society, A.C. *Cancer Facts and Figures 2011*. 2011 [cited 2014 24th April]; Available from: http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2011.
9. Devesa, S.S., et al., *International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising.* Int J Cancer, 2005. **117**(2): p. 294-9.
10. Reade, C.A. and A.K. Ganti, *EGFR targeted therapy in non-small cell lung cancer: potential role of cetuximab.* Biologics, 2009. **3**: p. 215-224.
11. Anraku, M. and T.K. Waddell, *Surgery for Small-Cell Lung Cancer.* Seminars in Thoracic and Cardiovascular Surgery, 2006. **18**(3): p. 211-216.
12. NSW, C.C. *Staging lung cancer*. 2012; Available from: http://www.cancercouncil.com.au/15564/cancer-information/cancer-diagnosis-and-symptoms/cancerdiagnosis/understanding-lung-cancer-staging-and-prognosis/.
13. Urschel, J.D., *Surgical treatment of peripheral small cell lung cancer.* Chest Surg Clin N Am, 1997. **7**(1): p. 95-103.
14. AJCC, *Cancer Staging Manual*. 6th ed. 2002, Philadelphia, PA.: Springer.
15. Videtic, G.M.M., et al., *Stereotactic body radiation therapy-based treatment model for stage I medically inoperable small cell lung cancer.* Practical Radiation Oncology, 2013. **3**(4): p. 301-306.
16. Das, M., et al., *Alternatives to Surgery for early stage non-small cell lung cancer-ready for prime time?* Current Treatment Options in Oncology, 2010. **11**: p. 24-35.
17. Koo, H.-K., et al., *Factors associated with recurrence in patients with curatively resected stage I–II lung cancer.* Lung Cancer, 2011. **73**(2): p. 222-229.
18. Jeremic, B., et al., *Radiation Therapy for Early Stage (I/II) Non-Small Cell Lung Cancer*. Frontiers of Radiation Therapy and Oncology, Volume 42 : Controversies in the Treatment of Lung Cancer. 2010, Basel, CHE: Karger Publishers.
19. Filippi, A.R., P. Franco, and U. Ricardi, *Is stereotactic ablative radiotherapy an alternative to surgery in operable stage I non-small cell lung cancer?* Reports of Practical Oncology & Radiotherapy, (http://dx.doi.org/10.1016/j.rpor.2013.05.005).
20. Ginsberg, R.J., et al., *Modern thirty-day operative mortality for surgical resections in lung cancer.* J Thorac Cardiovasc Surg, 1983. **86**(5): p. 654-8.

21. Belderbos, J.S.A., et al., *Final results of a Phase I/II dose escalation trial in non–small-cell lung cancer using three-dimensional conformal radiotherapy.* Int J Radiat Oncol Biol Phys, 2006. **66**(1): p. 126-134.
22. Qiao, X., et al., *The role of radiotherapy in treatment of stage I non-small cell lung cancer.* Lung Cancer, 2003. **41**(1): p. 1-11.
23. Coy, P. and G. Kenelley, *The role of curative radiotherapy in the treatment of lung cancer.* Cancer, 1980. **45**: p. 698.
24. Armstrong, J. and B. Minsky, *Radiation therapy for medically inoperable stage and 11 non-small cell lung cancer.* Cancer Treatment Reviews, 1989. **16**.
25. Haffty, B.G., et al., *Results of radical radiation therapy in clinical stage I, technically operable non-small cell lung cancer.* Int J Radiat Oncol Biol Phys, 1988. **15**(1): p. 69-73.
26. Kaskowitz, L., et al., *Radiation therapy alone for stage I non-small cell lung cancer.* Int J Radiat Oncol Biol Phys, 1993. **27**(3): p. 517-523.
27. Dosoretz, D.E., et al., *Radiation therapy in the management of medically inoperable carcinoma of the lungs: Results and implications for future treatment strategies.* Int J Radiat Oncol Biol Phys, 1992. **24**(1): p. 3-9.
28. Mehta, M., et al., *A new approach to dose escalation in non–small-cell lung cancer.* Int J Radiat Oncol Biol Phys, 2001. **49**(1): p. 23-33.
29. Curran, W.J., P.J. Moldofsky, and L.J. Solin, *Analysis of the influence of elective nodal irradiation on postirradiation pulmonary function.* Cancer, 1990. **65**(11): p. 2488-2493.
30. Krol, A.D.G., et al., *Local irradiation alone for peripheral Stage I lung cancer: Could we omit the elective regional nodal irradiation?* International Journal of Radiation Oncology*Biology*Physics, 1996. **34**(2): p. 297-302.
31. Williams, T.E., C.R. Thomas, Jr., and A.T. Turrisi, 3rd, *Counterpoint: better radiation treatment of non-small cell lung cancer using new techniques without elective nodal irradiation.* Semin Radiat Oncol, 2000. **10**(4): p. 315-23.
32. Slotman, B.J., I.E. Antonisse, and K.H. Njo, *Limited field irradiation in early stage (T1–2N0) non-small cell lung cancer.* Radiotherapy and Oncology, 1996. **41**(1): p. 41-44.
33. Robertson, J.M., et al., *Dose escalation for non-small cell lung cancer using conformal radiation therapy.* Int J Radiat Oncol Biol Phys, 1997. **37**(5): p. 1079-1085.
34. Leksell, L., *The stereotaxic method and radiosurgery of the brain.* Acta Chir Scand, 1951. **102**(4): p. 316-9.
35. Benedict, S.H., et al., *Stereotactic body radiation therapy: The report of AAPM Task Group 101.* Medical Physics, 2010. **68**(8).
36. Timmerman, R.D., *An Overview of Hypofractionation and Introduction to This Issue of Seminars in Radiation Oncology.* Seminars in Radiation Oncology, 2008. **18**(4): p. 215-222.
37. Potters, L., et al., *American Society for Therapeutic Radiology and Oncology* and American College of Radiology Practice Guideline for the Performance of Stereotactic Body Radiation Therapy.* Int J Radiat Oncol Biol Phys, 2004. **60**(4): p. 1026-1032.
38. Blomgren, H., et al., *Stereotactic High Dose Fraction Radiation Therapy of Extracranial Tumors Using An Accelerator: Clinical experience of the first thirty-one patients.* Acta Oncologica, 1995. **34**(6): p. 861-870.
39. Wulf, J., et al., *Stereotactic Radiotherapy of Targets in the Lung and Liver.* Strahlentherapie und Onkologie, 2001. **177**(12): p. 645-655.
40. Herfarth, K.K., et al., *Stereotactic single-dose radiation therapy of liver tumors: Results of a phase I/II trial.* Journal Of Clincial Oncology, 2001. **19**: p. 164-170.
41. Herfarth, K.K., J. Debus, and M.F. Wannenmacher, *Stereotactic radiation therapy of liver metastases: Update of the initial phase-I/II trial.* Frontiers in Radiation Therapy and Oncology, 2004. **38**: p. 100-105.
42. Timmerman, R., et al., *Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer.* Chest, 2003. **124**(5): p. 1946-55.

43. Whyte, R.I., et al., *Stereotactic radiosurgery for lung tumors: preliminary report of a phase I trial.* Ann Thorac Surg, 2003. **75**(4): p. 1097-101.
44. Fukumoto, S., et al., *Small-volume image-guided radiotherapy using hypofractionated, coplanar, and noncoplanar multiple fields for patients with inoperable Stage I nonsmall cell lung carcinomas.* Cancer, 2002. **95**(7): p. 1546-53.
45. Hara, R., et al., *Stereotactic single high dose irradiation of lung tumors under respiratory gating.* Radiother Oncol, 2002. **63**(2): p. 159-63.
46. Lee, S.W., et al., *Stereotactic body frame based fractionated radiosurgery on consecutive days for primary or metastatic tumors in the lung.* Lung Cancer, 2003. **40**(3): p. 309-15.
47. Nagata, Y., et al., *Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame.* Int J Radiat Oncol Biol Phys, 2002. **52**(4): p. 1041-6.
48. Onishi, H., et al., *Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study.* Cancer, 2004. **101**(7): p. 1623-31.
49. Uematsu, M., et al., *Computed tomography (CT)-guided stereotactic radiation therapy (SRT) for stage I non-small cell lung cancer (NSCLC): 8-year results of 50 initial patients.* Int J Radiat Oncol Biol Phys, 2003. **57**(2): p. S281.
50. Foote, M., et al., *Technique for stereotactic body radiotherapy for spinal metastases.* Journal of Clinical Neuroscience, 2011. **18**(2): p. 276-279.
51. Benzil, D.L., et al., *Safety and efficacy of stereotactic radiosurgery for tumors of the spine.* J Neurosurg, 2004. **101 Suppl 3**: p. 413-8.
52. Bilsky, M.H., et al., *Intensity-modulated stereotactic radiotherapy of paraspinal tumors: a preliminary report.* Neurosurgery, 2004. **54**(4): p. 823-30; discussion 830-1.
53. Chang, E.L., et al., *Phase I clinical evaluation of near-simultaneous computed tomographic image-guided stereotactic body radiotherapy for spinal metastases.* Int J Radiat Oncol Biol Phys, 2004. **59**(5): p. 1288-94.
54. Ryu, S., et al., *Image-guided and intensity-modulated radiosurgery for patients with spinal metastasis.* Cancer, 2003. **97**(8): p. 2013-8.
55. Ryu, S., et al., *Patterns of failure after single-dose radiosurgery for spinal metastasis.* J Neurosurg, 2004. **101 Suppl 3**: p. 402-5.
56. Chetty, I.J., et al., *Correlation of dose computed using different algorithms with local control following stereotactic ablative radiotherapy (SABR)-based treatment of non-small-cell lung cancer.* Radiotherapy and Oncology, 2013. **109**(3): p. 498-504.
57. Muriel, V.P., *Hypofractionation in radiotherapy.* Clinical and Translational Oncology, 2007. **9**: p. 21-27.
58. Onishi, H., et al., *Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study.* J Thorac Oncol, 2007. **2**(7 Suppl 3): p. S94-100.
59. Bentzen, S.M., et al., *Bioeffect modeling and equieffective dose concepts in radiation oncology – Terminology, quantities and units.* Radiotherapy and Oncology, 2012. **105**(2): p. 266-268.
60. Brown, J.M., D.J. Carlson, and D.J. Brenner, *The Tumor Radiobiology of SRS and SBRT: Are More than the 5 R's Involved?* International journal of radiation oncology, biology, physics, 2014. **88**(2): p. 254-262.
61. Fowler, J.F., *Sensitivity Analysis of Parameters in Linear-Quadratic Radiobiologic Modeling.* Int J Radiat Oncol Biol Phys, 2009. **73**(5): p. 1532-1537.
62. Timmerman, R., et al., *Stereotactic body radiation therapy for inoperable early stage lung cancer.* The Journal of the American Medical Association, 2010. **303**(11): p. 1070-1076.
63. ICRU, *ICRU REPORT 50.* JOURNAL OF THE ICRU, 1993.
64. Jin, J.-Y., et al., *Quantification of incidental dose to potential clinical target volume (CTV) under different stereotactic body radiation therapy (SBRT) techniques for non-small cell lung cancer – Tumor motion and using internal target volume (ITV) could*

improve dose distribution in CTV. Radiotherapy and Oncology, 2007. **85**(2): p. 267-276.
65. Jin, J.Y., et al., *A technique of using gated-CT images to determine internal target volume (ITV) for fractionated stereotactic lung radiotherapy.* Radiother Oncol, 2006. **78**(2): p. 177-84.
66. Timmerman, R., et al., *Accreditation and quality assurance for Radiation Therapy Oncology Group: Multicenter clinical trials using Stereotactic Body Radiation Therapy in lung cancer.* Acta Oncol, 2006. **45**(7): p. 779-86.
67. Ueda, Y., et al., *Craniocaudal Safety Margin Calculation Based on Interfractional Changes in Tumor Motion in Lung SBRT Assessed With an EPID in Cine Mode.* Int J Radiat Oncol Biol Phys, 2012. **83**(3): p. 1064-1069.
68. Khan, F., et al., *The Use of 4DCT to Reduce Lung Dose: A Dosimetric Analysis.* Medical Dosimetry, 2009. **34**(4): p. 273-278.
69. Kay, C.-S. and Y.-N. Kang, *Curative Radiotherapy in Metastatic Disease: How to Develop the Role of Radiotherapy from Local to Metastases*. Frontiers in Radiation Oncology. 2013.
70. Keall, P., et al., *The Management of Respiratory Motion in Radiation Oncology.* American Association of Physicists in Medicine, 2006. **91**.
71. Yu, C.X., D.A. Jaffray, and J.W. Wong, *The effects of intra-fraction organ motion on the delivery of dynamic intensity modulation.* Phys Med Biol, 1998. **43**(1): p. 91-104.
72. Li, W., et al., *Effect of Immobilization and Performance Status on Intrafraction Motion for Stereotactic Lung Radiotherapy: Analysis of 133 Patients.* Int J Radiat Oncol Biol Phys, 2011. **81**(5): p. 1568-1575.
73. Grills, I.S., et al., *Image-Guided Radiotherapy via Daily Online Cone-Beam CT Substantially Reduces Margin Requirements for Stereotactic Lung Radiotherapy.* Int J Radiat Oncol Biol Phys, 2008. **70**(4): p. 1045-1056.
74. Low, D.A., et al., *Phantoms for IMRT Dose Distribution Measurement and Treatment Verification.* Int J Radiat Oncol Biol Phys, 1998. **40**(5): p. 1231-1235.
75. McGarry, R.C., et al., *Stereotactic body radiation therapy of early-stage non–small-cell lung carcinoma: Phase I study.* Int J Radiat Oncol Biol Phys, 2005. **63**(4): p. 1010-1015.
76. Hiraoka, M. and Y. Nagata, *Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the Japanese experience.* Int J Clin Oncol, 2004. **9**(5): p. 352-5.
77. Onimaru, R., et al., *Steep Dose–Response Relationship for Stage I Non–Small-Cell Lung Cancer Using Hypofractionated High-Dose Irradiation by Real-Time Tumor-Tracking Radiotherapy.* Int J Radiat Oncol Biol Phys, 2008. **70**(2): p. 374-381.
78. Nagata, Y., et al., *Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame.* Int J Radiat Oncol Biol Phys, 2005. **63**(5): p. 1427-1431.
79. Ding, C., et al., *Optimization of normalized prescription isodose selection for stereotactic body radiation therapy: Conventional vs robotic linac.* Medical Physics, 2013. **40**(5).
80. Verbakel, W.F.A.R., et al., *Rapid delivery of stereotactic radiotherapy for peripheral lung tumors using volumetric intensity-modulated arcs.* Radiotherapy and Oncology, 2009. **93**(1): p. 122-124.
81. Papież, L., et al., *Extracranial Stereotactic Radioablation Physical Principles.* Acta Oncologica, 2003. **42**(8): p. 882-894.
82. RTOG. *RTOG 0236 A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer*. 2009 [cited 2014; Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0236.
83. RTOG. *RTOG 0915 A randomized phase II study comparing 2 stereotactic body radiation therapy (SBRT) schedules for medically inoperbale patients with stage 1 peripheral non-small cell lung cancer*. 2012; Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915.

84. RTOG. *RTOG 0813 Seamless phase I/II study of stereotactic lung radiotherapy (SBRT) for early stage, centrally located, non-small cell lung cancer (NSCLC) in medically inoperable patients*. 2012; Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813.
85. Paddick, I., *A simple scoring ratio to index the conformity of radiosurgical treatment plans.* J Neurosurg, 2000. **93**(Suppl 3): p. 219-222.
86. RTOG. *RTOG 1021: A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)*. 2011 1/05/2015]; Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1021.
87. Purdie, T.G., et al., *Cone-Beam Computed Tomography for On-Line Image Guidance of Lung Stereotactic Radiotherapy: Localization, Verification, and Intrafraction Tumor Position.* Int J Radiat Oncol Biol Phys, 2007. **68**(1): p. 243-252.
88. TROG, *A Randomised Phase III Trial of Highly Conformal Hypofractionated Image Guided ("Stereotactic") Radiotherapy (HypoRT) versus Conventionally Fractionated Radiotherapy (ConRT) for Inoperable Early Stage 1 Non-Small Cell Lung Cancer (CHISEL)*. Trans Tasman Radiation Oncology Group., 2009.
89. Ng, A.W.Y., S.Y. Tung, and V.Y.W. Wong, *Hypofractionated stereotactic radiotherapy for medically inoperable stage I non-small cell lung cancer – report on clinical outcome and dose to critical organs.* Radiotherapy and Oncology, 2008. **87**(1): p. 24-28.
90. De Ruysscher, D., et al., *European Organisation for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer.* Journal Of Clincial Oncology, 2010. **28**(38).
91. Lim, D., et al., *Optimal beam arrangement for stereotactic body radiation therapy delivery in lung tumors.* Acta Oncologica, 2010. **49**.
92. Fakiris, A.J., et al., *Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study.* Int J Radiat Oncol Biol Phys, 2009. **75**(3): p. 677-82.
93. Xiao, Y., et al., *Dosimetric Evaluation of Heterogeneity Corrections for RTOG 0236: Stereotactic Body Radiotherapy of Inoperable Stage I-II Non–Small-Cell Lung Cancer.* Int J Radiat Oncol Biol Phys, 2009. **73**(4): p. 1235-1242.
94. Richmond, N., et al., *Dosimetric Evaluation of a Conformal Seven-field Coplanar Technique for Planning Lung Stereotactic Body Radiotherapy.* Clinical Oncology, 2012. **24**(1): p. e24-e30.
95. Hurkmans, C.W., et al., *Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study.* Radiation Oncology, 2009. **4**(1).
96. Fukumoto, S.-i., et al., *Small-volume image-guided radiotherapy using hypofractionated, coplanar, and noncoplanar multiple fields for patients with inoperable Stage I nonsmall cell lung carcinomas.* Cancer, 2002. **95**(7): p. 1546-1553.
97. Ong, C.L., et al., *Stereotactic radiotherapy for peripheral lung tumors: A comparison of volumetric modulated arc therapy with 3 other delivery techniques.* Radiotherapy and Oncology, 2010. **97**(3): p. 437-442.
98. Onimaru, R., et al., *Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers.* Int J Radiat Oncol Biol Phys, 2003. **56**(1): p. 126-135.
99. Senan, S. and F. Lagerwaard, *Stereotactic radiotherapy for stage I lung cancer: Current results and new developments.* Cancer/Radiothérapie, 2010. **14**(2): p. 115-118.
100. Creach, K.M., et al., *Stereotactic body radiation therapy in the treatment of multiple primary lung cancers.* Radiotherapy and Oncology, 2012. **104**(1): p. 19-22.
101. Bradley, J.D., et al., *Stereotactic Body Radiation Therapy for Early-Stage Non–Small-Cell Lung Cancer: The Pattern of Failure Is Distant.* Int J Radiat Oncol Biol Phys, 2010. **77**(4): p. 1146-1150.

102. Onishi, H., et al., *Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma.* Cancer, 2004. **101**(7): p. 1623-1631.
103. Brock, J., et al., *Optimising Stereotactic Body Radiotherapy for Non-small Cell Lung Cancer with Volumetric Intensity-modulated Arc Therapy—A Planning Study.* Clinical Oncology, 2012. **24**(1): p. 68-75.
104. Wulf, J., et al., *Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: A noninvasive treatment approach in medically inoperable patients.* Int J Radiat Oncol Biol Phys, 2004. **60**(1): p. 186-196.
105. Webb, S., *The physical basis of IMRT and inverse planning.* The British Journal of Radiology, 2003. **76**: p. 678-689.
106. Holt, A., et al., *Volumetric-Modulated Arc Therapy for Stereotactic Body Radiotherapy of Lung Tumors: A Comparison With Intensity-Modulated Radiotherapy Techniques.* Int J Radiat Oncol Biol Phys, 2011. **81**(5): p. 1560-1567.
107. Videtic, G.M.M., et al., *Intensity-Modulated Radiotherapy–Based Stereotactic Body Radiotherapy for Medically Inoperable Early-Stage Lung Cancer: Excellent Local Control.* Int J Radiat Oncol Biol Phys, 2010. **77**(2): p. 344-349.
108. Le, Y., et al., *Stereotactic Body Radiotherapy (SBRT) Treatment of Lung Lesions using Volumetric Modulated Arc Therapy (VMAT).* Int J Radiat Oncol Biol Phys, 2010. **78**(3, Supplement): p. S797.
109. Kim, G., et al., *A Comparison of Lung SBRT Using Volumetric Modulated Arc Therapy With Static Field IMRT.* Int J Radiat Oncol Biol Phys, 2012. **84**(3, Supplement): p. S871-S872.
110. Wu, Q.J., et al., *The impact of respiratory motion and treatment technique on stereotactic body radiation therapy for liver cancer.* Medical Physics, 2008. **35**(4): p. 1440-1451.
111. Nguyen, D., et al., *Dosimetric impact of interplay effect on a volumetric modulated arc therapy (VMAT) stereotactic lung (SBRT) delivery: Validation using a 6D motion platform and 3D dosimeter.* Physica Medica, 2013. **29, Supplement 1**(0): p. e29-e30.
112. Ong, C., et al., *Dosimetric Impact of Interplay Effect on RapidArc Lung Stereotactic Treatment Delivery.* Int J Radiat Oncol Biol Phys, 2011. **79**(1): p. 305-311.
113. Feygelman, V., et al., *Dynamic Dose Interplay Does Not Meaningfully Affect Target Dose in VMAT SBRT Treatments.* Int J Radiat Oncol Biol Phys, 2013. **87**(2, Supplement): p. S700-S701.
114. Bedford, J.L. and A.P. Warrington, *Commissioning of Volumetric Modulated Arc Therapy (VMAT).* Int J Radiat Oncol Biol Phys, 2009. **73**(2): p. 537-545.
115. Elith, C., et al., *An introduction to the intensity-modulated radiation therapy (IMRT) techniques, tomotherapy, and VMAT*. 2011.
116. Chan, O.S.H., et al., *The superiority of hybrid-volumetric arc therapy (VMAT) technique over double arcs VMAT and 3D-conformal technique in the treatment of locally advanced non-small cell lung cancer – A planning study.* Radiotherapy and Oncology, 2011. **101**(2): p. 298-302.
117. Palma, D.A., et al., *Radiological and Clinical Pneumonitis After Stereotactic Lung Radiotherapy: A Matched Analysis of Three-Dimensional Conformal and Volumetric-modulated Arc Therapy Techniques.* Int J Radiat Oncol Biol Phys, 2011. **80**(2): p. 506-513.
118. McGrath, S.D., et al., *Volumetric modulated arc therapy for delivery of hypofractionated stereotactic lung radiotherapy: A dosimetric and treatment efficiency analysis.* Radiotherapy and Oncology, 2010. **95**(2): p. 153-157.
119. Verbakel, W., et al., *Flattening Filter-free Beams for SBRT: Advantages and Risks.* Int J Radiat Oncol Biol Phys, 2012. **84**(3, Supplement): p. S826-S827.
120. Lagerwaard, F.J., et al., *Outcomes of Stereotactic Ablative Radiotherapy in Patients With Potentially Operable Stage I Non-Small Cell Lung Cancer.* Int J Radiat Oncol Biol Phys, 2012. **83**(1): p. 348-353.
121. Takeda, A., et al., *Stereotactic Body Radiotherapy for Primary Lung Cancer at a Dose of 50 Gy Total in Five Fractions to the Periphery of the Planning Target Volume*

Calculated Using a Superposition Algorithm. Int J Radiat Oncol Biol Phys, 2009. **73**(2): p. 442-448.
122. Baumann, P., et al., *Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy.* J Clin Oncol, 2009. **27**(20): p. 3290-6.
123. Soldà, F., et al., *Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; Systematic review and comparison with a surgical cohort.* Radiotherapy and Oncology, 2013. **109**(1): p. 1-7.
124. Gorayski, P., et al., *Volumetric modulated arc therapy versus step-and-shoot intensity modulated radiation therapy in the treatment of large nerve perineural spread to the skull base: a comparative dosimetric planning study.* Journal of Medical Radiation Sciences, 2014.
125. Asai, K., et al., *Radiation-Induced Rib Fractures After Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors and Dose–Volume Relationship.* Int J Radiat Oncol Biol Phys, 2012. **84**(3): p. 768-773.
126. Dunlap, N.E., et al., *Chest Wall Volume Receiving 30 Gy Predicts Risk of Severe Pain and/or Rib Fracture After Lung Stereotactic Body Radiotherapy.* Int J Radiat Oncol Biol Phys, 2010. **76**(3): p. 796-801.
127. Kim, S.S., et al., *Clinical prognostic factors and grading system for rib fracture following stereotactic body radiation therapy (SBRT) in patients with peripheral lung tumors.* Lung Cancer, 2013. **79**(2): p. 161-166.
128. Kong, F.-M., et al., *Consideration of Dose Limits for Organs at Risk of Thoracic Radiotherapy: Atlas for Lung, Proximal Bronchial Tree, Esophagus, Spinal Cord, Ribs, and Brachial Plexus.* Int J Radiat Oncol Biol Phys, 2011. **81**(5): p. 1442-1457.
129. Pettersson, N., J. Nyman, and K.-A. Johansson, *Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: A dose– and volume–response analysis.* Radiotherapy and Oncology, 2009. **91**(3): p. 360-368.
130. Cancer Council Australia. *Lung cancer*. 2015 [cited 2015 14th, December 2015]; Available from: http://www.cancer.org.au/about-cancer/types-of-cancer/lung-cancer.html.
131. Fitzgerald, R., et al., *The effect of beam arrangements and the impact of non-coplanar beams on the treatment planning of stereotactic ablative radiation therapy for early stage lung cancer.* Journal of Medical Radiation Sciences, 2015.
132. Khodri, M., et al., *Volumetric-Modulated Arc Therapy for Stereotactic Body Radiotherapy of Lung Tumors: A comparison with 2 other delivery techniques (IMRT and 3DCRT).* Physica Medica, 2011. **27, Supplement 1**: p. S3.
133. Liu, R., et al., *Optimal number of beams for stereotactic body radiotherapy of lung and liver lesions.* Int J Radiat Oncol Biol Phys, 2006. **66**(3): p. 906-912.
134. Chan, C., et al., *Intensity-Modulated Radiotherapy for Lung Cancer: Current Status and Future Developments.* Journal of Thoracic Oncology, 2014. **9**(11): p. 1598-1608.
135. Fitzgerald, R., et al., *A comparison of three different VMAT techniques for the delivery of lung stereotactic ablative radiation therapy.* J Med Radiat Sci, 2016: p. n/a-n/a.
136. Stambaugh, C., et al., *Experimentally studied dynamic dose interplay does not meaningfully affect target dose in VMAT SBRT lung treatments.* Med Phys, 2013. **40**(9): p. 091710.
137. Peters, C.A., et al., *Stereotactic Ablative Radiation Therapy for Lung Tumors Using Helical Tomotherapy: A Cost-effective Treatment Regimen.* Int J Radiat Oncol Biol Phys, 2012. **84**(3, Supplement): p. S563-S564.
138. Sole, C.V., et al., *Stereotactic Ablative Radiation Therapy Delivered by Helical Tomotherapy for Early-Stage Non-small Cell Lung Cancer: Dosimetric Evaluation and Toxicity.* Int J Radiat Oncol Biol Phys, 2012. **84**(3, Supplement): p. S820.
139. Mehta, N., et al., *Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological*

equivalent dose and local control. Practical Radiation Oncology, 2012. **2**(4): p. 288-295.
140. Oku, Y., et al., *Stereotactic ablative body radiation therapy with dynamic conformal multiple arc therapy for liver tumors: Optimal isodose line fitting to the planning target volume.* Practical Radiation Oncology, 2014. **4**(1): p. e7-e13.
141. Takayama, K., et al., *Treatment planning of stereotactic radiotherapy for solitary lung tumor.* Int J Radiat Oncol Biol Phys, 2005. **61**(5): p. 1565-1571.
142. Takeda, A., et al., *Dose Distribution Analysis in Stereotactic Body Radiotherapy Using Dynamic Conformal Multiple Arc Therapy.* Int J Radiat Oncol Biol Phys, 2009. **74**(2): p. 363-369.
143. Sahgal, A., et al., *The Canadian Association of Radiation Oncology Scope of Practice Guidelines for Lung, Liver and Spine Stereotactic Body Radiotherapy.* Clinical Oncology, 2012. **24**(9): p. 629-639.

Appendices

11.1 APPENDIX A: PHASE 1 3DCRT RESULTS

11.1.1 Patient 1

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.08%	95.10%	95.15%	95.17%	95.02%	95.14%
	99% ≥ 90 % of PD	99.67%	99.82%	99.65%	99.88%	99.77%	99.73%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0.92	0.62	0	0.38	0	0
	21.9Gy max pt	13.1	12.9	11.8	12.7	8.1	11.7
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0.6	0.8	0.6	0.8	0.9	0.6
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	1	1.1	1	1	4.8	1
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.2	0.3	0.2	0.3	0	0.2
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	9.5	10.5	14.5	13.2	18.4	19.5
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	13.2	12.9	15.3	15.1	21.9	16.1
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	13.2	12.9	15.4	15.1	22	19.5
Trachea	4cc < 15Gy	0	0	0	0	3.26	2.95
	30Gy max pt	13.8	14	13.3	13.2	19	18.6
Comb Lung - ITV	1500cc < 10.5Gy	591.35	586.78	606.18	591.75	686.79	631.08
	1000cc < 11.4 Gy	550.55	545.51	569.14	555.56	628.4	583.09
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	12.8	13	13.9	13.7	18.2	15.8
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	34.8	34.9	30.5	31	26.5	31.8
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	22.8	23.1	21.5	22	24.5	17.5
CW	30cc < 30Gy	1.17	2.18	0.12	0.11	0	1.27
D2cm	<29.8Gy <34.7	36.4	37.6	33.2	33.5	28.4	32.1
R50%	<4.5 <5.5	6.96	6.52	6.71	6.33	5.43	6.73
TV(PTV)		24.04	24.05	24.06	24.06	24.02	24.06
TV		25.28	25.28	25.28	25.28	25.28	25.28
PIV		28.92	28.89	28.79	28.45	27.8	28.94
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.790485	0.7919642	0.795376	0.804881	0.820964	0.791254

11.1.2 **Patient 2**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.03%	95.11%	95.13%	95.06%	95.55%	95.11%
	99% ≥ 90 % of PD	99.77%	99.70%	99.85%	99.91%	99.77%	99.99%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0.61	0
	21.9Gy max pt	7.1	1	6.4	1.1	12.8	10.8
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0.1	0.23	0.11	0.22	0.28	0.13
Heart	15cc < 24Gy	0	0	0.19	0.26	0	0.71
	30Gy max pt	22.4	23.6	26	26	20.4	26.7
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.88	0.88	0.98	0.96	1.03	1
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	16	12.4	16.5	14.3	13.7	21.1
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	11.7	11.8	11.7	12	9	18.8
Pericardium	15cc < 24 Gy	0	0	1.12	0.27	0	0.74
	30Gy max pt	22.8	22.2	26	26	20.4	26.7
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	1	0.9	1.14	1.03	1.04	1.17
Comb Lung - ITV	1500cc < 10.5Gy	518.82	526.51	501.55	507.51	485.26	487.67
	1000cc < 11.4 Gy	484.4	488.68	473.35	476.7	443.43	430.37
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	9.5	1	11.9	6.7	8.2	12.1
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	34.7	26.7	33.3	25.2	24.7	31.4
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	31.7	20.2	25.5	24.8	19.7	20
CW	30cc < 30Gy	6.09	0.84	4.6	0.2	0	3.06
D2cm	<29.7 <34.6	35.3	31.8	32	31.2	27.2	30.1
R50%	<4.5 <5.5	6.2	5.39	6.05	5.26	4.5	5.83
TV(PTV)		22.83	22.86	22.86	22.85	22.96	22.86
TV		24	24	24	24	24	24
PIV		27.89	28.16	28.15	27.67	27.28	25.99
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.778668	0.77323	0.773504	0.786234	0.805171	0.83779

11.1.3 **Patient 3**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.12%	95.01%	95.18%	95.06%	95.06%	95.04%
	99% ≥ 90 % of PD	99.98%	99.97%	99.48%	99.96%	99.90%	99.99%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	1.12	0.82	0	0
	21.9Gy max pt	4	3.9	14.3	13.7	9.1	12.3
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0	0.03	0.04	0.03	0.06	0.03
Heart	15cc < 24Gy	1.26	1.29	1.95	2.15	3.59	8.72
	30Gy max pt	30	29	30	30	29.9	34.9
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	2	1.2	1.6	1.2	3.1	2.1
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	3.5	3.8	5.7	6.7	1.12	6.6
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	23.2	20.9	21.5	20.7	17.9	19.7
Pericardium	15cc < 24 Gy	1.26	1.29	1.95	2.15	3.59	8.75
	30Gy max pt	30	29	30	30	29.9	34.9
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	0.6	0.6	0.7	0.8	0.8	0.7
Comb Lung - ITV	1500cc < 10.5Gy	766.23	736.48	739.26	700.22	706.63	684.22
	1000cc < 11.4 Gy	730.12	686.94	692.88	650.08	652.52	651.76
Oesophagus	5cc < 17.7 Gy	2.72	2.23	0	0	0	0
	25.2Gy max pt	23.2	20.7	14.7	14	17.7	15.6
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	32.9	30.9	31.8	32.5	31.4	33
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	28	29.3	27.1	25.9	22	22.8
CW	30cc < 30Gy	1.41	1.28	0.76	0.65	0.11	0.64
D2cm	<31.6 <36.7	39.4	38	35	36.7	31	31.3
R50%	<4.3 <5.3	7.44	6.98	7.2	7.1	5.29	6.72
TV(PTV)		33.52	33.49	33.52	33.49	33.5	33.49
TV		35.2	35.2	35.2	35.2	35.2	35.2
PIV		39.93	41.44	39.6	40.32	39.16	39.01
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.799404	0.768897	0.806065	0.790255	0.81415	0.816792

11.1.4 Patient 4

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.16%	95.02%	95.01%	95.02%	99.03%	95.15%
	99% ≥ 90 % of PD	99.58%	99.51%	99.59%	99.65%	99.93%	99.76%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0.13	0	0	0	0	0.26
	21.9Gy max pt	13.1	1.1	6.9	0.92	6.5	12.8
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	1.08	1.15	1.13	1	1.16	1.12
Heart	15cc < 24Gy	0.16	0.2	0.06	0.29	0.19	0.02
	30Gy max pt	28	28.5	25.2	31	28	23.5
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.42	0.69	0.48	0.59	0.48	0.49
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	8.5	1.3	1.3	1.5	7.5	12.8
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	16	11.4	19	15.3	14.7	16.7
Pericardium	15cc < 24 Gy	2.27	1.11	3.81	1.68	1.64	10.6
	30Gy max pt	31.5	30.1	30.5	32.9	28.2	36
Trachea	4cc < 15Gy	0	0	0.58	0	0	0.1
	30Gy max pt	9.5	11.3	16.3	14.9	7.2	15.8
Comb Lung - ITV	1500cc < 10.5Gy	372.95	383.76	397.18	404.44	425.9	361.86
	1000cc < 11.4 Gy	348.61	344.77	366.63	368.26	378.04	318.12
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	9.2	11.3	16.8	15.3	6.8	15.3
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	25.5	26	29.5	23.2	28.4	26.1
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	22.7	22.5	20	19.8	18.7	16.1
CW	30cc < 30Gy	0	0	0	0	0	0
D2cm	<29.2 <34.0	30.9	27.4	30.3	28.8	28.4	29.2
R50%	<4.5 <5.5	4.53	3.9	4.41	4.16	4.12	4.45
TV(PTV)		21.81	21.77	21.77	21.77	22.46	21.8
TV		22.9	22.9	22.9	22.9	22.9	22.9
PIV		24.21	23.9	24.06	24.15	28.29	24.54
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.857988	0.865931	0.860173	0.856967	0.778666	0.845674

11.1.5 **Patient 5**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.09%	95.05%	95.01%	95.08%	95.41%	95.01%
	99% ≥ 90 % of PD	99.61%	99.62%	99.77%	99.84%	99.63%	99.88%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0	0
	21.9Gy max pt	10.3	11.1	8.7	8.9	8.3	11.1
BP	3cc < 20.4Gy						
	24Gy max pt						
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	10.1	11.1	15.4	15.9	10.1	12.5
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.5	0.6	0.4	0.5	0.6	0.4
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	12.3	13.5	10.5	12.1	11	16.3
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	10.1	10.9	13.5	13.8	11.2	12.6
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	16.1	17.3	18.9	19.5	20.4	22
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	10.6	11.5	12	12.4	9.1	15.3
Comb Lung - ITV	1500cc < 10.5Gy	499.53	452.27	530.94	496.73	552.82	515.61
	1000cc < 11.4 Gy	470.91	425.78	495.56	464.32	506.07	465.85
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	1.6	1.6	5.8	5.8	9	11.2
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	29.3	31.2	30	29.8	29.5	30.4
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	19.9	21.8	18.8	18.7	20.5	18
CW	30cc < 30Gy	0.07	0.28	0.04	0.1	0.02	0.23
D2cm	<30.5 <35.8	32.4	33.6	31.2	32.2	29.3	29.2
R50%	<4.4 <5.4	5.5	5.34	5.21	4.9	4.38	4.93
TV(PTV)		28.21	28.22	28.21	28.23	28.33	28.21
TV		29.7	29.7	29.7	29.7	29.7	29.7
PIV		32.86	32.46	31.64	31.32	31.85	30.7
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.815422	0.826055	0.846863	0.856729	0.848452	0.872793

11.1.6 **Patient 6**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	96.27%	95.14%	95.32%	95.27%	95.00%	95.09%
	99% ≥ 90 % of PD	99.00%	99.00%	99.02%	99.00%	99.17%	99.16%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0.3	0	0	0
	21.9Gy max pt	10.2	9.6	14.4	10.1	9.3	11.1
BP	3cc < 20.4Gy						
	24Gy max pt						
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	15.7	16.5	22.5	20.8	20.8	18.7
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	11	12.4	18.4	16.7	22	17.9
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	1.1	0.92	1.17	1.1	1.5	1.15
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	9.1	10.1	18.6	16.5	24.4	18.3
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	16.8	17.2	22.9	21.4	21.4	20.3
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	0	0	0	0	0.32	0
Comb Lung - ITV	1500cc < 10.5Gy	445.66	467.14	565.38	475.8	653.6	598.7
	1000cc < 11.4 Gy	418.79	436.11	525.21	441.67	603.76	504.59
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	9.3	10.3	11	15.6	13.7	17.3
Rib	5cc < 40Gy	3.73	3.57	3.71	3.96	3.54	3.93
	50Gy max pt	63.3	60.8	62.3	60.2	56.7	60.2
Skin	10cc < 30Gy	0	0	0	0.74	0	1.16
	33Gy max pt	30.6	30.9	32.6	33.8	29.6	34.7
CW	30cc < 30Gy	64.17	57.67	59.4	58.84	45.31	59.53
D2cm	< 36.4 <47.0	34.8	33	31.5	32.5	35.9	31.8
R50%	< 3.4 < 4.7	4.1	3.76	3.91	3.82	4	3.92
TV(PTV)		76.18	75.29	75.44	75.4	75.18	75.25
TV		79.12	79.12	79.12	79.12	79.12	79.12
PIV		93.45	89.21	89.38	91.68	93.22	90.84
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.784904	0.80311	0.804779	0.783758	0.766318	0.787861

11.1.7 Patient 7

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.00%	95.02%	95.04%	95.18%	95.55%	95.08%
	99% ≥ 90 % of PD	99.05%	99.67%	99.02%	99.56%	99.07%	99.24%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0	0
	21.9Gy max pt	10.1	9.6	7.7	8.6	8.1	11.6
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0.2	0.3	0.2	0.3	0.5	0.2
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	20.8	17.9	16.6	22.6	14.5	14.7
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	7.9	6.1	2	2	4.4	3.4
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	7	6	9.7	10.9	13.7	8.9
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	19.1	13.5	14.5	16.2	14.6	14.9
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	21.1	17.9	16.8	22.6	15.1	14.7
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	1.3	1.2	1.4	1.4	1.9	1.4
Comb Lung - ITV	1500cc < 10.5Gy	301.48	352.44	305.8	374.38	372.88	300.08
	1000cc < 11.4 Gy	285.87	325.42	278.91	329.87	332.83	278.59
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	4.2	8.7	14.1	15.8	5.1	10.5
Rib	5cc < 40Gy	3.12	3.27	3.09	3.06	2.59	3.12
	50Gy max pt	60.4	60.7	60.2	61.5	56.7	60.6
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	25.9	22.2	19.8	22.7	22.5	14.7
CW	30cc < 30Gy	39.33	36.84	41.14	37.47	34.66	38.93
D2cm	< 30.8 <34.1	31.9	30.3	31.5	31.6	30.6	26.5
R50%	<4.4 <5.4	4.94	4.55	4.89	4.71	4.4	4.65
TV(PTV)		30.2	30.2	30.2	30.24	30.37	30.22
TV		31.77	31.77	31.77	31.77	31.77	31.77
PIV		36.64	35.1	36.3	35.56	38.34	35.4
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.783504	0.81788	0.790843	0.80944	0.757217	0.812023

11.1.8 Patient 8

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.09%	95.09%	95.12%	95.10%	95.02%	95.07%
	99% ≥ 90 % of PD	99.79%	99.76%	99.90%	99.61%	99.70%	99.15%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0.06	0.14	0.34	0	0.23	1.1
	21.9Gy max pt	12.8	13.4	13.8	11.6	13.4	13.5
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	3.9	3.8	3.3	3.1	0.5	0.7
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	15.7	9	14.8	17.7	14.1	11.8
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	1.5	4.5	1.6	4.3	5.8	1.6
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	12.9	2.5	12.2	8.3	13.2	11.2
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	13	8.7	12.3	7.3	14.9	10.2
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	15.9	18	14.8	17.7	16.7	16
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	1.8	1.8	2	1.9	9.7	1.9
Comb Lung - ITV	1500cc < 10.5Gy	449.36	415.56	486.02	408.27	529.21	390.56
	1000cc < 11.4 Gy	418.96	381.81	448.29	364.25	457.8	333.98
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	9.5	8.9	10.8	16.6	13.3	11.1
Rib	5cc < 40Gy	4.3	4.51	4.11	4.05	3.23	4.11
	50Gy max pt	58.7	59.1	58.4	58.5	59.1	58.6
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	21.1	21	20	19.4	17	21.2
CW	30cc < 30Gy	53.27	49.39	52.75	49.78	45.33	51.61
D2cm	< 31.6 <36.7	31.7	30.6	30.6	28.6	30.9	28.9
R50%	<4.3 <5.3	5.36	5.17	5.26	5.05	4.96	5.16
TV(PTV)		31.88	31.89	31.89	31.88	31.88	31.9
TV		33.5	33.5	33.5	33.5	33.5	33.5
PIV		40.43	39.96	39.35	38.87	39.9	38.9
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.750392	0.759694	0.771471	0.780508	0.760359	0.780885

11.1.9 **Patient 9**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.08%	95.11%	95.09%	95.01%	95.11%	95.08%
	99% ≥ 90 % of PD	99.15%	99.04%	99.75%	99.48%	99.21%	99.50%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0.05	0	0.15	0.56
	21.9Gy max pt	9.3	9.7	12.6	10.5	13.7	14.3
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	1.8	1.9	1.8	1.8	1.9	1.8
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	0.9	1	1	1	1	1
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.2	0.3	0.2	0.3	0.3	0.2
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	11.3	13.8	19.5	23.4	18	15.5
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	13.2	12.1	18.5	21.6	9.7	13.9
Pericardium	15cc < 24 Gy	0	0	0	0.28	0	0
	30Gy max pt	13.2	13.8	21	24.3	18	15.6
Trachea	4cc < 15Gy	0	0	0.33	0.04	0	1.16
	30Gy max pt	14.7	12.9	17.6	15.2	12.8	16.8
Comb Lung - ITV	1500cc < 10.5Gy	189.99	196.3	216.62	195.96	240.97	199.02
	1000cc < 11.4 Gy	175.18	181.11	195.48	184.6	220.82	186.64
Oesophagus	5cc < 17.7 Gy	0	0	0.51	0	0	0
	25.2Gy max pt	13.1	12.1	19.7	16.7	11.7	15.6
Rib	5cc < 40Gy	1.43	1.25	1.45	1.28	1.19	1.43
	50Gy max pt	59.6	59.8	59.8	59.8	56.7	59.4
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	22.7	20.7	20.2	21.5	17.8	14.5
CW	30cc < 30Gy	18.18	17.45	17.32	15.35	14.2	16.82
D2cm	<28.3 Gy <33.2	31.2	31	29.1	27.8	28.3	27.9
R50%	<4.6 <5.6	5.33	4.81	5.05	4.7	4.57	5.04
TV(PTV)		17.44	17.45	17.44	17.42	17.44	17.44
TV		18.33	18.33	18.33	18.33	18.33	18.33
PIV		20.36	20.72	19.89	19.35	20.04	19.93
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.814991	0.801749	0.834249	0.855565	0.828005	0.832575

11.1.10 **Patient 10**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.12%	95.04%	95.18%	95.34%	95.14%	95.13%
	99% ≥ 90 % of PD	99.21%	99.68%	99.67%	99.05%	99.42%	99.94%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	1.14	1.18
	21.9Gy max pt	11.5	10.8	9.4	9.6	14.1	13.3
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0	0.03	0	0.03	0	0
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	11	14.5	11.6	10.8	18.7	15
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	10.8	11.7	11.3	10.5	8	14.9
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.8	0.7	0.8	0.7	1	0.9
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	5.4	6.3	7.8	10.2	18.6	14.2
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	11	14.5	11.6	10.8	18.7	15
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	0.1	0.1	0.1	0.1	0.2	0.1
Comb Lung - ITV	1500cc < 10.5Gy	366.05	422.14	379.61	410.82	507.14	486.45
	1000cc < 11.4 Gy	336.86	388.02	343.05	364.05	458.41	437.78
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0.35	0
	25.2Gy max pt	1.9	10.5	4.3	6.3	18	15
Rib	5cc < 40Gy	1.35	2.21	1.69	1.45	1.26	2.08
	50Gy max pt	60.5	61.9	60.6	58.5	56.7	63
Skin	10cc < 30Gy	2.96	3.43	2.97	3	3.88	4.09
	33Gy max pt	47	52	46.5	46.8	48.4	51.5
CW	30cc < 30Gy	14.97	14.9	15.09	14.58	14.58	16.07
D2cm	< 29.2 <34	33.8	33.9	33.8	33.5	29	31
R50%	<4.5 <5.5	5.21	4.86	5.18	5.16	5.28	5.02
TV(PTV)		21.7	21.68	21.71	21.74	21.7	21.7
TV		22.8	22.8	22.8	22.8	22.8	22.8
PIV		29.11	26.59	27.56	29.42	28.07	25.86
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.709484	0.775292	0.750077	0.704598	0.73577	0.798649

11.2 APPENDIX B: PHASE 1 IMRT RESULTS

11.2.1 Patient 1

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.09%	95.03%	95.06%	95.03%	95.17%	95.05%
	99% ≥ 90 % of PD	99.91%	99.98%	99.79%	99.80%	99.98%	99.74%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0	0
	21.9Gy max pt	12	12.3	12.2	10.7	10.8	11.8
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0.7	0.8	0.6	0.8	0.9	0.7
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	1.2	1.2	1.2	1.2	5.7	1.2
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.2	0.3	0.2	0.3	0.3	0.2
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	12.6	13.3	22	21.7	14.8	18.8
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	13.4	13	22.4	22	12.4	18.1
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	13.4	13.3	22.4	22.1	16.6	18.1
Trachea	4cc < 15Gy	0	0	0	0	0	1.14
	30Gy max pt	14.5	14.3	12.7	14.3	15.2	16.4
Comb Lung - ITV	1500cc < 10.5Gy	619.22	599.11	656.78	663.01	642.03	695.51
	1000cc < 11.4 Gy	573.12	552.12	606.48	612.58	586.64	638.72
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	13.4	13.1	15.3	13.6	9.1	15.7
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	29.4	29.3	29.1	28.6	29.9	27.7
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	22.9	22.6	22.4	23.2	19.1	20
CW	30cc < 30Gy	0.06	0	0	0	0	0
D2cm	<29.8 <34.7	29.6	29.6	29.5	29.8	29.1	27.5
R50%	<4.5 <5.5	6.79	6.18	6.54	6.21	5.35	6.63
TV(PTV)		24.05	24.03	24.03	24.03	24.07	24.03
TV		25.28	25.28	25.28	25.28	25.28	25.28
PIV		26.94	26.27	27.32	27.59	26.23	27.84
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.849289	0.869502	0.836084	0.827902	0.873729	0.820467

11.2.2 **Patient 2**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.22%	95.06%	95.05%	95.17%	96.38%	95.13%
	99% ≥ 90 % of PD	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0	0.13
	21.9Gy max pt	6.8	1.5	5.8	1.1	10.1	12.5
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0.1	0.2	0.1	0.2	0.3	0.14
Heart	15cc < 24Gy	0	0	0.12	0.34	0	0.89
	30Gy max pt	22.7	22.6	24.6	25.9	20.1	26.3
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	1	1	1.1	1.1	1.2	1.1
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	16.8	15.6	19.2	20	8.5	20.5
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	14.9	14.5	15.7	17.8	9.4	18
Pericardium	15cc < 24 Gy	0	0	0.14	0.35	0	0.9
	30Gy max pt	23.1	22.6	24.6	25.9	20.1	26.3
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	1.1	1	1.3	1.2	1.1	1.3
Comb Lung - ITV	1500cc < 10.5Gy	509.43	528.46	556.35	551.94	425.36	523.56
	1000cc < 11.4 Gy	471.23	482.05	509.31	496.5	382.47	466.12
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	10.8	1.2	14.9	15.8	10.7	11.7
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	28.5	27.6	28	26.5	25	19
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	22.3	22.9	20.8	23.6	18.5	19
CW	30cc < 30Gy	1.1	0.4	0.55	0	0.08	1.35
D2cm	<29.7 <34.6	28	27.8	27.3	27.8	24	28.2
R50%	<4.5 <5.5	5.82	5.68	5.58	5.24	4.44	6.23
TV(PTV)		22.88	22.85	22.84	22.87	23.16	22.86
TV		24	24	24	24	24	24
PIV		24.73	25.11	24.38	24.33	24.66	24.97
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.882016	0.866392	0.891553	0.895734	0.906302	0.872012

11.2.3 **Patient 3**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.13%	95.10%	95.21%	95.19%	95.10%	95.22%
	99% ≥ 90 % of PD	99.98%	99.94%	100.00%	99.99%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0	1.06
	21.9Gy max pt	6.4	4	11.6	11.9	5.8	13.7
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0	0.03	0	0.03	0.06	0
Heart	15cc < 24Gy	2.54	2.7	5.52	3.72	2.56	6.63
	30Gy max pt	30.4	31.5	31.2	30	28.1	31.5
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	2.1	1.8	1.8	1.8	4.3	1.9
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	7	7.5	10.3	8.7	1.2	7.5
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	21.3	21.5	19.2	19.4	20.7	21
Pericardium	15cc < 24 Gy	2.54	2.7	5.51	3.72	2.56	6.63
	30Gy max pt	30.4	31.5	31.2	30	28.1	31.5
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	0.7	0.7	0.9	0.8	1	0.8
Comb Lung - ITV	1500cc < 10.5Gy	666.32	719.91	618.38	674.5	646.46	640.8
	1000cc < 11.4 Gy	633.29	678.4	591.2	647.28	590.87	610.75
Oesophagus	5cc < 17.7 Gy	0.23	0.28	0	0	0	0
	25.2Gy max pt	18.6	19	9.6	12.5	13	14.4
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	30.3	31.5	36	35.8	34.5	32.4
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	26.3	24.7	25.5	25.6	20.6	22.4
CW	30cc < 30Gy	0	0.24	1.77	1.81	0.36	0.29
D2cm	<31.6 <36.7	35	35.6	33.7	34	30	30
R50%	<4.3 <5.3	7.06	7.08	6.05	6.9	5.1	6.04
TV(PTV)		33.53	33.74	33.56	33.55	33.51	33.55
TV		35.2	35.2	35.2	35.2	35.2	35.2
PIV		38.98	40.61	35.72	37.41	35.36	36.51
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.819375	0.796369	0.895756	0.854781	0.902182	0.875852

11.2.4 **Patient 4**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.17%	95.09%	95.06%	95.03%	99.07%	95.05%
	99% ≥ 90 % of PD	100.00%	99.99%	99.93%	99.99%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0.26	0	0	0	0	0
	21.9Gy max pt	15.5	2	8.1	1	7.7	11.6
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	1.2	1.2	1.2	1.1	1.2	1.2
Heart	15cc < 24Gy	0.13	0.1	0.13	0.15	0	0.16
	30Gy max pt	26.8	26.5	24	27.7	23.8	27.1
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.5	0.6	0.5	0.6	0.5	0.5
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	7.5	1.6	1.4	6.5	9.7	10.7
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	16.3	11.7	81.7	12	15.5	14.7
Pericardium	15cc < 24 Gy	3.04	1.84	4.88	1.72	0.79	4.26
	30Gy max pt	30.6	29.8	30.6	30.4	27.5	31.6
Trachea	4cc < 15Gy	0	0	1.29	0	0	0
	30Gy max pt	11.7	11.7	18	12.4	7.8	13.3
Comb Lung - ITV	1500cc < 10.5Gy	446.98	396.01	464.64	422.38	436.26	422.81
	1000cc < 11.4 Gy	423.02	357.11	426.62	379.6	382.69	385.55
Oesophagus	5cc < 17.7 Gy	0	0	1.36	0	0	0
	25.2Gy max pt	11.2	11.5	18.8	12.7	7.2	12.9
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	26.1	24	26.2	22.8	25.5	23.5
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	21.2	21.8	19.4	21.5	17.9	16.3
CW	30cc < 30Gy	0	0	0	0	0	0
D2cm	<29.2 <34.0	29.5	25.6	29.5	26.6	26.6	25.6
R50%	<4.5 <5.5	5.49	4.47	5.04	4.3	4.41	4.82
TV(PTV)		21.81	21.79	21.78	21.78	22.7	21.78
TV		22.9	22.9	22.9	22.9	22.9	22.9
PIV		23.43	22.87	24.21	23.61	26.64	23.24
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.886551	0.906594	0.855629	0.877373	0.84466	0.891342

11.2.5 Patient 5

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.23%	95.10%	95.17%	95.05%	95.00%	95.08%
	99% ≥ 90 % of PD	99.93%	100.00%	100.00%	100.00%	99.98%	100.00%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0	0.3
	21.9Gy max pt	10.8	10.2	10.5	9.6	9.3	12.7
BP	3cc < 20.4Gy						
	24Gy max pt						
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	10.6	12	14.6	17.4	11.5	11.9
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.5	0.7	0.5	0.7	0.8	0.5
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	13.2	13.8	13.3	13.4	13.3	15.5
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	10.5	11	13.8	15.4	17.3	12.5
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	16.4	19	22	23	20.6	22.6
Trachea	4cc < 15Gy	0	0	0	0	0	0.34
	30Gy max pt	11	11.4	11.7	13.5	10.8	17.5
Comb Lung - ITV	1500cc < 10.5Gy	565.32	495.59	564.72	522.39	573.01	535.41
	1000cc < 11.4 Gy	533.45	464.41	526.53	487.4	505.17	484.38
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	1.8	1.6	4.2	4.8	10.3	11.1
Rib	5cc < 40Gy	0	0	0	0	0	0
	50Gy max pt	30.8	29.8	31.5	30	30.5	30.4
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	22	22.4	20.1	19.9	22	19.7
CW	30cc < 30Gy	0.68	0.14	0.17	0.03	0.07	0.19
D2cm	<30.5 <35.8	31.3	29.4	27.3	28.1	27	26.2
R50%	<4.4 <5.4	5.91	5.3	5.41	5.16	4.44	5.25
TV(PTV)		28.28	28.24	28.26	28.23	28.21	28.24
TV		29.7	29.7	29.7	29.7	29.7	29.7
PIV		30.5	30.27	29.92	30	29.36	29.77
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.882882	0.887075	0.898724	0.894425	0.912628	0.901974

11.2.6 **Patient 6**

ROI	Objective		7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD		95.19%	95.11%	95.06%	95.21%	95.11%	95.25%
	99% ≥ 90 % of PD		99.97%	99.96%	99.97%	100.00%	100.00%	100.00%
SC	0.35cc <18Gy		0	0	0	0	0	0
	1.2cc < 12.3Gy		0	0	0	0	0	0
	21.9Gy max pt		9.4	9.3	11.4	8.3	11.8	12.2
BP	3cc < 20.4Gy							
	24Gy max pt							
Heart	15cc < 24Gy		0	0	0	0	0	0
	30Gy max pt		12.2	11.4	20.3	19.8	20.7	16.4
IVC	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		11.7	10.1	19.2	18.8	19.9	14.7
SVC	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		1.2	1	1.3	1.1	1.5	1.2
Aorta	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		12.1	10.4	13.7	14	15.6	12.6
Pericardium	15cc < 24 Gy		0	0	0	0	0	0
	30Gy max pt		15.5	13.5	22.2	21.8	21.5	17.1
Trachea	4cc < 15Gy		0	0	0	0	0	0
	30Gy max pt		0.2	0.2	0.2	0.2	0.4	0.2
Comb Lung - ITV	1500cc < 10.5Gy		473.99	455.25	457.24	444.24	576.9	473.99
	1000cc < 11.4 Gy		440.67	420.1	429.35	406.3	522.87	444.85
Oesophagus	5cc < 17.7 Gy		0	0	0	0	0	0
	25.2Gy max pt		12	10..2	10	12.7	12.4	14.4
Rib	5cc < 40Gy		4.23	4.34	4.71	4.24	4.38	3.85
	50Gy max pt		56.2	56.3	56.4	55.8	55.3	56.5
Skin	10cc < 30Gy		0.55	0.77	0.72	0.42	0.3	0.32
	33Gy max pt		35.8	36.5	36	34.5	32.7	33.4
CW	30cc < 30Gy		65.77	68.66	67.63	57.9	58.88	58.43
D2cm	< 36.4	<47.0	28.1	28.3	27.4	26.6	28.6	26.1
R50%	< 3.4	< 4.7	3.98	4.03	4.1	3.67	3.81	3.74
TV(PTV)			75.34	75.28	75.24	75.35	75.28	75.38
TV			79.12	79.12	79.12	79.12	79.12	79.12
PIV			82.89	83.05	82.37	80.27	81.35	80.39
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$		0.865492	0.862449	0.868645	0.893978	0.880472	0.893355

11.2.7 **Patient 7**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.25%	95.03%	95.14%	95.13%	96.81%	95.32%
	99% ≥ 90 % of PD	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0	0
	21.9Gy max pt	10.7	10	7.5	9.2	10.4	11.7
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	0.2	0.2	0.3	0.3	0.4	0.2
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	23.3	20.1	18.6	22.1	12.9	14.7
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	8.8	6.1	4.1	2.2	6.4	4.6
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	6.5	6	5.6	8.5	6.3	6.7
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	11.3	11.1	16	16.2	12	14.5
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	23.3	20.1	19.3	22.1	12.9	14.7
Trachea	4cc < 15Gy	0	0	0	0	0	0
	30Gy max pt	1.4	1.3	1.5	1.4	1.3	1.6
Comb Lung - ITV	1500cc < 10.5Gy	311.88	381.63	310.46	362.42	301.19	311.9
	1000cc < 11.4 Gy	295.18	346.28	294.49	335.3	267.84	293.56
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	5.2	8.7	10.7	13.9	7.6	10.1
Rib	5cc < 40Gy	5.1	5.24	4.83	4.58	3.83	4.51
	50Gy max pt	56.6	56.5	56.7	56.2	56.7	56.6
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	24.3	22.1	21.8	23.3	19.3	16
CW	30cc < 30Gy	59.44	57.06	57.98	51.97	37.56	50.35
D2cm	< 30.8 <34.1	31.9	31.8	31.5	31	25.8	27.6
R50%	<4.4 <5.4	6.7	6.15	6.23	5.82	4.3	5.41
TV(PTV)		30.27	30.21	30.24	30.23	30.76	30.29
TV		31.77	31.77	31.77	31.77	31.77	31.77
PIV		35.01	34.46	33.74	34.68	33.84	32.72
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.823788	0.833622	0.853103	0.82943	0.880086	0.882608

11.2.8 **Patient 8**

ROI	Objective		7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD		95.15%	95.00%	95.29%	95.16%	95.12%	95.16%
	99% ≥ 90 % of PD		100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
SC	0.35cc <18Gy		0	0	0	0	0	0
	1.2cc < 12.3Gy		0	0	0.63	0	0	0.52
	21.9Gy max pt		8.7	9.4	13.6	11.4	9.6	13.1
BP	3cc < 20.4Gy		0	0	0	0	0	0
	24Gy max pt		2.3	3.9	2.7	3.5	0.5	0.8
Heart	15cc < 24Gy		0	0	0	0	0	0
	30Gy max pt		15.9	9.9	12.7	11.9	13.4	10.5
IVC	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		3.7	5.8	2	5.1	6.5	2
SVC	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		13.2	4	11.2	8.7	9.9	9.5
Aorta	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		12.7	9	10.6	9.1	11.3	10.5
Pericardium	15cc < 24 Gy		0	0	0	0	0	0
	30Gy max pt		16.2	16	13.1	15.7	14.4	12.1
Trachea	4cc < 15Gy		0	0	0	0	0	0
	30Gy max pt		2.1	1.8	2.1	1.8	7.1	2.1
Comb Lung - ITV	1500cc < 10.5Gy		454.58	390.24	337.43	356.93	404.17	344.07
	1000cc < 11.4 Gy		416.02	323.78	292.44	302.21	340.95	304.03
Oesophagus	5cc < 17.7 Gy		0	0	0	0	0	0
	25.2Gy max pt		6.1	8	8.4	12.6	13.9	10.8
Rib	5cc < 40Gy		4.6	4.83	4.11	4.68	4.52	4.35
	50Gy max pt		57.3	57.6	58.5	56.3	56.5	56.4
Skin	10cc < 30Gy		0	0	0	0	0	0
	33Gy max pt		24.6	21.6	19.5	19.1	20.9	19.1
CW	30cc < 30Gy		57.4	57.94	48.69	58.13	55	54.79
D2cm	< 31.6	<36.7	31.9	29.2	25.5	27.7	26.9	26.3
R50%	<4.3	<5.3	5.87	5.45	4.42	5.23	5.01	5
TV(PTV)			31.9	31.86	31.95	31.91	31.89	31.91
TV			33.5	33.5	33.5	33.5	33.5	33.5
PIV			35.18	34.75	34.07	35.9	34.89	35.48
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$		0.863457	0.871951	0.894386	0.84667	0.870088	0.856693

11.2.9 **Patient 9**

ROI	Objective	7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD	95.24%	95.26%	95.01%	95.26%	95.30%	95.40%
	99% ≥ 90 % of PD	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0	0	0	0
	1.2cc < 12.3Gy	0	0	0	0	0.59	0.13
	21.9Gy max pt	12	10.9	11	11.1	14.7	12.7
BP	3cc < 20.4Gy	0	0	0	0	0	0
	24Gy max pt	2	2	2	2.1	2.2	2.1
Heart	15cc < 24Gy	0	0	0	0	0	0
	30Gy max pt	1	1	1	1	1.1	1
IVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	0.2	0.4	0.2	0.4	0.4	0.2
SVC	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	12.9	11.9	20.6	20.7	20.8	17.6
Aorta	10cc < 39Gy	0	0	0	0	0	0
	45Gy max pt	12.3	12.1	18.8	19.1	11.8	12.8
Pericardium	15cc < 24 Gy	0	0	0	0	0	0
	30Gy max pt	12.9	12.5	21.2	21.1	20.8	17.6
Trachea	4cc < 15Gy	0	0	0	0	0	0.58
	30Gy max pt	13.8	13.6	14.6	14.4	15.1	16.1
Comb Lung - ITV	1500cc < 10.5Gy	214.19	220.36	213.97	219.1	231.37	220.04
	1000cc < 11.4 Gy	202	203.37	203.5	207.93	212.91	209.82
Oesophagus	5cc < 17.7 Gy	0	0	0	0	0	0
	25.2Gy max pt	12.3	12.1	15.2	14.8	14.1	13.9
Rib	5cc < 40Gy	1.54	1.6	1.45	1.48	1.63	1.51
	50Gy max pt	58.3	58.8	56.1	56.6	55.1	56.7
Skin	10cc < 30Gy	0	0	0	0	0	0
	33Gy max pt	20.7	20.2	18.7	18.2	17.6	15
CW	30cc < 30Gy	21.24	21.07	18.74	19.45	18.06	20.01
D2cm	<28.3 Gy <33.2	28.6	28.3	26	25.5	24.6	25.8
R50%	<4.6 <5.6	5.59	5.53	5.19	5.23	5.03	5.46
TV(PTV)		17.47	17.47	17.43	17.48	17.48	17.5
TV		18.33	18.33	18.33	18.33	18.33	18.33
PIV		19.06	18.99	18.66	18.72	19.14	18.8
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.873576	0.876796	0.88822	0.89046	0.87092	0.888701

11.2.10 **Patient 10**

ROI	Objective		7FLDC	7FLDNC	9FLDC	9FLDNC	10FLDNC	13FLDC
PTV	95% ≥ 100 % of PD		95.08%	95.21%	95.30%	95.05%	95.19%	95.20%
	99% ≥ 90 % of PD		99.96%	99.97%	100.00%	99.99%	99.99%	99.97%
SC	0.35cc <18Gy		0	0	0	0	0	0
	1.2cc < 12.3Gy		0	0	0	0	0	0.43
	21.9Gy max pt		11.5	11.5	10.9	10.2	1.5	14.3
BP	3cc < 20.4Gy		0	0	0	0	0	0
	24Gy max pt		0	0	0	0	0	0
Heart	15cc < 24Gy		0	0	0	0	0	0
	30Gy max pt		15.9	14.6	12.6	12.4	9.5	13.2
IVC	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		15.3	14.1	12.6	12.1	3.7	31.2
SVC	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		0.8	0.7	0.9	0.8	3.3	1.03
Aorta	10cc < 39Gy		0	0	0	0	0	0
	45Gy max pt		3	3.5	10.4	9.5	10.6	9.3
Pericardium	15cc < 24 Gy		0	0	0	0	0	0
	30Gy max pt		15.9	14.6	12.6	12.4	9.5	13.2
Trachea	4cc < 15Gy		0	0	0	0	0	0
	30Gy max pt		0.1	0.1	0.1	0.1	4.3	0.1
Comb Lung - ITV	1500cc < 10.5Gy		341.54	328.43	403.47	393.11	337.98	412.7
	1000cc < 11.4 Gy		306.65	293.62	365.98	353.47	296.18	362.04
Oesophagus	5cc < 17.7 Gy		0	0	0	0	0	0
	25.2Gy max pt		2	1.9	7.5	6.8	9	10.1
Rib	5cc < 40Gy		2.5	2.68	2.49	2.68	2.54	2.4
	50Gy max pt		58.7	57.1	57.1	56.2	56.1	58
Skin	10cc < 30Gy		4.78	5.58	4.75	6.1	5.61	5.15
	33Gy max pt		51.5	51.8	50.5	52	51.1	52
CW	30cc < 30Gy		18.06	18.66	17.56	19.44	18.75	18.26
D2cm	< 29.2	<34	26	24.3	24.3	23.3	24.8	25.1
R50%	<4.5	<5.5	4.39	4.46	4.59	4.63	4.5	4.69
TV(PTV)			21.68	21.72	21.74	21.68	21.71	21.71
TV			22.8	22.8	22.8	22.8	22.8	22.8
PIV			24.36	24.12	23.61	23.85	24.02	24.07
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$		0.846265	0.857842	0.877987	0.864361	0.860621	0.858833

11.3 APPENDIX C: PHASE 1 VMAT RESULTS

11.3.1 Patient 1

ROI	Objective	VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.03%	95.09%	95.08%
	99% ≥ 90 % of PD	99.98%	99.77%	99.96%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	12.1	12	9.1
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	0.7	0.6	0.8
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	1.3	1.1	1.4
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.2	0.2	0.1
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	16.1	15.5	18
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	17.1	10.9	15.5
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	17.2	15.5	18
Trachea	4cc < 15Gy	3.81	0.24	0
	30Gy max pt	18.9	16.3	12.6
Comb Lung - ITV	1500cc < 10.5Gy	604.2	663.85	565.54
	1000cc < 11.4 Gy	553.56	625.42	511.52
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	17.2	11.2	8.5
Rib	5cc < 40Gy	0	0	0
	50Gy max pt	29.7	33.7	31
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	16.6	21.5	15
CW	30cc < 30Gy	0.04	4.26	0.12
D2cm	<29.8 <34.7	28.9	34	29.1
R50%	<4.5 <5.5	6.26	8.2	5.26
TV(PTV)		24.03	24.04	24.04
TV		25.28	25.28	25.28
PIV		25.88	30.6	25.81
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.882604627	0.747085712	0.885735094

11.3.2 **Patient 2**

ROI	Objective	VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.01%	95.18%	95.03%
	99% ≥ 90 % of PD	99.93%	99.81%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	7.6	5.3	3.2
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	0.1	0.1	0.1
Heart	15cc < 24Gy	0.06	0	0
	30Gy max pt	24.2	20.5	18.5
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	1.1	1	1.2
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	20.3	17.4	14
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	16	12.2	10.5
Pericardium	15cc < 24 Gy	0.06	0	0
	30Gy max pt	24.2	20.5	18.5
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	1.3	1.1	2.5
Comb Lung - ITV	1500cc < 10.5Gy	452.39	500.06	402.09
	1000cc < 11.4 Gy	408.22	460.96	364.47
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	10.7	7.3	5.5
Rib	5cc < 40Gy	0	0	0
	50Gy max pt	28.8	30.5	26.2
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	17.8	18.4	14.2
CW	30cc < 30Gy	1.57	3.85	0.28
D2cm	<29.7 <34.6	27.7	31.9	24.8
R50%	<4.5 <5.5	5.46	6.14	4.45
TV(PTV)		22.83	22.87	22.83
TV		24	24	24
PIV		24.44	25.99	23.6
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.888585822	0.838522669	0.920213453

11.3.3 **Patient 3**

ROI	Objective	VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.11%	95.08%	95.05%
	99% ≥ 90 % of PD	99.99%	99.86%	99.99%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0.62	0.05	0
	21.9Gy max pt	12.8	12.4	7
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	0	0	0.03
Heart	15cc < 24Gy	8.55	15.4	2.88
	30Gy max pt	30.7	36.8	29
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	2	1.6	4.3
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	9.1	9.1	6.5
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	22.5	23.2	19.4
Pericardium	15cc < 24 Gy	8.57	15.74	2.88
	30Gy max pt	30.7	36.8	30
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	0.8	0.7	1.1
Comb Lung - ITV	1500cc < 10.5Gy	620.05	609.68	539.66
	1000cc < 11.4 Gy	588.85	578.47	506.39
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	14.5	14.3	9.7
Rib	5cc < 40Gy	0	0.79	0
	50Gy max pt	35.8	45.5	36.5
Skin	10cc < 30Gy	0	0cc	0
	33Gy max pt	23.4	28.9	20.1
CW	30cc < 30Gy	1.68	13.3	1.42
D2cm	<31.6 <36.7	30.5	40	29.7
R50%	<4.3 <5.3	5.72	7.7	5.08
TV(PTV)		33.52	33.55	33.5
TV		35.2	35.2	35.2
PIV		35.72	48.51	34.89
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.893622111	0.65919076	0.913789116

11.3.4 **Patient 4**

ROI	Objective	VFULLARC		VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.11%		95.16%	97.46%
	99% ≥ 90 % of PD	99.87%		99.90%	100.00%
SC	0.35cc <18Gy	0		0	0
	1.2cc < 12.3Gy	0		0	0
	21.9Gy max pt	8.2		4.9	3.5
BP	3cc < 20.4Gy	0		0	0
	24Gy max pt	1		1	2.5
Heart	15cc < 24Gy	0		0	0
	30Gy max pt	20.8		23	24.6
IVC	10cc < 39Gy	0		0	0
	45Gy max pt	0.4		0.4	0.7
SVC	10cc < 39Gy	0		0	0
	45Gy max pt	10.6		7.9	4.3
Aorta	10cc < 39Gy	0		0	0
	45Gy max pt	14.4		11.9	9.5
Pericardium	15cc < 24 Gy	5.27		3.52	2.33
	30Gy max pt	30.5		30.1	30
Trachea	4cc < 15Gy	0		0	0
	30Gy max pt	14.3		11.8	7.6
Comb Lung - ITV	1500cc < 10.5Gy	370.59		354.66	401.9
	1000cc < 11.4 Gy	331.85		326.8	366.98
Oesophagus	5cc < 17.7 Gy	0		0	0
	25.2Gy max pt	13		10.2	6.5
Rib	5cc < 40Gy	0		0	0
	50Gy max pt	25.3		28.8	19.9
Skin	10cc < 30Gy	0		0	0
	33Gy max pt	10.2		13	13
CW	30cc < 30Gy	0		0	0
D2cm	<29.2	<34.0	28	31.5	24
R50%	<4.5	<5.5	4.68	4.84	4.5
TV(PTV)		21.79		21.81	22.34
TV		22.9		22.9	22.9
PIV		23.83		24.23	24.73
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.870071485		0.857279492	0.88126544

11.3.5 **Patient 5**

ROI	Objective	VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.01%	95.06%	95.75%
	99% ≥ 90 % of PD	99.98%	99.97%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	10.2	7.8	5.5
BP	3cc < 20.4Gy			
	24Gy max pt			
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	11.1	10.2	8.2
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.5	0.4	0.7
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	15.4	12.9	13.2
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	11.8	9.2	8.2
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	21.8	20.4	21.6
Trachea	4cc < 15Gy	0.08	0	0.05
	30Gy max pt	16	14.2	15.3
Comb Lung - ITV	1500cc < 10.5Gy	478.78	522.79	450.3
	1000cc < 11.4 Gy	441.96	470.99	409.39
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	8.5	6.5	4.8
Rib	5cc < 40Gy	0	0	0
	50Gy max pt	30.5	31.8	31.5
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	11.3	14.1	10.5
CW	30cc < 30Gy	0.3	0.87	0.24
D2cm	<30.5 <35.8	26.7	29.1	24.5
R50%	<4.4 <5.4	4.84	4.98	4.38
TV(PTV)		28.21	28.23	28.43
TV		29.7	29.7	29.7
PIV		29.69	30.16	29.61
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.90248403	0.889680291	0.919091739

11.3.6 **Patient 6**

ROI	Objective		VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD		95.12%	95.06%	95.09%
	99% ≥ 90 % of PD		99.98%	99.87%	99.99%
SC	0.35cc <18Gy		0	0	0
	1.2cc < 12.3Gy		0	0	0
	21.9Gy max pt		11.6	11.9	8.7
BP	3cc < 20.4Gy				
	24Gy max pt				
Heart	15cc < 24Gy		0	0	0
	30Gy max pt		17.7	13.8	11.6
IVC	10cc < 39Gy		0	0	0
	45Gy max pt		18.1	13.8	9.6
SVC	10cc < 39Gy		0	0	0
	45Gy max pt		1.4	1.3	1.9
Aorta	10cc < 39Gy		0	0	0
	45Gy max pt		15.6	12.9	6.2
Pericardium	15cc < 24 Gy		0	0	0
	30Gy max pt		18.7	16.6	15.2
Trachea	4cc < 15Gy		0	0	0
	30Gy max pt		0.2	0.2	0.2
Comb Lung - ITV	1500cc < 10.5Gy		436.88	483.48	423.14
	1000cc < 11.4 Gy		403.57	443.03	384.4
Oesophagus	5cc < 17.7 Gy		0	0	0
	25.2Gy max pt		13.5	13.6	6.4
Rib	5cc < 40Gy		3.7	4.23	3.87
	50Gy max pt		56.7	55.6	56.1
Skin	10cc < 30Gy		1.11	2.21	0.39
	33Gy max pt		38.5	39.5	33
CW	30cc < 30Gy		52.36	62.07	53.33
D2cm	< 36.4	<47.0	26.6	28	26.1
R50%	< 3.4	< 4.7	3.53	3.68	3.49
TV(PTV)			75.28	75.24	75.8
TV			79.12	79.12	79.12
PIV			79.53	84.56	81.13
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$		0.900620773	0.846147978	0.895098144

11.3.7 **Patient 7**

ROI	Objective	VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.14%	95.08%	96.48%
	99% ≥ 90 % of PD	100.00%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	11.6	8.6	7.1
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	0.2	0.2	0.2
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	14.3	16	17.3
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	4.1	4	3.4
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	5.7	3.5	2.5
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	14.9	12.7	11.81
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	14.3	16	17.3
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	1.5	1.4	2.6
Comb Lung - ITV	1500cc < 10.5Gy	275.02	290.26	293.55
	1000cc < 11.4 Gy	256.76	271.87	272.11
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	10.2	7.4	5
Rib	5cc < 40Gy	3.28	3.29	3.17
	50Gy max pt	56.1	55.8	56.7
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	13.6	14.8	13.9
CW	30cc < 30Gy	38	38.18	36.04
D2cm	< 30.8 <34.1	24.9	26.4	25.1
R50%	<4.4 <5.4	4.37	4.33	4.3
TV(PTV)		30.24	30.22	30.66
TV		31.77	31.77	31.77
PIV		33.29	33.14	33.83
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.864634506	0.867399567	0.874631448

11.3.8 Patient 8

ROI	Objective	VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.04%	95.06%	96.00%
	99% ≥ 90 % of PD	100.00%	99.99%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0.17	0.03
	21.9Gy max pt	12.1	12.8	12.3
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	1.9	1.2	1
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	11	12.3	11.9
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	2	2.5	2.1
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	9.4	12.7	12
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	11.8	10.7	6.6
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	14.1	15.5	14.9
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	2.2	2.2	3.1
Comb Lung - ITV	1500cc < 10.5Gy	331.54	409.53	340.26
	1000cc < 11.4 Gy	299.72	357.88	296.93
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	13.4	9.4	8.6
Rib	5cc < 40Gy	3.35	3.66	3.7
	50Gy max pt	57.2	57.7	56.7
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	18.9	21.9	18.9
CW	30cc < 30Gy	42.91	46.13	40.43
D2cm	<31.6 <36.7	26	29.3	25.6
R50%	<4.3 <5.3	4.41	4.69	4.28
TV(PTV)		31.87	31.87	32.19
TV		33.5	33.5	33.5
PIV		36.32	37.17	35.65
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.834782777	0.815693044	0.867636097

11.3.9 **Patient 9**

ROI	Objective	VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD	95.18%	95.14%	95.58%
	99% ≥ 90 % of PD	100.00%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0.49	0	0
	21.9Gy max pt	13.5	11.9	7.4
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	1.8	1.7	3.1
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	1.1	1	1.1
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.2	0.2	0.1
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	15.7	14	12.9
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	13.3	8.9	7.3
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	16.2	14	12.9
Trachea	4cc < 15Gy	0.8	0	0
	30Gy max pt	16.5	12.5	11
Comb Lung - ITV	1500cc < 10.5Gy	192.88	203.93	193.71
	1000cc < 11.4 Gy	184.08	191.5	176.88
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	14.2	10.8	7.5
Rib	5cc < 40Gy	1.36	1.33	1.31
	50Gy max pt	56.3	57.5	56.7
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	11.9	12.8	10.4
CW	30cc < 30Gy	17.79	19.08	16.01
D2cm	<28.3 <33.2	26.2	27	22.1
R50%	<4.6 <5.6	4.94	5.09	4.41
TV(PTV)		17.46	17.45	17.53
TV		18.33	18.33	18.33
PIV		18.7	18.45	18.78
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.889373955	0.900392828	0.892700503

11.3.10 **Patient 10**

ROI	Objective		VFULLARC	VPARARC	VNONCOP
PTV	95% ≥ 100 % of PD		95.18%	95.16%	95.56%
	99% ≥ 90 % of PD		100.00%	99.98%	100.00%
SC	0.35cc <18Gy		0	0	0
	1.2cc < 12.3Gy		0	0	0
	21.9Gy max pt		9.8	7.6	4.2
BP	3cc < 20.4Gy		0	0	0
	24Gy max pt		0	0	0
Heart	15cc < 24Gy		0	0	0
	30Gy max pt		11.4	9.9	6.2
IVC	10cc < 39Gy		0	0	0
	45Gy max pt		10.7	10.1	5.4
SVC	10cc < 39Gy		0	0	0
	45Gy max pt		1	0.9	1.4
Aorta	10cc < 39Gy		0	0	0
	45Gy max pt		8.6	7.1	4.4
Pericardium	15cc < 24 Gy		0	0	0
	30Gy max pt		11.4	9.9	6.2
Trachea	4cc < 15Gy		0	0	0
	30Gy max pt		0.1	0.1	0.1
Comb Lung - ITV	1500cc < 10.5Gy		385.56	309.7	299.11
	1000cc < 11.4 Gy		335.55	273.22	266.86
Oesophagus	5cc < 17.7 Gy		0	0	0
	25.2Gy max pt		9.5	7.5	3.9
Rib (9th)	5cc < 40Gy		2.29	2.2	2.61
	50Gy max pt		56.7	57.6	56.2
Skin	10cc < 30Gy		3.78	2.84	4.52
	33Gy max pt		51.7	51.3	51
CW	30cc < 30Gy		14.86	13.48	16.49
D2cm	< 29.2	<34	24	24.8	22.3
R50%	<4.5	<5.5	4.36	4.13	4.48
TV(PTV)			21.89	21.71	21.79
TV			22.8	22.8	22.8
PIV			23.94	23.92	24.21
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$		0.877874694	0.864218631	0.860171054

11.4 APPENDIX D: PHASE 2 RESULTS

11.4.1 Patient 11

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.14%	95.16%	95.01%
	99% ≥ 90 % of PD	99.48%	99.99%	99.93%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	10.5	9.8	10.7
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	1.7	1.7	1.9
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	0.8	0.8	0.9
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.2	0.2	0.1
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	19	20.7	19.5
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	18.9	17.5	17
Pericardium	15cc < 24 Gy	0	0	0.03
	30Gy max pt	23.7	23.1	24
Trachea	4cc < 15Gy	3.89	3.99	1.37
	30Gy max pt	22.9	22.7	19.5
Comb Lung - ITV	1500cc < 10.5Gy	483.31	493.66	422.56
	1000cc < 11.4 Gy	444.87	454.78	388.92
Oesophagus	5cc < 17.7 Gy	1.19	0.31	0
	25.2Gy max pt	20.2	19.6	16.7
Rib	5cc < 40Gy	0	0	0
	50Gy max pt	23.6	23.1	23.5
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	22.4	19.1	12.3
CW	30cc < 30Gy	0cc	0	0
D2cm	<29.7 <34.6	28.5	25.5	26.6
R50%	<4.5 <5.5	4.65	4.89	4.51
TV(PTV)		23.42	23.42	23.38
TV		24.6	24.6	24.6
PIV		27.3	25.16	24.85
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.816725334	0.886192433	0.894185274

11.4.2 Patient 12

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.07%	95.14%	95.17%
	99% ≥ 90 % of PD	99.39%	100.00%	99.97%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	4.5	6.6	3.8
BP	3cc < 20.4Gy			
	24Gy max pt			
Heart	15cc < 24Gy	0.78	0.65	0.27
	30Gy max pt	30.6	27.4	26.3
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.6	0.7	3
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	10.7	12.9	3.1
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	15	20.9	7.7
Pericardium	15cc < 24 Gy	10.86	5.44	2.12
	30Gy max pt	40.8	34	31.2
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	2.5	4	3.8
Comb Lung - ITV	1500cc < 10.5Gy	489.45	477.83	278.82
	1000cc < 11.4 Gy	446.56	427.45	257.93
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	3.1	7	4
Rib	5cc < 40Gy	5.79	6.08	6.03
	50Gy max pt	60	58.3	61.6
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	21.8	26.5	15.8
CW	30cc < 30Gy	74.69	70.17	69.32
D2cm	<34.9Gy	36.6	31.2	28
R50%	<3.7	4.7	4	3.6
TV(PTV)		60.46	60.51	60.52
TV		63.6	63.6	63.6
PIV		76.81	63.03	63.26
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.748275292	0.913376604	0.91035658

11.4.3 Patient 13

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	99.57%	99.68%	99.72%
	99% ≥ 90 % of PD	100.00%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0.06	0	0
	21.9Gy max pt	12.9	9.6	11.3
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	0.4	0.4	0.2
Heart	15cc < 24Gy	0.1	0.02	0.28
	30Gy max pt	25.3	23.8	25.7
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	1.6	1.6	1.6
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	13.5	12.1	14.7
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	16.4	16.6	10.2
Pericardium	15cc < 24 Gy	0.31	0.19	0.59
	30Gy max pt	27	26.2	26.7
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	6.1	6.4	2.5
Comb Lung - ITV	1500cc < 10.5Gy	339.11	384.26	360.7
	1000cc < 11.4 Gy	293.81	349.03	321.21
Oesophagus	5cc < 17.7 Gy	0.47	0.25	0.09
	25.2Gy max pt	22	19.1	18.5
Rib	5cc < 40Gy	0	0	0
	50Gy max pt	19.8	17.9	18.1
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	17.8	17.5	10.7
CW	30cc < 30Gy	0	0	0
D2cm	30.2Gy	29.3	24.3	23.5
R50%	<4.4	4.2	4.36	4.4
TV(PTV)		27.57	27.6	27.61
TV		27.7	27.7	27.7
PIV		35.35	32.22	33.79
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.776254883	0.853518343	0.814450797

11.4.4 Patient 14

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.03%	95.04%	95.08%
	99% ≥ 90 % of PD	99.29%	99.98%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	1.18	0.41	0.37
	21.9Gy max pt	16	13.8	13.7
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	15.8	9.8	10
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	1.1	1.1	0.6
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.1	0.1	0.1
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	8.9	12.5	9
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	11.3	12.8	7
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	11.3	12.8	10.6
Trachea	4cc < 15Gy	3.99	0.36	0.19
	30Gy max pt	21.6	15.9	15.8
Comb Lung - ITV	1500cc < 10.5Gy	229.87	263.91	208.94
	1000cc < 11.4 Gy	205.89	224.63	191.63
Oesophagus	5cc < 17.7 Gy	1.49	0	0
	25.2Gy max pt	23	17.5	15.5
Rib	5cc < 40Gy	2.13	1.9	1.82
	50Gy max pt	56.7	56.6	55.8
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	15.2	20.3	12.9
CW	30cc < 30Gy	19.36	16.26	15.46
D2cm	<28.6Gy	26.5	24.5	22.2
R50%	<4.6	5.49	4.64	4.43
TV(PTV)		18.45	18.46	18.47
TV		19.4	19.4	19.4
PIV		22.02	20.18	20.48
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.796844715	0.87044333	0.858622191

11.4.5 Patient 15

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.19%	95.18%	95.12%
	99% ≥ 90 % of PD	99.93%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0.05
	21.9Gy max pt	10.3	11.5	12.4
BP	3cc < 20.4Gy			
	24Gy max pt			
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	16.8	16.8	9.1
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	1.5	1.6	2.3
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	12	9.1	7.2
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	14.8	13.3	7.5
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	17.1	17	12.6
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	10.3	7.2	3.1
Comb Lung - ITV	1500cc < 10.5Gy	486.53	411.24	273.77
	1000cc < 11.4 Gy	398.87	353.41	241.94
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	13.5	16	10.6
Rib	5cc < 40Gy	1.98	2.42	2.03
	50Gy max pt	56.5	56.7	56.5
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	20.2	20.8	16.2
CW	30cc < 30Gy	32.83	30.1	27.57
D2cm	<30.2Gy	28.2	26	22.9
R50%	<4.4	5.07	4.54	4.15
TV(PTV)		26.06	26.25	26.05
TV		27.4	27.4	27.4
PIV		30.33	28.17	27.46
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.81719528	0.892732212	0.901912403

11.4.6 Patient 16

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.10%	95.14%	95.01%
	99% ≥ 90 % of PD	99.79%	99.98%	99.98%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	0.5	0.5	3.3
BP	3cc < 20.4Gy			
	24Gy max pt			
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	3.4	3.8	4.2
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.3	0.4	0.1
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	8.9	6.5	6.8
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	17.9	17.2	13.3
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	19.8	19.3	20.4
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	11.2	11.2	7.9
Comb Lung - ITV	1500cc < 10.5Gy	482.85	438.89	331.86
	1000cc < 11.4 Gy	433.56	379.41	304.37
Oesophagus	5cc < 17.7 Gy	0.16	0	0
	25.2Gy max pt	18	17.4	8.2
Rib (9th)	5cc < 40Gy	0	0	0
	50Gy max pt	33.4	30.4	33.3
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	22.5	20	17.7
CW	30cc < 30Gy	0.15	0	0
D2cm	<28.6Gy	27.7	26	26.5
R50%	<4.6	5.18	4.89	4.9
TV(PTV)		18.63	18.63	18.61
TV		19.6	19.6	19.6
PIV		21.99	20.15	19.6
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.805275357	0.878809186	0.901530873

11.4.7 Patient 17

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.04%	95.02%	95.12%
	99% ≥ 90 % of PD	99.15%	99.84%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	11	8	4.7
BP	3cc < 20.4Gy	0	0	0
	24Gy max pt	2	2.4	1.9
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	4.1	2	5
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.3	0.4	0.2
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	21.1	23.1	25
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	21.1	23.3	24
Pericardium	15cc < 24 Gy	0.07	0.42	0.69
	30Gy max pt	24.8	27.2	27.4
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	10.5	10.4	11
Comb Lung - ITV	1500cc < 10.5Gy	608.93	586.39	449.69
	1000cc < 11.4 Gy	548.83	521.71	416.67
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	6.6	7.4	7.7
Rib (3rd)	5cc < 40Gy	2.62	4.62	4.48
	50Gy max pt	56.2	56	55.2
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	21.4	19.7	19.5
CW	30cc < 30Gy	34.18	33.86	41.6
D2cm	<35.6	32.2	25.5	25.3
R50%	<3.5	3.44	3.3	3.35
TV(PTV)		70.02	70	70.08
TV		73.65	73.65	73.65
PIV		79	74.65	74.23
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.842644461	0.891237634	0.898330147

11.4.8 Patient 18

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.68%	95.21%	95.15%
	99% ≥ 90 % of PD	99.02%	100.00%	100.00%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0.94	0.3	0.28
	21.9Gy max pt	13	13	13
BP	3cc < 20.4Gy	0.12	0	0
	24Gy max pt	23.5	19.7	19.5
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	1.4	3.6	1.8
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.3	0.3	0.2
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	23.3	19.4	18.7
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	22.8	19.5	10.6
Pericardium	15cc < 24 Gy	2.01	0	0
	30Gy max pt	30	22.5	20.7
Trachea	4cc < 15Gy	3.85	2.45	1.41
	30Gy max pt	21.8	19.7	18.8
Comb Lung - ITV	1500cc < 10.5Gy	406.43	433.49	357.82
	1000cc < 11.4 Gy	389.56	414.42	344.09
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	10.3	14.6	13.5
Rib (4th)	5cc < 40Gy	5.24	6.95	6.44
	50Gy max pt	56.7	56.2	55.3
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	23.5	21.3	15.8
CW	30cc < 30Gy	60.82	67.53	65.19
D2cm	<36.7	39.4	28.2	26.5
R50%	<3.41	3.84	3.62	3.41
TV(PTV)		79.69	80.05	79.27
TV		83.3	83.3	83.3
PIV		91.82	84.39	82.22
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.830281505	0.91156299	0.91747712

11.4.9 **Patient 19**

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.00%	95.12%	95.10%
	99% ≥ 90 % of PD	99.78%	100.00%	99.99%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	6.4	4.4	6
BP	3cc < 20.4Gy			
	24Gy max pt			
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	0.8	0.7	1.7
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.2	0.2	0.1
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	12.8	16	8.6
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	12.2	13.7	5.6
Pericardium	15cc < 24 Gy	0	0	0
	30Gy max pt	15.2	17.5	8.6
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	8.7	10.8	7.5
Comb Lung - ITV	1500cc < 10.5Gy	309.93	345.95	264.16
	1000cc < 11.4 Gy	270.51	311.24	239.4
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	10.7	13.3	6.1
Rib (4th)	5cc < 40Gy	1.39	1.09	0.88
	50Gy max pt	54.3	52.4	51.1
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	21	19.5	10.6
CW	30cc < 30Gy	5.7	5.72	6.53
D2cm	<28.6Gy	26.3	23.8	23.8
R50%	<4.6	4.2	4.65	4.44
TV(PTV)		18.46	18.49	18.48
TV		19.43	19.43	19.43
PIV		21.44	19.81	20.34
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.81802356	0.888211816	0.864132192

11.4.10 **Patient 20**

ROI	Objective	3DCRT	IMRT	VMAT
PTV	95% ≥ 100 % of PD	95.04%	95.17%	95.03%
	99% ≥ 90 % of PD	99.72%	99.98%	99.95%
SC	0.35cc <18Gy	0	0	0
	1.2cc < 12.3Gy	0	0	0
	21.9Gy max pt	8.8	10	4.1
BP	3cc < 20.4Gy			
	24Gy max pt			
Heart	15cc < 24Gy	0	0	0
	30Gy max pt	8.4	5.8	3.3
IVC	10cc < 39Gy	0	0	0
	45Gy max pt	0.4	0.4	0.3
SVC	10cc < 39Gy	0	0	0
	45Gy max pt	17.6	18.9	5.1
Aorta	10cc < 39Gy	0	0	0
	45Gy max pt	19.1	21.1	18.3
Pericardium	15cc < 24 Gy	0.24	0.54	0.67
	30Gy max pt	26.4	28.8	28
Trachea	4cc < 15Gy	0	0	0
	30Gy max pt	11.1	9.7	7.6
Comb Lung - ITV	1500cc < 10.5Gy	561.13	598.37	534.46
	1000cc < 11.4 Gy	518.99	555.51	499.71
Oesophagus	5cc < 17.7 Gy	0	0	0
	25.2Gy max pt	17.3	17.9	9.1
Rib	5cc < 40Gy	0	0	0
	50Gy max pt	38.3	36.9	39.6
Skin	10cc < 30Gy	0	0	0
	33Gy max pt	24.6	25.7	12.2
CW	30cc < 30Gy	2.32	1.42	4.31
D2cm	<31Gy	29.8	28.6	27.7
R50%	<4.3	5.14	5.2	5.27
TV(PTV)		30.81	31.06	30.8
TV		32.4	32.4	32.4
PIV		36.97	33.94	32.78
CI	$\frac{(TV_{PTV})^2}{TV \times PIV}$	0.792481141	0.877295809	0.893197448