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Optimizing Respiratory Gated Intensity Modulated Radiation Therapy Planning and Delivery of Early-Stage Non-Small Cell Lung Cancer

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Graduate Program in Medical Biophysics A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy © Ilma Xhaferllari 2016

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Abstract

Stereotactic ablative body radiotherapy (SABR) is the standard of care for inoperable earlystage non-small cell lung cancer (NSCLC) patients. However, thoracic tumours are susceptible to respiratory motion and, if unaccounted for, can potentially lead to dosimetric uncertainties. Respiratory gating is one method that limits treatment delivery to portions of the respiratory cycle, but when combined with intensity-modulated radiotherapy (IMRT), requires rigorous verification. The goal of this thesis is to optimize respiratory gated IMRT treatment planning and develop image-guided strategies to verify the dose delivery for future early-stage NSCLC patients.

Retrospective treatment plans were generated for various IMRT delivery techniques, including fixed-beam, volumetric modulated arc therapy (VMAT), and helical tomotherapy. VMAT was determined the best technique for optimizing dose conformity and efficiency.

A second treatment planning study that considered patients exhibiting significant tumour motion was conducted. Respiratory ungated and gated VMAT plans were compared. Significant decreases in V_{20Gy} and $V_{50\%}$, predictors for radiation pneumonitis and irreversible fibrosis, respectively, were observed.

The predominant uncertainty of respiratory gating lies in the ability of an external surrogate marker to accurately predict internal target motion. Intrafraction triggered kV imaging was validated in a programmable motion phantom study as a method to determine how correlated the internal and external motion are during ungated and gated VMAT deliveries and to identify potential phase shifts between the motions.

KV projections acquired during gated VMAT delivery were used to reconstruct gated conebeam CT (CBCT), providing 3D tumour position verification. Image quality and target detectability, in the presence of MV scatter from the treatment beam to the kV detector, was evaluated with various imaging parameters and under real-patient breathing motion conditions. No significant difference in image quality was observed for the CBCT acquisitions with or without the presence of MV scatter.

This thesis explores the benefits of combining respiratory gating with IMRT/VMAT for the treatment of early stage NSCLC with SABR, and evaluates advanced on-board imaging capabilities to develop dose delivery verification protocols. The results of this thesis will provide the tools necessary to confidently implement a respiratory gated radiotherapy program aimed at improving the therapeutic ratio for early-stage NSCLC.

Keywords

lung cancer, respiratory motion, respiratory gating, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic ablative body radiotherapy (SABR), flattening filter free (FFF), , intrafraction imaging, cone-beam CT (CBCT).

Co-Authorship Statement

The following thesis is comprised of five manuscripts: two published manuscripts, one manuscript in press, two manuscripts under preparation for submission.

In Chapter 2, "Comprehensive dosimetric planning comparison for early stage non-small cell lung cancer with SABR: fixed-beam IMRT versus VMAT versus tomotherapy" by Ilma Xhaferllari, Omar El-Sherif, and Stewart Gaede accepted in the *Journal of Applied Clinical Medical Physics*, is presented. Mr. El-Sherif aided in constructing graphics used in the manuscript. Various dosimetrist computed the tomotherapy and most fixed beam treatment plans. I computed the remaining treatment plans, extracted the dosimetric data, analyzed and interpreted the results, and wrote the manuscript under guidance and supervision of Dr. Gaede.

In Chapter 3, "Dosimetric planning study of respiratory-gated volumetric modulated arc therapy for early-stage lung cancer with stereotactic body radiation therapy" published in *Practical Radiation Oncology* vol. 5 (3): pp. 156-61 (2015) by Ilma Xhaferllari, Jeff Chen, Michael MacFarlane, Edward Yu, and Stewart Gaede, is presented. Dr. Chen and Mr. MacFarlane provided the treatment planning scripts employed for the early-stage NSCLC with SABR. Dr. Yu provided part of the patient database used in this study. I computed the treatment plans, analyzed the data, and wrote the manuscript under guidance and supervision of Dr. Gaede.

In Chapter 4, "The use of on-board kV imaging during respiratory gated VMAT delivery to evaluate the correlation between tumour motion and external surrogate motion in patient-specific waveforms" to be submitted in the *Medical Physics* journal in August 2016, by Ilma Xhaferllari, Omar El-Sherif, Todd Stevens, and Stewart Gaede, is presented. All authors contributed to the study design and interpretation of results. I completed the experiments, interpreted the results, and wrote the manuscripts under guidance and supervision of Dr. Gaede.

In Chapter 5, "Investigation of image quality of intrafraction cone beam CT for 3D verification of respiratory-gated VMAT delivery" in preparation for submission to *Physics*

in Medicine and Biology journal in September 2016, co-authored by Ilma Xhaferllari, Kurtis Dekker, George Hajdok, and Stewart Gaede, is presented. Mr. Dekker provided the CBCT reconstruction code used in this work. Drs. Hajdok and Gaede contributed to the study conception, experimental design and aided in interpretation of results. I contributed to the study conception, carried out the experiments, analyzed the data, and interpreted the results under the supervision of Dr. Gaede.

Appendix A is adapted from, "Automated IMRT planning with regional optimization using planning scripts" published in *Journal of Applied Clinical Medical Physics* vol. 14 (1): pp.4052 (2013) by Ilma Xhaferllari, Eugene Wong, Karl Bzdusek, Micheal Lock, Jeff Chen. Drs. Wong, Lock, and Chen designed the experimental study. Mr. Bzdusek provided on-going aid in Pinnacle Treatment Planning System. I wrote all the treatment scripts discussed in this study, interpreted the results, and wrote the manuscript under the supervision of Dr. Chen.

Dedication

To my loving parents, who embody the perfect example of hard work and resilience

Acknowlegments

During my graduate degree, I had the pleasure of meeting and working with a lot of great minds, who have impacted my development as a professional and researcher, and have made the completion of this thesis possible. First and foremost, I would like to acknowledge my supervisor, Dr. Stewart Gaede for providing me with this opportunity, thank you for believing in me and taking me under your wing. Your passion and enthusiasm in research and the field of medical physics are contagious and I can only hope to live up to the example you set. You openly shared your personal experiences in graduate school and career showing that with hard work and perseverance our goals can be achieved. You have been the true definition of a mentor by continuously supporting and guiding my journey through graduate school.

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During my graduate degree, I was involved in the quality assurance program of linear accelerators and as a teaching assistant in Practical Radiotherapy. I would like to thank Drs. Rob Stodilka, Rob Barnett, Kathleen Surry, and Scott Karnas for allowing me to have

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List of Abbreviations

3D-CRT	Three-Dimensional Conformal Radiation therapy
4D-CT	Four-Dimensional Computed Tomography
AAA	Analytical Anisotropic Algorithm
ABC	Active Breathing Control
ANOVA	A one-way analysis of variance
AP	Anterior-Posterior
AXB	Acuros XB
BEV	Beams-Eye-View
CBCT	Cone-Beam Computed Tomography
CCC	Collapsed Cone Convolution
CI _{xx%}	Conformality index of the xx% isodose volume to the target volume
CNR	Contrast-to-Noise
СТ	Computed Tomography
CTDI	Computed Tomography Dose Index
CU	Calibration Unit
D _{2cm}	Percent of maximum dose 2-cm away from the PTV to prescription dose
D _{max}	Maximum dose of target

DIBH	Deep Inspiration Breath Hold
DICOM	Digital Imaging and Communication in Medicine
DMPO	Direct Machine Parameter Optimization
DRR	Digital Reconstructed Radiograph
DVH	Dose Volume Histogram
EPID	Electronic Portal Imaging Device
FB	Fixed beam – Intensity Modulated Radiation Therapy
FDK	Feldkamp-Davis-Kress algorithm
FF	Flattening Filter
FFF	Flattening Filter Free
FOV	Field-of-View
FWHM	Full Width Half Maximum
GTV	Gross Target Volume
Gy	Gray
HT	Helical Tomotherapy
IGRT	Image Guided Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
ITV	Internal Target Volume
kV	Kilo-voltage

LINAC	Linear Accelerator		
LLL	Left Lower Lobe		
LUL	Left Upper Lobe		
MIP	Maximum Intensity Projection		
MLC	Multi-Leaf Collimator		
MLD	Mean Lung Dose		
MV	Mega-voltage		
NSCLC	Non-Small Cell Lung Cancer		
NTCP	Normal Tissue Complication Probability		
OAR	Organ at Risk		
OBI	On-Board Imaging		
OSLD	Optically Stimulated Luminescence Dosimeter		
OS	Overall Survival		
OSC	Ordered Subset Convex iterative algorithm		
PTV	Planning Target Volume		
RA	RapidArc		
RF	Radiofrequency		
RLL	Right Lower Lobe		
RML	Right Middle Lobe		

RMSE	Root-mean-square-error		
ROI	Region-of-Interest		
RPB	Real-patient breathing		
RPM	Real-Time Position Management		
SA	SmartArc		
SABR	Stereotactic Ablative Body Radiotherapy		
SCLC	Small Cell Lung Cancer		
SD	Standard Deviation		
SDD	Source-Detector-Distance		
SI	Superior-Inferior		
SS	Step-and-Shoot fixed beam		
SW	Sliding Window fixed beam		
ТСР	Tumour Control Probability		
TERMA	Total Energy Released per unit Mass		
TNM	Tumour, Node, Metastasis classification system		
TV	Total Variations minimization iterative algorithm		
VMAT	Volumetric Modulated Radiation Therapy		
V50%	Absolute volume of healthy lung receiving 50% of the prescription dose.		
V _{xxGy}	Percent volume of healthy lung receiving xx Gy or more		

V_{xxGyC} Percent volume of contralateral lung receiving xx Gy or more

- VPD Volume Percent Difference
- XML Extensible Markup Language
- XVMC X-ray Voxel Monte Carlo

Chapter 1

"The purpose of education is to replace an empty mind with an open one"

- Malcom Forbes

1 Introduction

1.1 Lung Cancer

Cancer has recently surpassed cardiovascular disease as the leading cause of death in most countries¹. In Canada, cancer accounted for 29.9% of all deaths compared to 19.7% from heart disease in 2011². More specifically, lung cancer is the leading cause of cancer death with a five-year survival rate of only 17% and 20,600 deaths estimated in 2015². Lung cancer can be further subdivided into two main groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with 85% of all lung cancer diagnosed in the latter category. SCLC is a fast progressing disease and typically initiates in the centre of the lung³. NSCLC is subdivided into adenocarcinoma, where growth starts in the glandular cells in the outer part of the lung, squamous cell carcinoma, which initiates in squamous cells lining the bronchus, and large cell carcinoma, which can grow anywhere in the lung and exhibits rapid progression. Patients are classified based on the TNM staging system, that describes the characteristics of the tumour, node, and metastasis (Table 1-1). Earlystage (T1-2, N0) NSCLC where lesions are localized and have not metastasized to regional lymph nodes, account for approximately 14% of the total lung cancer⁴. Effective treatment options for these lesions are either surgery, radiation therapy, or both. In this thesis, we focus on contemporary radiation therapy techniques.

Stage	Tumor (T)	Nodal (N)	Metastasis (M)	5-year survival
Occult Carcinoma TX		NO	M0	
0	Tis	NO	M 0	
IA	T1a,b	NO	M 0	49%
IB	T2a	NO	M 0	45%
IIA	T2b	NO	M 0	30%
	T1a,b	N1	M 0	
	T2a	N1	M 0	
IIB	T2b	N1	M 0	31%
	Т3	NO	M 0	
IIIA	T1a,b T2a,b	N2	M 0	14%
	T3	N1, N2	M 0	
	T4	N0, N1	M 0	
IIIB	T4	N2	M 0	5%
	Any T	N3	M 0	
IV	Any T	Any N	M1a,b	1%

Table 1-1: The TNM staging of NSCLC. Table adapted from Edge et al.^{2,5}

T denotes tumour size:

x: Primary tumour cannot be assessed, tumour proven by presence of malignant cells but not visualized by imaging or bronchoscopy

is: Carcinoma in situ

1: Surrounded by lung or visceral lung without bronchoscopic evidence of invasion more proximal than lobar bronchus.

1a: Tumor 2 cm or less in greatest direction

1b: Tumor more than 2 cm but less than 3 cm in greatest direction

2: Tumor has any of: involves main bronchus, 2 cm or more from carina; or invades visceral pleura; associated with atelectasis, or obstructive pneumonitis that extends to the hilar region but does not involve entire lung

2a: Tumor more than 3 cm but less than 5 cm in greatest direction

2b: Tumor more than 5 cm but less than 7 cm in greatest direction

3: Tumor more than 7 cm or one that directly invades any of: parietal wall, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina but not involving the carina; or associated atelectasis or obstructive pneumonitis of the entire lung, or separate tumor nodule(s) in the same lobe

4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumour nodules in a different ipsilateral lobe

N denotes extent of regional lymph nodes spread

0: No regional lymph node metastasis

1: Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

2: Metastasis in ipsilateral mediastinal and/or sub-carinal lymph nodes

3: Metastasis in: contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, and supraclavicular nodes

M denotes distant metastases

0: No distant metastasis

1: Distant metastases

1a: Separate tumour nodule(s) in a contralateral lobe, tumour with pleural nodules or malignant pleural effusion

1b: Distant metastasis (in extrathoracic organs)

1.2 Treatment Strategies for Early-Stage NSCLC

1.2.1 Surgical Resection

Surgical resection through lobectomy or sublobar resection, remains the standard of care in treatment of early-stage NSCLC patients. Lobectomy provides superior outcomes over sublobar resection with improved local control and extended overall survival (OS)⁶. Estimated 3-year OS for lobectomy is 79% and 80% for local and nodal recurrence free survival⁷, respectively. Although surgical resection has shown promising outcomes, it is often precluded due to significant co-morbidities, poor cardiac function, or decreased pulmonary reserve exhibited by the patient.

1.2.2 Radiation therapy

1.2.2.1 Conventional Radiation Therapy

Options for early-stage NSCLC patients deemed inoperable or who refuse to undergo surgery are radiation therapy, or observation without cancer specific treatment. In external beam radiation therapy, the tumour is targeted using high energy x-rays. However, some dose is deposited to normal tissue along the x-ray beam paths to the tumour, as demonstrated for a sample patient in Figure 1-1.



Figure 1-1. Colour wash of the dose distribution for an early-stage NSCLC patient. The prescription dose was 54 Gy (absorbed energy per unit mass, J/kg). The purple colour depicts the low dose deposited along the paths of the beams.

In deciding the prescription dose and dose distribution, the goal of radiation therapy is to provide the optimal tradeoff between targeting the tumour to increase tumour control probability (TCP), while reducing normal tissue complication probability (NTCP)⁸. Conventional three-dimensional conformal radiation therapy (3D-CRT) is delivered with a prescribed tumour dose of 60 Gy or more delivered over the course of six weeks, in 30 daily fractions. The fractionation scheme of 2 Gy per fraction resulted in low NTCP, but unfortunately, outcomes of such conventional fractionations also yielded low TCP and overall survival, leading inoperable patients to forego any treatment options^{9,10}. Dose escalation to early-stage NSCLC lesions has been shown to provide improved TCP^{11,12}, but the increase in fractionation dose is associated with increased dose to normal lung, and potential worsening of NTCP.

Dosimetric lung parameters used to predict radiation induced lung toxicities are the percent volume of lung receiving 20 Gy or more (V_{20Gy}), the absolute volume of lung receiving 50% of the prescription dose ($V_{50\%}$), and the mean lung dose (MLD)^{13–15}. Treatment planning requires maintaining these dosimetric parameters as low as possible to help avoid potential radiation-induced lung toxicities.

1.2.2.2 Stereotactic Ablative Body Radiotherapy (SABR)

Over the past decade, stereotactic ablative body radiotherapy (SABR), a hypo-fractionated treatment technique imitating the surgical knife in ablating the tumor with a high dose of radiation delivered within a two-week period, has been implemented in the clinic¹⁶. Outcome studies for SABR have revealed impressive 3-year local control rates upwards of 90%^{17–21}. More recently, a study concluded SABR as a viable treatment option in operable early-stage NSCLC patient, with 3-year OS, and local or nodal recurrence free survival of 95% and 86%, respectively, surpassing surgical outcomes of 79% and 80%, respectively⁷.

SABR treatment prescriptions vary based on organs at risk (OAR) in proximity to the target; lesions located adjacent to the chest wall are prescribed 55 Gy in five fractions, lesions located within 2 cm of the mediastinum are prescribed 60 Gy in eight fractions, and centrally located lesions are prescribed 54 Gy in three fractions, spanned over one or two

weeks. Conventional treatment for NSCLC includes a prescription dose of 60-66 Gy in 30 daily fractions (or 6 weeks).

1.2.2.3 Intensity Modulated Radiation therapy (IMRT)

Treatment with intensity modulated radiation therapy (IMRT) in SABR leads to improvement in target dose conformity and reduction in toxicities to normal tissue²². Treatment is optimized by reducing the objective function based on set objectives for the target and normal tissue sparing. Intensity gradients of dose are created by modulating the fluence of incident beams using a computer controlled multi-leaf collimator (MLC) to produce beam segments within each treatment beam. Efficiency in IMRT can be improved by incorporating automated treatment planning to set the beam geometry, create regions of interest to aid treatment planning, and to determine optimization objectives (Appendix A). There are different modalities to deliver IMRT that can be classified into: fixed beam IMRT (FB-IMRT)^{22,23}, volumetric modulated arc therapy (VMAT)^{24,25}, and helical tomotherapy (HT)²⁶⁻²⁸. FB-IMRT implies the gantry is held stationary (per beam) while all segments required to modulate the beam are delivered. The FB-IMRT group can be further subdivided into step-and-shoot and sliding window techniques. In step-and-shoot delivery, the beam intensity pattern is the weighted summation of all its segments. During each segment, the MLC leaves remain stationary. In sliding window delivery, the MLC leaves transition during irradiation. VMAT treatments are designed using a broad treatment beam as the gantry rotates, simultaneously varying gantry speed, dose rate, and MLC leaf positions²⁵. Modulation is dynamically achieved as the gantry rotates in an arc. Equally spaced positions along the arc are initially coarsely sampled (Figure 1-2A) followed by added sampling points equally spaced between previous points until desired spacing in sampling points is achieved (Figure 1-2)²⁵. Another rotational IMRT modality, HT delivery, is a slice-by-slice treatment delivery using a fan beam, a binary MLC, and synchronizing couch motion through the bore, to gantry rotation during treatment. In the clinic, there is a lack of consensus on which IMRT technique is optimal for radiotherapy planning in SABR^{22-24,26}. Chapter 2 of this thesis compares these various treatment options and techniques.



Figure 1-2. Continuous treatment beam and MLC motion in VMAT is modeled as static source positions initially coarsely spaced (a). During treatment planning optimization, sampling points are added midway between previous points (b, c). The next sample set are added starting at the beginning of the gantry range (d). Additional samples are continuously added until the desired sampling frequency of gantry rotation is reached. Adapted from Otto²⁵

1.2.2.4 Dose Calculation Algorithms

With increasing complexity of treatment planning and delivery, as in IMRT, the dose calculation algorithm selected during treatment planning is an important step to ensure quality of treatment plan. There are multiple dose calculation algorithms available, where Monte Carlo technique is considered the gold standard. Monte Carlo technique is a randomized statistical method to determine the probability of certain events occurring. In radiation therapy planning, for a large number of histories, the path of a particle is simulated by using knowledge of the probability of photon and electron interactions^{29,30}. However, Monte Carlo based dose algorithms require long computational times. Other dose calculation algorithms modelled include collapsed cone convolution (CCC), and Acuros XB.

In convolution-based dose calculation algorithm, the modelled primary energy fluence is projected through the medium. The total energy released per unit mass (TERMA) is calculated at each voxel based on the mass attenuation coefficient of the medium and the primary fluence. The dose distribution is calculated by convolving TERMA with the dose point spread function, or kernels, at each voxel. Dose point spread functions are modelled

using Monte Carlo for a homogeneous phantom. Dose heterogeneity corrections are required to account for different densities. Dose calculation time is reduced from voxel based in convolution, to a set of arrays, or cones, in CCC to be convolved with TERMA^{31,32}. CCC is applied clinically in all IMRT treatment delivery techniques described above.

Acuros XB dose algorithm is based on a solution to the linear Boltzmann transport equation and directly handles the effects of tissue heterogenity^{33,34}. The linear Boltzmann transport equation describes primary and secondary particle interactions as they travel through a medium. Acuros XB dose algorithm treatment planning results in similar dose distribution from Monte Carlo based algorithms for small fields with tissue heterogeneity, as in earlystage NSCLC³⁵⁻³⁷. Both, CCC and Acuros XB dose algorithm, are applied in Chapter 2 of this thesis.

1.3 Respiratory-Induced Target Motion

In the treatment of thoracic cancer, interfractional changes include patient's weight loss, tumour growth or shrinkage, and variations in respiratory motion pattern, and intrafractional motion includes cardiac, muscular and respiratory breathing motion. Respiratory motion induces variability in target position for both interfraction and intrafraction conditions.

Respiratory breathing is comprised of involuntary and voluntary physiological mechanisms. In quiet breathing, the alveolar pressure, or the intrapulmonary pressure, is controlled by the diaphragm and intercostal muscles, Figure 1-3. During inhalation, the diaphragm, a dome-shaped muscle, contracts and descends, while the external intercostal muscles contract, and move the rib cage upwards and outwards. This allows a decrease of alveolar pressure relative to the atmospheric pressure, and air flows into the thoracic cavity. During expiration, the diaphragm muscle relaxes and ascends, and the intercostal muscles move downwards and inwards, simultaneously. The alveolar pressure increases relative to barometric pressure and air will flow out of the thoracic cavity.



Figure 1-3. Diagram displaying the process of quiet breathing. Adapted from Silverthorn et al.³⁸

The individual lungs are enclosed by the visceral pleura, and an outer membrane, the parietal pleura, surrounds the thoracic cavity maintaining separation from the mediastinum. The space in-between the visceral and parietal pleura creates the intrapleural space and helps keep the lungs inflated through the intrapleural pressure. Trans-pulmonary pressure is the difference between the alveolar pressure and the intrapleural space, typically about - 3 mmHg³⁸. Pneumothorax, or collapsing of the lung, occurs if trans-pulmonary pressure drops to zero, causing fluid or air to fill the intrapleural space.

The elasticity required to aid in exhalation and the lung tissue viscoelasticity causes an increase in the volume at the same pressure during inhalation, leading to lung hysteresis. This can lead to variabilities in the respiratory motion.

The diaphragm is the most important muscle in quiet breathing accounting for 60% to 75% of lung volume changes. The contraction and relaxation of the diaphragm can lead to an increase in motion magnitude of proximal tumours, primarily in the superior-inferior (SI) direction. The intercostal muscles connect adjacent ribs and help enlarge the chest cavity in the anterior-posterior (AP), and lateral direction to allow more airflow³⁸. In thoracic cancers, the lesion will move in conjunction with respiratory breathing motion. A study by Yu et al³⁹ has reported a median tumour motion of 4.2 mm in the SI direction for early-stage NSCLC. For lesions located in the lower lobes, a median tumour motion of 9.2 mm in the SI direction was observed³⁹. Respiratory motion is unpredictable and variable

between patients and within the same patient over the course of treatment^{40–45}. Therefore, different techniques have been developed to monitor breathing patterns during irradiation.

1.3.1 Motion-Induced Dosimetric Uncertainties

In the presence of motion, the static dose distribution to the target will be blurred, potentially causing under-dosage to the tumour and over-dosage to surrounding normal tissue. In a single IMRT fraction, the impact of intrafraction motion can result in errors up to 18% to 20% compared to the intended static target dose⁴⁶⁻⁴⁸. IMRT-defined radiation fields are not exclusively restricted by the primary collimators, but are defined by moving MLC leaves. The motion of the target is independent of the motion of the MLC leaves allowing for the potential of the target to unintentionally move in and out of these gradients. The lack of synchronicity between the MLC leaves and tumour motion causes an "interplay effect" and is not accounted for in radiation treatment planning systems. As radiation fields become more modulated, the potential for errors due to the interplay effect increases. Over the course of treatment, studies have shown that the interplay effect may average out for conventional fractionations, causing an estimated 2% error^{47,49}. However, lung SABR treatments are often limited to three to eight fractions, resulting in less opportunity for the interplay effect to average out. On the other hand, individual SABR treatments are longer, due to the increased dose per fraction, reducing the interplay effect on tumours that move by up to $1 - \text{cm}^{50-54}$.

Respiratory motion management is required for patients exhibiting large tumour motion amplitudes, highly modulated fields, and fast beam delivery⁵⁴. According to the AAPM task group 76 on respiratory motion effects in radiation therapy, respiratory management techniques are advised for tumour motion greater than 5 mm to help reduce uncertainty in dose delivery and normal tissue toxicity⁵⁵. Respiratory motion can expose surrounding healthy tissue to radiation and increase the risk of radiation-induced pulmonary toxicities^{56–58}. Two common toxicities associated with lung cancer radiotherapy are radiation pneumonitis, an early adverse effect, and irreversible fibrosis, a late effect^{13,59,60}, further investigated in Chapter 3.

1.3.2 Motion Artifacts in CT Image Acquisition

The precision of dose delivery relies on an accurate representation of a patient's internal anatomy depicted by computed tomography (CT) imaging. A stationary subject is assumed during CT simulation, and respiratory motion hinders image quality by causing imaging artifacts in thoracic CT^{61-64} . During acquisition of an image slice, variability in respiratory phase causes slice displacement artifacts in the reconstructed CT volume. Tumour movement in-between the image slice acquisitions, inflicts geometric uncertainties in the reconstructed CT volume⁶¹, as shown by Figure 1-4.



Figure 1-4. Respiratory motion induced imaging artifacts in CT. A) Target motion as CT slices are acquired, B) Distorted reconstructed volume representation. Adapted from Balter et al.⁶¹

Severity of imaging distortions are related to the sampling time per slice, slice thickness, gantry speed, respiratory motion period and amplitude, and size of the lesion. The resulting target volume exhibits geometric uncertainties i.e. shrinking or lengthening of the target, and discontinuities in the edge geometry (Figure 1-5). Respiratory motion induced artifacts from CT simulation are manifested as tumour and normal tissue delineation errors. These
distortions can adversely affect treatment plans, dose calculation accuracy, and in turn, treatment delivery.



Figure 1-5. Reconstructed CT volume images with respiratory motion induced artifacts; A. True geometry for the static spherical object; B-E. Different artifacts obtained by standard axial CT scanning. Adapted from Rietzel et al⁶³.

Respiratory motion is more problematic for images acquired on a treatment machine for patient setup guidance before treatment, referred to as "on-board imaging". The slow rotation speed in on-board CT imaging causes substantial respiratory induced artifacts, such as blurring, doubling, streaking, breakup, and distortions^{65–69} (Figure 1-6).



Figure 1-6. Respiratory induced artifacts in on-board CT imaging. The image on the left is static square-shaped phantom, and the magnitude of motion applied to the phantom in the SI direction (or up and down direction) increases from left to right. Adapted from Song et al^{68} .

1.4 Respiratory Motion Management Techniques

Respiratory motion should be considered during both CT simulation and treatment delivery. The impact of respiratory motion in early-stage NSCLC can be limited through breath-hold methods, tumour immobilization, respiratory tumour tracking, and respiratory gating. Reduction in target motion results in smaller treatment field sizes, and potentially reduced normal tissue toxicity. A brief overview of each method will be provided in the following subsections while respiratory gating will be explained in greater detail in section 1.5.

1.4.1 Motion-Encompassing Methods (4D-CT)

Respiratory motion introduces imaging artifacts and hinders accurate localization of the tumour and internal structures acquired during 3D-CT simulation. Large margins for the tumour can be incorporated to ensure full target coverage for the observed range of motion, but cause greater risk of radiation induced toxicities to normal tissues. Imaging techniques that allow for better visualization of the envelope of target motion, and permit more accurate margins are required.

Four-dimensional CT (4D-CT) is the most common approach that integrates organ motion into the acquisition of the CT dataset to facilitate treatment planning^{63,70–73}. Here, volumetric image data is acquired at different respiratory phases by oversampling each slice position in synchrony with a respiratory breathing signal (Figure 1-7). Helical and cine acquisition mode are two techniques utilized to acquire 4D-CT dataset⁷⁴. Slice positions in helical 4D-CT are oversampled by reducing the pitch, or reducing the ratio of the scanning table translation per gantry rotation. In cine mode, sequential CT data is acquired over a full breathing cycle at fixed scanning table positions.

During 4D-CT acquisition, the respiratory motion of an external surrogate labelled with infrared reflective markers is tracked using an infrared camera. The external surrogate is placed between the xyphoid process and umbilicus, and records the AP motion of the abdomen surface. Respiratory phase is determined from the respiratory signal and the image data acquired simultaneously is tagged according to the corresponding respiratory phase (Figure 1-7B). Retrospectively, all acquired image data are sorted into different

phase bins (Figure 1-7A). If a respiratory trace is divided into ten bins, the 0% phase represents the end inhalation, 10% - 40% phase represent mid exhalation, 50% phase represents the end exhalation, and 60% - 90% phase represents mid-inhalation. A 3D-CT volume reconstructed from image data acquired from a single phase, represents a 3D volumetric image at one respiratory phase bin. A 4D-CT dataset is the collection of the 3D-CT volumes reconstructed from all phases.



Figure 1-7. 4D-CT phase-sorting process. In this simplified example, the acquired CT images are sorted into only four distinct bins (A) based on respiratory phase of the respiratory signal (B). Adapted from Vedam et al⁷¹.

In early-stage NSCLC, 4D-CT imaging can facilitate target delineation to provide a representation of target excursions caused by full breathing motion. The gross target volume (GTV), can be contoured in each of the phases of the 4D-CT, where the union of all the phases represents the internal target volume (ITV), as shown in Figure 1-8.



Figure 1-8. 4D-CT image displays the gross target volume (GTV) in the end-inhalation (A), end-exhalation (B), the internal composite target volume (ITV) in green with the planning target volume (PTV) in yellow (C). Adapted from Glide-Hurst et al⁷⁵.

However, delineating the GTV and all OARs in all of the 4D-CT phases substantially reduces workflow efficiency. Instead, post-processing tools can derive 3D-CT datasets to provide a representation of the target. A time-averaged intensity CT image is generated from the average voxel value across the breathing cycle image data acquired to represent a blurred volume. Maximum intensity projection (MIP) 4D-CT is derived by fusing the 3D-CT volumes of the different respiratory phases based on the maximum intensity of each voxel⁷⁶⁻⁷⁸. In MIP images, the high density tumour appears brighter than low density lung⁶³. MIP 4D-CT is useful for peripheral tumours but delineation of tumours in proximity to the chest wall, mediastinum, or diaphragm becomes more difficult.

For SABR, 4D-CT dataset acquisition for treatment planning aids in determining the mean⁷⁹, and range of tumour motion⁸⁰. Improved delineation of the tumour and critical structures mitigates potential target misses, especially for tumours exhibiting large magnitude of motion⁸¹.

The disadvantage of using motion-encompassing methods includes irradiating larger target volumes and, as a consequence, larger normal lung volumes. In tumours exhibiting motion greater than 5 mm, other methods to minimizing tumour motion during treatment delivery can yield significant normal tissue sparing⁵⁵.

1.4.2 Breath-hold Methods

A method to minimize target volumes during treatment is through control of respiratory breathing either voluntarily or by an occlusion valve 55,82 . An occlusion valve is used in active breathing control (ABC), where air flow to the patient is temporarily blocked at end-inhalation, immobilizing the lung and stalling target motion^{83,84}. The treatment beam irradiation is enabled once the target has been immobilized according to the desired tidal volume. Another common breath-hold technique uses deep inspiration breath-hold (DIBH) where the patient *voluntarily* controls his or her breathing while interactively observing their respiratory trace^{82,85–88}. Prior to treatment, the patient is coached through quiet breathing followed by two breathing periods of slow deep inspiration and expiration prior to the breath hold, as in Figure 1-9⁸⁵. This provides reproducible motion control at end-inhalation. In both techniques, the breath is held for 10 - 20 seconds for every iteration. Respiratory motion is tracked during treatment using spirometry, surface markers, or an external surrogate. Regardless of the technique used for breath-holding during treatment (ABC or DIBH), the same management technique should be also used during CT simulation.

Motion management through the use of breath-hold at deep-inspiration provides tumour immobilization and the added benefit of a reduced lung density that enhances tumour contrast and visualization⁸⁵.



Figure 1-9. Deep inspiration breath-hold (DIBH) consists of slow quiet breathing session followed by a reproducible deep breath hold. Adapted from Hanley et al⁸⁵.

DIBH relies on active participation of the patients but inoperable NSCLC patients treated with SABR often exhibit poor pulmonary function and are often fragile, making breathhold a very challenging task. Another limitation during breath-hold is that some patients exhibit continuous diaphragm oscillatory motion, leading to fluctuations in tumour position⁵⁵.

1.4.3 Tumour Immobilization Methods

The magnitude of respiratory motion during treatment and CT simulation can be minimized mechanically by forced shallow breathing. Abdominal compression is the most common approach where a body frame with pressure plate is applied to the patient's abdomen to limit diaphragm motion⁸⁹⁻⁹¹. The maximum possible pressure a patient can comfortably manage is pressed against the abdomen. The position and pressure applied during CT simulation, is recorded to provide reproducible setup during each treatment fraction.

While attempting to minimize respiratory motion, abdominal compression is not well tolerated by patients⁹². Studies have shown a statistically significant increase in interfractional variation of tumour position for SABR lung patients treated with abdominal compression methods^{90,92,93}.

1.4.4 Respiratory Tumour Tracking Methods

In the above techniques, large margins are required to encompass the target as it moves during full respiratory motion, or suppressing tumour motion through breath-hold and abdominal compression causes discomfort to the patients that may be intolerable. In respiratory tumour tracking, the patient breathes freely and target margins are reduced by tracking the tumour motion within the radiation beam⁹⁴. Safe incorporation of respiratory tracking requires monitoring of the tumour trajectory, and compensation for the tumour motion geometrically and dosimetrically.

The motion trajectory of the target can be acquired through imaging, such as fluoroscopy, for lesions located centrally in the lung where normal structures will not obstruct visibility; however, lesions located adjacent to normal tissue (diaphragm, mediastinum, and chest wall) will lack visibility. Fiducial markers are high atomic number metals, typically gold pellets, and can provide high contrast when implanted within the lesion of interest using a percutaneous or bronchoscopic implanting technique. Three or more fiducial markers are required to allow for measurements of rotation and translation between the markers⁵⁵. The position of fiducial markers within the tumour, is determined using imaging or from an emitted radiofrequency (RF) signal. However, placement of fiducial markers is an invasive procedure, and can be susceptible to migration during treatment. External surrogates on the chest can be used alternatively to account for breathing motion if the correlation with tumour trajectory motion can be verified.

The radiation beam mechanically follows the tumour using MLC tracking^{95,96} or a robotic linear accelerator with six degrees of freedom^{97–99}. However, delays in linear accelerator reposition once motion coordinates are determined can occur; in the case of MLC tracking, time delays of 200 ms or more occur¹⁰⁰. There are additional time delays for determining the coordinates of the tumour in the images. Position predictive algorithms based on previously acquired motion trajectory are used to prospectively adapt the radiation beam. These algorithms assume periodicity of motion from planning to treatment delivery¹⁰¹. As mentioned in section 1.3.1, respiratory motion may exhibit both inter- and intra- fractional variability^{42,45,102}.

Radiation treatment planning requires computation of dose distributions in all the respiratory phases of the 4D-CT dataset because of geometric displacements and lung density changes. The relationship between respiratory phase and the tumour motion trajectory, adapts the treatment dosimetrically¹⁰³.

A summary of the different motion management techniques is provided in Table 1-2.

Table 1-2. Summary of the different methods of respiratory management and variations in intra- and inter-fraction motion. Abbreviations: BH: breath-hold, ABC: active breathing control, SD: standard deviation, LR: left-right, AP: anterior-posterior, SI: superior-inferior, DIBH: deep inspiration breath-hold, *includes setup error, 3D—3-dimensional error, mDIBH moderately deep inspiration breath-hold. Adapted from Keall et al⁵⁵.

Motion Management Technique	Advantages	Disadvantages	Study	Mitigation Method	Intra-fraction variation (cm)	Inter-fraction variation (cm)
Breath-hold	- Limited tumour motion	- May require patient active participation	Cheung et al ¹⁰⁴	BH at inspiration with ABC	-	SD: 0.18 LR, 0.23 AP, 0.35 SI
	- Reduced lung density	- Patient exhibit continuous	Dawson et al ¹⁰⁵	BH at exhalation with ABC	SD: 0.25	SD: 0.44
	- Does not	motion	Remouch- amps et al ¹⁰⁶ Hanley et al ⁸⁵	mDIBH with ABC DIBH	Mean: 0.14	Mean: 0.19
	require specialized software and hardware				SD: 0.17	SD: 0.22
	- Efficient due				Mean: 0.1	Mean: 0.25
	to continuous treatment beam during breath hold				SD: 0.09	SD: 0.16
Tumour Immobiliza- tion	- Limit tumour motion	- Not well tolerated by patients	Negoro et al ¹⁰⁷	Abdominal compression	Mean 3D: 0.7 Range: 0.2– 1.1	Mean 3D: 0.49* Range: 0.4–0.8*

			Significant interfraction variation	Wulf et al ⁸⁹	Abdominal compression	-	SD: 0.33 LR, 0.34 AP, 0.44 SI
				Bissonnette et al ⁹⁰	Abdominal compression	Mean 3D: 0.24	Mean 3D: 0.3
				Mampuya et al ⁹³	Abdominal compression	-	SD: 0.21 LR, 0.19 AP, 0.31 SI
Respiratory Tracking	 Patient breathi Treatm time is limited Adapts full 3D motion 	is free ng nent not to the	 Requires periodic respiratory breathing Mechanical delay uncertainties 	Hoogeman et al ¹⁰⁸	Robotic linear accelerator	SD: 0.19 LR, 0.25 AP, 0.19 SI	-
Respiratory gating	- Limit t motion	umour	Increased treatment time	Ford et al ¹⁰⁹	Gating at exhalation with RPM	Mean: 0.26 SD: 0.17	Mean: 0.0 SD: 0.39
	breathing and ext surroga correlat uncerta	and external surrogate correlation uncertainty	Wagman et al ¹¹⁰	Gating at exhalation with RPM	Mean: 0.20	-	

1.5 Respiratory Gating Methods

Respiratory gating also allows the patient to breath freely, and the treatment beam is triggered only within a predetermined portion of the breathing cycle^{111–116}. In respiratory gating, the portion of the breathing waveform where the treatment beam is activated, is coined the "gating window". The gating window is predetermined according to the stable portion of the breathing cycle, most often during the end-exhalation period. The respiratory motion within the gating window is considered as the residual motion¹¹⁷. The respiratory gating efficiency, or duty cycle, is defined as a percentage of the "beam on" time to total treatment time¹¹². The gating window is determined based on a tradeoff between limiting residual motion, and optimizing the duty cycle to reduce overall treatment time. A subset of the 4D-CT dataset corresponding to the respiratory phases within the intended gating window are averaged to form the subset average 4D-CT dataset that is used for treatment planning. The subset average 4D-CT incorporates the residual motion within the gating window. The ITV, in this case, is generated based on the blur of the target volume in the subset 4D-CT. Planning and set-up uncertainties are included in the planning target volume (PTV) by the addition of a margin to the ITV, in early-stage NSCLC 5 mm margin is used¹¹⁷. The result is a significant reduction in the target margins compared to conventional free breathing ungated radiotherapy and as a result, reduced normal tissue irradiation¹¹¹.

Internal respiratory gating, similarly to respiratory tracking, is facilitated through the use of fiducial markers¹¹⁸. Originally developed by Mitsubishi Electronics Co. (Tokyo, Japan), internal gating defines the gating window through fluoroscopic detection of fiducial markers during treatment. Position of the fiducial markers is identified during treatment in three dimensions using four sets of diagnostic x-ray imaging systems. Within the gating window, the x-ray kV acquisition pulses are interlaced with the treatment MV pulses to avoid scatter from the MV reaching the fluoroscopic detectors. As mentioned previously, implantation of the fiducial markers is an invasive procedure generally not well tolerated by inoperable SABR patients.

External respiratory gating relies on surrogate signals of a respiratory motion, and is a non-invasive alternative method for respiratory gating applicable to almost all patients⁵⁵. The

external surrogate is an infrared reflective plastic box (Figure 1-10A) placed between the xyphoid process and the umbilicus, to maximize the AP motion. During 4D-CT acquisition, a mark is tattooed on the patient's skin to ensure reproducible placement of the external surrogate box during treatment. Infrared markers on the surrogate box have fixed non-symmetric positions to facilitate observation of potential misalignment during geometric calibration. The displacement of the external surrogate box is detected by the position sensors with the in-room infrared camera (Figure 1-10B) generating a respiratory trace.



Figure 1-10. Respiratory gating external surrogate box with infrared markers (A) and infrared Polaris Spectra NDI camera that tracks the markers (B).

Prior to each treatment session, the starting phase of the respiratory trace is matched to the corresponding phase in the reference trace, recorded during 4D-CT acquisition (Figure 1-11) and used in treatment planning. Irregularities between 4D-CT acquisition and treatment session breathing traces can be reduced through respiratory breathing training. If the recorded waveform period does not match the reference waveform, the treatment beam is triggered "off" and will not be allowed to begin.

In Figure 1-11, the gating window is dictated by the upper and lower gating thresholds. If the thresholds are set to the same range, system will consider the gate as fully open and beam holding will not occur.



- 1. Upper gating threshold (blue line)
- 2. Lower gating threshold (orange line)
- 3. Respiratory waveform(black waveform)
- 4. Reference curve (green waveform)
- 5. Gating window (yellow shaded area)

Figure 1-11. Respiratory chart demonstrating the gating window (yellow shaded area) defined by the upper and lower gating thresholds (blue and orange lines, respectively). The reference trace from the 4D-CT acquisition is demonstrated by the green waveform, and the treatment waveform is displayed by the black waveform. Adapted from VitalBeam imaging manual¹¹⁹.

1.5.1 Amplitude Gating

Amplitude gating is based upon the displacement of the external surrogate box as a representative metric of the tumour at a certain position (Figure 1-12)¹¹⁶. The total displacement in the respiratory signal is the position difference between end-inhalation and end-exhalation. The respiratory waveform shown in Figure 1-12 displays the amplitude, or motion above the baseline, versus time. The gating window, shown by the highlighted yellow area in Figure 1-12, is defined as a window of displacement (solid line) allowed from end-exhalation.



Figure 1-12. Amplitude based respiratory gating waveform. The solid black curve represents the waveform trace as a function of time, whereas the dashed black lines represent the recurring respiratory phase (0 to 2π radians) as a function of time. The upper and lower thresholds are displayed by the blue and orange lines, respectively. The gating window is shown in the shaded yellow area.

1.5.2 Phase Gating

A sinusoidal pattern is used to approximate the real-patient waveform and analyze the respiratory waveform. Phase values of a full breathing cycle (0 to 2π radians) are converted into percent and divided into 10 equal bins ranging between 0% to $100\%^{119}$. In the "needle diagram" (Figure 1-13A) the end-inhalation is represented by 0% and end-exhalation by 50%. Inhalation occurs when the needle is in the left half of the dial (50%-100%), whereas exhalation occurs in the right half of the dial (0%-50%). In phase gating, the gating window is represented by two angular positions (dashed line) of the respiratory waveform (Figure 1-13B)¹¹⁶.



Figure 1-13. Phase based respiratory gating waveform: A) Needle diagram representing cyclic phase where the orange tick mark represents the entry to the gating window, and the blue tick mark represents the exit of the gating window; B) Displacement waveform as a function of time is shown in the solid black line, whereas the dashed black lines represent the respiratory phase as a function of time. The entrance and exit of the gating window are displayed by the orange and blue lines, respectively. The gating window is shown in the shaded yellow area.

1.5.3 Learning Respiratory Motion

For both amplitude gating and phase gating, the respiratory waveforms are analyzed for reproducibility. Raw data points from the external surrogate box are converted into a smooth wave using polynomial fitting¹¹⁹. The end-inhalation and end-exhalation are attained through a peak and trough detection to produce an estimate of the breathing respiratory period. Each peak is assigned at 0%, with succeeding peak assigned at 100%. A fixed value for end-exhale is not assigned but it is estimated to be around 50%. The respiratory phase of end-exhalation depends on the pattern of the breathing cycle, in respiratory traces exhibiting longer inhalation than exhalation, end-exhalation will occur at phases <50%, whereas, respiratory traces exhibiting shorter inhalation than exhalation, end-exhalation will occur at phases >50%.

Patient breathing characteristics are measured during the learning period that lasts for four complete breathing cycles. Within the learning period, respiratory motion is required to be periodic in order to provide a reproducible breathing trace. Fast breathing peaks in the

learning period, defined as less than 1.5 seconds between consecutive inhalation or exhalation peaks, or 0.5 seconds between inhalation and exhalation peak, are ignored and not included in the motion characteristics analysis. The average end-exhale position is measured over the learning period and assigned as the baseline value. The baseline value is set to zero in the respiration chart and is only updated if re-learning of the breathing trace is required. The respiratory trace acquired during 4D-CT is used as a reference and re-learned if necessary, prior to every treatment session.

The periodicity of respiratory breathing trace is measured by calculating a phasedisplacement scattergram (Figure 1-14). Predictive filters are employed to correct for irregular, non-periodic breathing by setting a threshold for the beam "on"¹²⁰. The predictive filter aids in restricting inaccurate treatment delivery by triggering the beam "off" when the motion does not match the 4D-CT reference values within a predefined tolerance. In respiratory gating, the treatment beam is paused if respiratory position falls outside of the gating window, or if the motion periodicity falls outside of the predictive filter margins.



Figure 1-14. Characterizing periodicity in respiratory breathing trace. Examples for a regular and irregular breathing cycles are shown. A sample gating window is displayed for amplitude (blue shaded) and phase (red shaded) gating with a 40% duty cycle.

1.5.4 Respiratory Gating Limitations

The respiratory gating window is optimized based on a tradeoff between duty cycle and residual target motion. As duty cycle is minimized, treatment session times are increased. Increased treatment time may cause intrafractional setup errors due to potential movement from patient discomfort. Patient throughput on the treatment machine is also reduced by increased treatment times. Studies have indicated potential reduced tumour control for treatments that require longer than 20 mins^{122,122}. This becomes increasingly important with the combination of high dose per fraction SABR prescriptions, with respiratory gating.

Respiratory phase analysis relies on a sinusoidal approximation, leading to substantial inconsistencies for patients that exhibit irregular respiratory motion (Figure 1-14). Phase calculations are based on preceding breathing cycles so that inconsistencies between breathing cycles will produce incorrectly defined respiratory phases. By comparison, amplitude gating has demonstrated less variability when respiratory motion lacks periodicity^{123–125}.

The large uncertainty in external respiratory gating lies in the accuracy of an external surrogate marker to predict the internal motion of the tumour. The magnitude of displacement between the external surrogate and tumour motion does not need to be the equal but must be correlated. However, correlation is contingent on the external signal phase predicting the internal tumour respiratory phase. The inability to observe tumour motion directly leads to uncertainties in the displacement and phase relationship between the surrogate and the tumour¹²⁶.

The internal and external correlation is disrupted or lost completely by transient and continuous changes in respiratory motion breathing or instability in oscillatory mechanical systems^{55,127}. Lack of correlation can cause the radiation beam to trigger incorrectly in parts of the breathing cycle (Figure 1-15). The external surrogate and internal target correlation is further investigated in Chapter 4 of this thesis.



Figure 1-15. Comparison of the internal and external motion without a phase shift (a), and with a phase shift (b). The red lines indicate beam exposure times that are out of synchrony with the target motion. Adapted from Keall et al⁵⁵

Respiratory gated treatments are susceptible to inter-fraction variability in tumour and external surrogate relationship, requiring relearning of periodicity before each fraction. The risk of baseline variations increases with treatment time leading to the tumour movement outside the gating window¹²⁸. Intrafractional variation can cause discrepancies in dose delivery with some targets being on the verge of under-dosage^{129,130}.

1.6 High Dose Rate Gated SABR

1.6.1 TrueBeam Linear Accelerator

The Varian TrueBeamTM (Varian Medical Systems, Palo Alto, USA) linear accelerator (LINAC) is a recent technical development that allows for the integration of respiratory gating with VMAT and is the subject of Chapters 3-5. Respiratory-gated VMAT provides the ability to safely combine the normal tissue sparing capabilities of respiratory gating to superior treatment efficiency achieved through VMAT¹³¹. In respiratory gated VMAT, the interplay effect contributes insignificantly to dose delivery errors due to minimal residual motion, although increased motion irregularity in patients treated with gated VMAT has shown to negatively affect the intended dose distribution^{50,132}.

Treatment delivery efficiency is improved by removing the flattening filter to enhance dose rate. The flattening filter is located prior to the monitor chambers and succeeding the target and primary collimators. The distribution of photons after the target is strongly forward peaked, and the conical shaped flattening filter is used to obtain a uniform dose distribution at a referenced depth. However, the role of the flattening filter is negligible for SABR treatments due to the associated small field sizes (Figure 1-16). The advantage of flattening filter free (FFF) beams is an increase in photon fluence allowing for higher treatment dose rates (monitor units (MU) per minute). For example, a 10 MV FFF x-ray beam has a peak dose rate of 2400 MU/minute, and a 6MV FFF beam has a peak dose rate of 1400 MU/min. A conventionally flattened beam, on the other hand, has a peak dose rate of only 600 MU/minute¹³³. The application of FFF beams in SABR treatments has significantly improved efficiency^{134–136} while radiobiological properties are maintained¹³⁷. Increased efficiency in treatment times reduces potential intrafraction errors from patient movement, as has been observed for treatment session times lasting more than 30 minutes¹³⁸.



Figure 1-16. Axis dose profile at different depths in water, comparing flattened beams (A), and FFF beams (B). The dose rates have been renormalized at a central depth of 2 cm.

Another feature of TrueBeam linac is the "Research Mode" interface that allows a knowledgeable user to program motion trajectories of major accelerator components. Research Mode provides access to the user to go beyond clinically approved modalities

and investigate novel treatment and imaging techniques in a non-clinical setting^{139–143}. The user formulates specific axes of motion for each of the imaging and treatment delivery trajectories, such as gantry, collimator, on-board kV imaging source and detector, etc, as a function of cumulative dose, written in extensible markup language (XML).

1.6.2 Pre-Treatment Verification

As radiotherapy planning and delivery is becoming increasingly complex, dose delivery verification (i.e. quality assurance) are even more necessary. For respiratory gated radiotherapy, verification of the intended gating window and the relationship between the external surrogate motion and internal tumour motion is required during treatment delivery. Image-guided radiation therapy (IGRT) has therefore been implemented prior and during treatment to facilitate patient set-up, detect patient deformation from CT-simulation to treatment delivery, and for dose verification.

Prior to treatment delivery, on-board imaging (OBI) or the electronic portal imaging device (EPID) can be used to facilitate patient set-up and ensure there are not any significant deformations in patient anatomy between the plan and the delivery session (Figure 1-17).



Figure 1-17. Varian TrueBeam mounted on-board imaging (red squares) and electronic portal imaging detector (orange square).

The EPID uses the MV beam to acquire a single image of the patient for setup verification. Patient bony anatomy landmarks on the image can be used to guide patient alignment. High energy photons reduce the overall noise in MV images¹⁴⁴. However, poor image contrast from the MV energy x-rays hinder soft tissue and, often, bony anatomy visualization.

On-board kV imaging, achieves contrast superior to images acquired with an MV source¹⁴⁵. The TrueBeam LINAC allows acquisition of a pair of orthogonal respiratory gated kV radiographs. During respiratory gated patient setup, these planar images are compared to digital reconstructed radiographs (DRR) generated from the planning CT dataset^{145,146}.

The TrueBeam LINAC allows for kV fluoroscopy. The ability to also acquire a respiratory trace simultaneously with the external marker block brings forth real-time monitoring and correlation of visible lung structures. The position of the tumour can be determined as a function of time. If the visibility of the tumour is poor, another moving anatomic surrogate, such as the diaphragm, can be used to define the relationship of internal motion with the

external surrogate motion. The gating window should be adjusted if a consistent time delay of 0.5 sec or greater exists between internal and external surrogate motion⁵⁵. To limit radiation dose during continuous imaging, the imaging voltage and current can be lowered, at the cost of image quality.

Continuous kV imaging acquired at multiple gantry angles allows for generation of a volumetric cone-beam CT (CBCT)¹³⁸. Volumetric CBCT permits soft tissue matching with the treatment planning CT. There are two different types of filter applied to modify the kV energy spectrum, in order to improve image quality. A 0.89 mm titanium filter is applied to remove low-energy x-rays in the beam. Whereas, the bowtie filter is an aluminum shaped filter applied to compensate for greater attenuation by the patient at center field, and reduce patient skin dose. In full-fan CBCT, using a full-bowtie filter, the FOV is limited by the detector size. In scans where patient size surpasses the detector size, such as thoracic scans, half-fan CBCT scanning technique is used. In half-fan CBCT, using the half-bowtie filter, the FOV width is increased by offsetting the position of the detector and scanning only half of the patient for part of the rotation and offsetting the position of the detector in the opposite direction for the remainder of rotation. The shifted projections are retrospectively stitched together.

1.6.3 Intrafraction Treatment Verification

Pre-treatment verification aids in diminishing inter-fractional uncertainties. However, intra-fractional uncertainties are still persistent during SABR lung treatments¹²⁸ and can inhibit treatment delivery accuracy if not accounted for.

Acquiring MV portal imaging during treatment can allow for a dosimetric and real-time verification of radiation dose delivery. The EPID can acquire beam's-eye-view (BEV) projections throughout treatment. Either a "single shot" image can be acquired or a synchronized MV, or cine loop, can be used to acquire continuous readout of images between beam pulses¹⁴⁷. Both provide a utility to verify the target is within the gating region. For dosimetric verification using unsynchronized MV, the EPID can be operated in integrated mode and continuously reads out and assimilates acquisitions, resulting in a single image representing the total dose delivered per beam. These images can be used to

reconstruct the 3D dose distribution for comparison to the planned dose distribution; deviations in the accumulated dose could be accounted for in subsequent fractions¹⁴⁸. MV imaging using FFF beams during treatment provides shaper images compared to standard flattened beams, due to a reduction in primary head scatter¹⁴⁹.

A technique to combine kV and MV imaging for intra-treatment verification in VMAT and fixed beam IMRT is discussed by Ren et al¹³⁹. For clinical respiratory-gated delivery verification, kV imaging can been triggered prior to or at the exit from the gating window^{150–152}. However, triggered kV imaging is limited in examining residual motion inside the gating window. Geometrical verification and residual motion analysis can be investigated through kV fluoroscopy during treatment¹⁵³. Fluoroscopic imaging acquired during respiratory gated SABR treatment provides additional intrafraction information at the cost of additional imaging dose. Also, the ability to trigger fluoroscopic imaging only within the gating window is not possible in current clinical mode of operation. Therefore, longer treatment times associated with respiratory gated SABR, make this application impractical due to the significant increase in imaging dose to the patient and the strain on the x-ray tube. In chapters 3 and 4 of this thesis, respiratory gated kV imaging is investigated using Research Mode of operation.

The image quality of in-treatment fluoroscopy is significantly reduced due to patient scatter of the treatment beam to the kV detector¹⁵⁴. The percent of the scatter dose from the isocenter to the detector ranges between 0.0154% to 0.0174% for 10 cm by 10 cm field size with a 10 MV beam (Appendix B)¹⁵⁵. Different groups have investigated removing the MV contribution to the kV detector through readout of unexposed kV frames¹⁵⁶, and interlacing kV projections between MV pulses^{157,158}.

1.7 Research Questions and Hypothesis

The aim of this research is to optimize and improve radiation treatment planning and delivery using state of art technologies for early-stage NSCLC patients treated with SABR. SABR fractionation schemes consist of high doses (54 Gy - 60 Gy) delivered in only a few

fractions (3–8), requiring very high precision in sparing normal tissue and dose target conformity to the target. However, respiratory motion is the major roadblock in treatment accuracy. High dose SABR treatment delivery lessens potential averaging of respiratory motion uncertainties, as observed in conventional dose fractionations, and therefore escalates consideration of the moving target.

Respiratory gating can mitigate the effects of respiratory motion, while the combination of respiratory gating with VMAT using high dose rate delivery of FFF beams can increase treatment efficiency. However, additional uncertainties are introduced in respiratory gated VMAT by the additional degrees of freedom, such as the gantry rotation and variable dose rate. Respiratory gating window will lead to multiple stops of the gantry motion, causing ramping up-and-down of the dose rate when entering and exiting the gating window. These potential uncertainties introduced in dose delivery must be studied. Advanced on-board imaging protocols in TrueBeam Research mode can be generated to provide intrafraction verification of respiratory gated VMAT. The following questions were articulated to address these concerns:

- Which IMRT delivery technique optimizes dose distribution and delivery for earlystage NSCLC patients?
- Will respiratory-gated VMAT reduce the potential for radiation induced normal lung toxicity?
- Can we safely use intra-treatment kV imaging for delivery verification of respiratory gating?

The answer to these questions can be summed up under the hypothesis of this thesis:

Simultaneous real-time kV imaging during radiation treatment delivery will improve the precision of respiratory gated VMAT for early-stage NSCLC such that the expected benefits can ultimately be realized clinically.

1.8 Research Objectives

The goal of this thesis is to validate and improve respiratory gated treatment planning and delivery for early-stage NSCLC patients with SABR. More specifically, the focus of this thesis is to investigate treatment planning using high dose rate IMRT and respiratory gated VMAT, and to verify treatment delivery with real-time on-board gated kV imaging synchronized to the treatment beam. The breakdown of the research objectives to attain this goal are formulated as:

- To compare various IMRT treatment techniques by determining which provides the optimal trade-off between treatment efficiency and dose conformity in early-stage NSCLC treated with SABR.
- To assess the reduction of radiation induced lung toxicities, pneumonitis and fibrosis, by the combination of respiratory gated VMAT in early-stage NSCLC patients exhibiting significant tumour motion.
- To determine if on-board kV imaging can be used as a tool to ensure that the motion of the external surrogate used for respiratory gating correlates well with internal target motion using patient specific waveforms during respiratory-gated VMAT treatment delivery.
- To investigate imaging parameters in intrafraction CBCT by using gated kV fluoroscopy acquired during respiratory-gated and ungated VMAT.

1.9 Thesis Roadmap

1.9.1 Chapter 2 - Dosimetric planning comparison of IMRT techniques for early stage non-small cell lung cancer with SABR

Retrospectively, radiation treatment plans for ten patients with early-stage NSCLC were computed with eight various IMRT modalities: 1) Three FB-IMRT methods; 2) Two VMAT methods; and 3) Three Tomotherapy methods. The goal of this work was to determine which modality provided the optimal trade-off between dose conformity and

treatment efficiency. Dosimetric parameters including dose conformity (minimum PTV dose, conformity indices of the PTV etc), dose volume histogram metrics (maximum dose to healthy structures, mean lung dose, contralateral V_{5Gy} , etc), and treatment efficiency (MLC degradation, treatment delivery time, etc) were compared amongst each of the treatment planning techniques. This chapter is adapted from a research paper entitled "Comprehensive dosimetric planning comparison for early stage non-small cell lung cancer with SABR: fixed-beam IMRT versus VMAT versus tomotherapy" by Xhaferllari I, El-Sherif O, and Gaede S. in press at the *Journal of Applied Clinical Medical Physics*

1.9.2 Chapter 3 - The potential for respiratory-gated VMAT to reduce normal lung toxicity in SABR patients

In this chapter, respiratory gated VMAT is compared theoretically to ungated VMAT for 20 early-stage NSCLC patients exhibiting significant breathing-induced tumour motion. Dosimetric parameters (V_{20Gy} and mean lung dose) corresponding to early induced lung toxicities, such as pneumonitis, and ($V_{50\%}$) corresponding to late induced lung toxicities, such as fibrosis, were calculated for all retrospective treatment plans. This chapter is adapted from research paper entitled "Dosimetric planning study of respiratory-gated volumetric modulated arc therapy for early-stage lung cancer with stereotactic body radiation therapy" published in *Practical Radiation Oncology* vol. 5 (3): pp. 156-61 (2015) by Xhaferllari I, Chen JZ, MacFarlane M, Yu E, Gaede S.

1.9.3 Chapter 4 - The use of on-board kV imaging during respiratory gated VMAT delivery to evaluate the correlation between tumour motion and external surrogate motion in patient-specific waveforms

Correlation of the internal target motion and the external surrogate marker motion was investigated using different real-patient breathing waveforms in free breathing ungated, amplitude gated and phase gated conditions. In this chapter, on-board gated fluoroscopy during VMAT was investigated as a tool to correlate the external marker motion with internal target motion, and to calculate pre-determined simulated phase shifts. This work was performed using the TrueBeam Research mode and a programmable respiratory motion phantom. This chapter is based on a research paper entitled "The use of on-board kV imaging during respiratory gated VMAT delivery to evaluate the correlation between tumour motion and external surrogate motion in patient-specific waveforms" by Xhaferllari I, El-Sherif O, Stevens T, Gaede S to be submitted to the *Medical Physics* journal.

1.9.4 Chapter 5 – Investigation of image quality of intrafraction cone beam CT for 3D verification of respiratory-gated VMAT delivery

Despite MV degradation of image quality, intra-fractional kV CBCT during SABR VMAT treatment delivery was investigated as a volumetric dosimetric verification method. Imaging parameters to optimize image quality and target delineation were explored. Respiratory motion artifacts were studied by using a programmable respiratory motion phantom embedded with multiple sized spheres under free breathing ungated, amplitude gated, and phase gated conditions. The contents of this chapter are in preparation for a submission entitled "Investigation of image quality of intrafraction cone beam CT for 3D verification of respiratory-gated VMAT delivery" by Xhaferllari I, Dekker K, Hajdok G, Gaede S to *Physics in Medicine and Biology* journal.

1.9.5 Chapter 6 - Conclusions and Future Work

In this final chapter, an overview of the important findings and conclusions of the thesis are summarized. Main limitations from Chapters 2-5 are discussed. The thesis concludes with potential topics of interest that can further build upon this work.

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Chapter 2

2 Dosimetric planning comparison of IMRT techniques for early stage non-small cell lung cancer with SABR

This chapter is adapted from a research paper entitled "Comprehensive dosimetric planning comparison for early stage non-small cell lung cancer with SABR: fixed-beam IMRT versus VMAT versus tomotherapy" accepted in the Journal of Applied Clinical Medical Physics by Xhaferllari I, El-Sherif O, and Gaede S.

2.1 Introduction

Cancer is the leading cause of death worldwide, with non-small cell lung cancer (NSCLC) being the most common cause of cancer related mortality¹. In the treatment of early-stage NSCLC, surgical resection is considered the standard of care². However, some patients are deemed medically inoperable due to age, decreased pulmonary reserve, cardiac function, or significant co-morbidities³. Medically inoperable patients, as well as patients unwilling to undergo surgery, have the option to be treated using stereotactic ablative radiotherapy (SABR). SABR is a hypofractionated technique where a very high ablative dose per treatment is delivered in few fractions, normally three to eight. Therefore, tumor conformality and sparing of normal tissue is increasingly crucial with SABR in comparison to conventional fractionation. SABR treatments are computed using multiple beam angles to achieve sharp dose gradients needed to spare healthy tissue. Outcome studies have shown SABR has an overall survival of 41.2% compared to 66.1% for patients who undergo lobectomy at five years, meanwhile, local control at three years has improved with SABR, 87.8%, compared to lobectomy resection, 85%².

Although non-coplanar three-dimensional conformal therapy (3D-CRT) remains a popular technique for delivering SABR, intensity modulated radiation therapy (IMRT) has become increasingly popular due to the ability to improve dose conformality and reduce toxicities to normal tissue⁴. There are various techniques available to compute IMRT: fixed beam (FB)^{4,5}, volumetric modulated arc therapy (VMAT)⁶, and helical tomotherapy (HT)⁷. FB involves holding the gantry fixed in each beam direction as each segment of the beam, formed using a multi-leaf collimator (MLC), is delivered. FB can be accomplished by step-

and-shoot delivery (SS) and sliding window (SW). VMAT techniques deliver radiation using gantry rotation up to 360° around the patient while simultaneously varying gantry speed, leaf motion, and dose rate⁸. Both FB and VMAT can be optimized using direct machine parameter optimization (DMPO) capable with the Pinnacle³ treatment planning system (Philips Medical Systems, Fitchburg, USA) and Acuros XB (AXB) v11.3 dose calculation algorithm capable with the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, USA). HT delivery is accomplished by synchronizing couch motion through the bore to the gantry rotation; intensity modulation is attained by a thin fan beam of various sizes and binary multi-leaf collimator ⁹, and most recently with dynamic jaws¹⁰.

Lung SABR treatment plans consist of small fields with substantial heterogeneity from the high density tumour and the low density lung. Dose calculation algorithms available in commercial products vary in accuracy of dose computation^{11,12}. The dose calculation algorithm available with Pinnacle³ and TomoTherapy treatment planning systems is collapsed cone convolution¹³, and in Eclipse treatment planning system, AXB is employed ¹⁴.

The goal of this retrospective planning study was to provide an extensive comparison of the various FB, VMAT, and HT techniques for delivering IMRT based treatment for earlystage NSCLC patients with SABR. This study will conclude which technique and vendor provides the highest dosimetric benefit by comparing indices for the region of interest and organs at risk.

2.2 Material and Methods

2.2.1 Patient selection and contouring

A total of ten patients with medically inoperable early-stage NSCLC were enrolled in this retrospective planning study. These patients were chosen based on criteria of motion greater than 0.5 cm, and internal target volume (ITV) in the range of 4.4 - 53.1 cm³, as typically observed in NSCLC SABR treatment cases. Patient specific characteristics, including staging, lesion location, and target volumes are shown in Table 2.1.

Defieut	Ct	T 1	- 4	ITV size	PTV size
Patient	Stage	Tumor loc	ation	(cm ³)	(cm ³)
1	T1bN0M0	RLL^*	Central	17.2	47.3
2	T1aN0M0	RLL	Peripheral	4.8	22.5
3	T2aN0M0	RLL	Central	22.6	58.8
4	T2aN0M0	RLL	Peripheral	35.2	78.0
5	T2aN0M0	RLL	Central	27.7	69.5
6	T2aN0M0	RLL	Peripheral	53.1	106.0
7	T1aN0M0	RML [§]	Peripheral	16.2	42.8
8	T2aN0M0	RML	Central	48.8	103.8
9	T2bN0M0	LLL^{\ddagger}	Central	40.9	92.2
10	T1aN0M0	LUL ¹¹	Peripheral	4.4	17.9

Table 2-1. General patient demographics

Abbreviations: *RLL-Right Lower Lobe; *RML-Right Middle Lobe; [‡]LLL-Left Lower Lobe; ¹¹LUL- Left Upper Lobe

Four-dimensional computed tomography (4D-CT) scans, reconstructed into 10 phases, were acquired for each patient using Varian's Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA) in the Philips Brilliance Big Bore CT scanner (Philips Medical Systems, Cleveland, OH). The gross target volume, (GTV), was contoured on each of the ten respiratory phases and motion encompassing internal target volume, (ITV), was created by summing the ten individual GTVs. Consecutively, the

planning target volume (PTV) was created by adding a 5 mm expansion to the ITV in the untagged average 4D-CT. Target volumes and contours of the critical structures were imported onto the untagged average 4D-CT and employed for treatment planning across different techniques.

2.2.2 Treatment Planning

For each patient, eight treatment plans were optimized: three FB, two VMAT, and three HT plans; for 80 treatment plans total. A dose of 54 Gy in three fractions was prescribed for each patient. To ensure target coverage and provide normalization, 95% of the PTV must be covered by the prescription isodose (RTOG 0618)¹⁵.

FB plans were computed by separate board certified dosimetrists who specialize in Eclipse, and Pinnacle treatment planning. Prior to FB planning, the dosimetrists were instructed to use nine-eleven coplanar beams in each of their plans to have the highest quality plan attainable. For each patient, two SS plans, with a maximum allowed segments of 33 and 100 to represent low modulation (SS-LM) and high modulation (SS-HM), respectively, were retrospectively planned in Pinnacle³ v9.1 treatment planning system, and the dose was calculated using collapsed cone convolution. The SW plans were generated by a different board certified dosimetrist than the SS plans using Eclipse treatment planning system; therefore, SW was composed of nine to eleven coplanar beams and did not have the same beam arrangement as SS. All the FB plans were recomputed using 10X flattening filter free (FFF) beams to optimize the efficiency of expected treatment delivery, and SW was recomputed using AXB dose algorithm version 11.3. Once recomputed, each of the plans was validated to ensure they are clinically acceptable, and if needed, the plans were re-optimized.

SA treatment plans were generated by employing clinically used Pinnacle host script via Pinnacle³ planning system with collapsed cone convolution, and RA treatment plans were computed with a clinically approved protocol in Eclipse planning system with AXB dose calculation algorithm. Two partial arcs were used depending on the location of the lesion in the lung to avoid overdosage to the contralateral lung. According to the clinical script, the SA plans consisted of two 225^o beam arcs with the dimensions of 180.1^o- 45^o clockwise

and $45^{\circ} - 180^{\circ}$ counterclockwise if the lesion was located in the right lung, or $315^{\circ}-179.9^{\circ}$ clockwise and $180^{\circ}-315^{\circ}$ counterclockwise if the lesion was located in the left lung. Whereas, the RA plans were computed using two 210° beam arcs with the dimensions of $180.1^{\circ}-30^{\circ}$ clockwise and $30^{\circ}-180^{\circ}$ counterclockwise if the lesion was in the right lung, and $330^{\circ}-179.9^{\circ}$ clockwise and $180^{\circ}-330^{\circ}$ counterclockwise if the lesion was situated in the left lung. Both partial arcs were generated using 10X FFF beam energy and a maximum 2400 MU/min dose rate.

All FB and VMAT techniques were prepared utilizing FFF beams to maximize efficiency in these hypofractionated deliveries. FFF beams allow for safe treatment delivery with dose rates up 2400 MU/min, significantly reducing treatment time^{16,17}. Clinical assessment of utilizing FFF beams to treat early-stage NSCLC patients with SABR have demonstrated early local control rates upwards of 89%¹⁷.

The three HT plans with varying beam fan width of 1 cm, 2.5 cm, and 5 cm (HT-1cm, HT-2.5cm, and HT-5cm respectively) were generated by a board certified dosimetrist using HiART TomoPlan 3.1.1 (Accuracy Inc, Sunnyvale, CA). For the patients in this study, a 0.172 pitch and 1.3 modulation factor were used. All HT plans were designed using a 6X beam with 600 MU/min dose rate and optimized with inverse planning based on least squares optimization method. The dose was calculated by employing collapsed cone convolution algorithm^{18,19}.

Pinnacle, Eclipse and HT treatment planning systems have different optimization methods, as well as varying cost functions. The planning constraints cannot be set the same between the different planning systems to achieve highest dose computation results within each treatment planning system. However, all plans computed in this study were clinically acceptable and satisfied SABR protocol^{20,21}.

2.2.3 Plan Comparison

The dose distribution from planning in all the different techniques and one set of contours were transferred to MiM v.5.6.5 (MiM Software Inc., Cleveland, OH) for analysis purposes. The independent software allows for consistent and unbiased plan evaluation

based on dose volumetric histogram (DVH) parameters by using the same sampling algorithm. Parameters that characterize dose conformality, DVH statistics, and treatment delivery efficiency were obtained and compared. Further analysis to identify main difference amongst fixed beam, VMAT and HT was performed by grouping the most clinically appropriate plans SS-LM and SS-HM plans, RA and SA VMAT plans, and HT-2.5cm and HT-5cm plans. SW and HT-1cm were not included in the combined group analysis due to their inherent lack of efficiency^{18,22}.

2.2.3.1 Dose conformality

To evaluate dose fall-off from the PTV to normal tissue, the maximum dose at least two centimeters from the PTV, D_{2cm} , was calculated. For the PTV, the maximum and mean dose have been computed, and the conformality index was calculated for the 95% (CI_{95%}), 80% (CI_{80%}), and 50% (CI_{50%}) isodose levels according to the RTOG model defined by:

$$CI_{RI} = \frac{V_{RI}}{TV}$$

Where V_{RI} represents the volume covered by the reference isodose and TV is the volume of the PTV²³.

2.2.3.2 DVH statistics

The maximum point dose (D_{max}) to nearby critical organs at risk (OAR), such as the esophagus, spinal cord, heart, trachea, and proximal bronchus, was compared amongst all patients. Lung toxicity parameters analyzed include the absolute volume of normal lung covered by 50% of the prescription or more ($V_{50\%}$), predictive of fibrosis²⁴, the mean dose to the normal lung (MLD), the normal lung receiving 5, 10, 20, 27 Gy or more (V_{5Gy} , V_{10Gy} , V_{20Gy} , V_{27Gy} , respectively), and contralateral lung receiving at least 5, or 10 Gy (V_{5GyC} , V_{10GyC} , respectively).

2.2.3.3 Treatment delivery efficiency

The intensity gradients in IMRT planning were acquired using multiple MLC based control points. Increased modulation induces increased MLC travel, potentially causing a devaluation of the MLC track, requiring more frequent replacement. The total MLC travel

was compared between all fixed beam and VMAT plans. The total monitor units required for each treatment technique was analyzed to evaluate treatment efficiency. The treatment delivery time was simulated for each beam of the fixed beam and VMAT plans based on the dose rate for each segment. Plan automation, available with TrueBeam linear accelerators, was assumed to calculate time for gantry rotation in the FB treatment plans. Meanwhile, the treatment delivery time in HT treatment plans was estimated based on the pitch and monitor units, available in the DICOM header of the radiation plan dose files.

2.2.4 Statistical Analysis

All dosimetric parameters compared in this study were summarized by their respective means and standard deviation. Statistical analysis was performed in IBM SPSS v.20 (IBM SPSS Statistics for Windows, Armonk, NY) using Shapiro-Wilk normality tests followed by one-way analysis of variance. The data significantly deviates from a normal distribution if Shapiro-Wilk test was less than 0.05, and the null hypothesis was rejected. If the distribution was considered not normal, a non-parametric test, Kruskal-Wallis one-way analysis of variance, was utilized to find significance; followed by a Wilcoxon-Mann-Whitney test to find between-subject significance. Whereas, the data was considered normally distributed if the Shapiro-Wilk test was greater than 0.05 and the null hypothesis was accepted. For normally distributed parameters, a one-way analysis of variance (ANOVA) was computed to find significance followed by a Tukey's post hoc test to check for between-subject significances.

2.3 Results

Dose distribution for the eight various IMRT techniques compared in this study are displayed in Figure 2-1 for one patient, and the corresponding DVH of the PTV and normal lung tissue, the lung tissue minus the ITV, are provided in Figure 2-2. In the axial slice for all HT plans (Figure 2-1), the contralateral lung is covered by the 5 Gy or higher isodose volume. As the width of the fan beam in HT increases to the 5 cm plan, an increase in the low dose spillage is noticed in the superior-inferior direction shown in the coronal slice.



Figure 2-1. Dose distributions of the axial and coronal slice for each of the eight different planning techniques for patient 4, from top left to bottom right: SS-LM FB, SS-HM FB, SW FB, SA, RA, HT-1cm, HT-2.5cm, and HT-5cm.

HT planning achieved dose homogeneity in the PTV surpassing other techniques, as can be observed in the cumulative DVH (Figure 2-2); however, for SABR treatment, dose uniformity and lack of hot spots within the target is not an essential priority for ablative radiotherapy. Although hypoxic regions are irradiated with all IMRT techniques, the increased heterogeneity within the PTV is regarded as clinically desirable, and provides the ability to deliver inherently higher doses to potential hypoxic regions^{25–27}.



Figure 2-2. Cumulative DVH for patient 4 for the PTV (solid lines) and the normal lung tissue (dashed lines) obtained from the eight techniques used. All plans are normalized such that 95% of the PTV receives 54 Gy or more.

Table 2.2 summarizes the average and standard deviation (SD) of the ten patients for each of the parameters described in this study. Parameters for dose conformality, DVH related statistics, and treatment efficiency amongst different planning modalities are displayed along with between- and within-subject significance. Although every plan met the SABR COMET criteria²⁰, all HT techniques showed a significance decrease in the PTV D_{max} and mean dose compared to all other modalities in this study. This is further supported by the dose homogeneity seen in the PTV in Figure 2-2. On the contrary, there was a significant increase in conformality index, CI_{80%}, CI_{50%}, observed for the HT-5cm plan compared to all other modalities in contralateral V_{5Gy} was observed for all HT plans (p=0.002) compared to SS and VMAT. A significant increase in mean lung dose was attained for the HT-5cm plan (p=0.002). In both scenarios, RA&SA achieved the lowest values.

		SS- LM	SS-HM	SW	RA	SA	HT-1 cm	HT-2.5 cm	HT-5 cm	p- value
PTV	D _{max} (Gy)	$\begin{array}{c} 73.8 \pm \\ 4.1^{\mathrm{f},\mathrm{g},h} \end{array}$	${}^{65.8\pm}_{23.2^{\rm f,g,h}}$	$\begin{array}{c} 71.7 \pm \\ 3.3^{\rm f,g,h} \end{array}$	$71.2 \pm 3.8 _{\rm f,g,h}$	${}^{74.3~\pm}_{2.9^{f,g,h}}$	$62.9 \pm 2.4^{a,b,c,d,e}$	$\begin{array}{c} 63 \pm \\ 5.8^{a,b,c,d,e} \end{array}$	$64.1 \pm 7.4^{a,b,c,d,e}$	< 0.001
	Mean dose (Gy)	$62.6 \pm 1.9 _{\rm f,g,h}$	$62.5 \pm 1.9 _{\rm f,g,h}$	${\begin{array}{c} 62.5 \pm \\ 1.4^{\rm f,g,h} \end{array}}$	$62\pm1.5~^{f,g,h}$	$61.4 \pm 1.2^{\rm f,g,h}$	${58.7 \pm \atop {1.8^{a,b,c,d,e}}}$	$\begin{array}{c} 58.6 \pm \\ 3.4^{a,b,c,d,e} \end{array}$	$58.8 \pm 4.1^{a,b,c,d,e}$	< 0.001
	D _{2cm} (%)	58.6 ± 8	$58.4\pm6.8^{\circ}$	$62.4 \pm 5.5^{b,d}$	$53.2 \pm 4.3 _{c,e,h}$	60.5 ± 6^{d}	57.2 ± 6	58.7 ± 6.6	$60.9\pm6.7^{\text{d}}$	< 0.05
	CI95%	$\begin{array}{c} 1.28 \pm \\ 0.08^{h} \end{array}$	1.28 ± 0.08^{h}	1.3 ± 0.09	${1.23} \pm \\ 0.09^{\rm f,g,h}$	${1.23 \pm \atop 0.06^{f,g,h}}$	$1.37 \pm 0.13^{d,e}$	$1.35 \pm 0.14^{d,e}$	$1.43\pm0.19^{a,b,d,e}$	< 0.01
	CI _{80%}	$\begin{array}{c} 1.96 \pm \\ 0.23^{h} \end{array}$	1.97 ± 0.24^{h}	$\begin{array}{c} 1.88 \pm \\ 0.18^{h} \end{array}$	$1.78\pm0.2^{\rm h}$	$\begin{array}{c} 1.89 \pm \\ 0.19^{h} \end{array}$	1.96 ± 0.21^{h}	$\begin{array}{c} 2.07 \pm \\ 0.31 \end{array}$	$\begin{array}{c} 2.35 \pm \\ 0.47^{a,b,c,d,e,f} \end{array}$	< 0.01
	CI50%	$\begin{array}{c} 4.75 \pm \\ 0.77^h \end{array}$	$4.73\pm0.77^{\rm h}$	$\begin{array}{c} 4.75 \pm \\ 0.72^h \end{array}$	$4.31\pm0.75^{\rm h}$	$\begin{array}{c} 4.56 \pm \\ 0.84^h \end{array}$	$4.43\pm0.57^{\rm h}$	$\begin{array}{c} 4.92 \pm \\ 0.83^h \end{array}$	6.03 ± 1.38*	< 0.05
Cord	D _{max} (Gy)	14.3 ± 4	13.3 ± 3.9	15.8 ± 7.1	11.2 ± 3.2	11.2 ± 1.4	13.9 ± 5.2	13.7 ± 5.5	13.8 ± 5.2	> 0.05
Bronchus	D _{max} (Gy)	13.2 ± 9.3	13.4 ± 8.7	15.5 ± 10.8	16.2 ± 9.2	17 ± 11.1	17.2 ± 11.9	18.7 ± 13.9	19.6 ± 14	> 0.05
Esophagu s	D _{max} (Gy)	14.1 ± 6.3	14.1 ± 6.2	16.2 ± 8.5	14.9 ± 5.5	16.2 ± 6.4	15.6 ± 5.4	14.1 ± 3.9	14.4 ± 5.7	> 0.05
Heart	D _{max} (Gy)	14.5 ± 6.4	15 ± 6.7	17.9 ± 7.6	17.1 ± 7.2	18 ± 6.4	19.2 ± 10.9	18.4 ± 11.3	17.6 ± 10.2	> 0.05
Trachea	D _{max} (Gy)	$2.4\pm5.2^{\rm h}$	$2\pm4.3^{\rm h}$	1.5 ± 2.7	$1.1\pm2.1^{\rm h}$	1.5 ± 2.6	1.4 ± 2.4	1.7 ± 2.4	$2.7\pm3^{a,b,d}$	> 0.05
Total lung	MLD (Gy)	$4.8\pm1.3^{\rm h}$	$4.8\pm1.3^{\text{ h}}$	$4.9\pm1.4^{\ h}$	$4.7\pm1.2^{\rm \ h}$	4.6 ± 1^{h}	5.1 ± 1.3 ^h	5.8 ± 1.6	$7.1 \pm 1.7^{a,b,c,d,e,f}$	< 0.01
	V _{50%} (cm ³)	191 ± 78	189 ± 80	185 ± 77	172 ± 66	173 ± 67	179 ± 75	200 ± 83	250 ± 108	> 0.05

Table 2-2. Mean values \pm standard deviation of all parameters compared. A p-value < 0.05 determines significance.</th>

	V50% (%)	4.1 ± 1.6	4 ± 1.6	4 ± 1.5	3.7 ± 1.4	3.7 ± 1.3	3.8 ± 1.6	4.3 ± 1.7	5.3 ± 2	> 0.05
	$V_{20Gy}(\%)$	6.3 ± 2.3	6.2 ± 2.2	6.2 ± 2.4	5.9 ± 2.2	6 ± 2.1	5.9 ± 2.3	6.7 ± 2.6	8.3 ± 2.9	> 0.05
	V _{10Gy} (%)	$12.9 \pm 4.6_{h}$	$12.8\pm4.4^{\text{ h}}$	14.3 ± 5	13.9 ± 4.4	12.3 ± 2.7 h	14.1 ± 4.8	16.7 ± 6	$20.7\pm7^{a,b,e}$	< 0.01
	V _{5 Gy} (%)	$23.5 \pm 6.9 _h$	23.7 ± 6.9^{h}	$24.7 \pm 7.7_{h}$	22.9 ± 6.8^{h}	$22\pm 6.2^{g,h}$	29 ± 8.2^{h}	33.4 ± 9.1 ^e	$\begin{array}{c} 40.8 \pm 11.8 \\ _{a,b,c,d,e,f} \end{array}$	< 0.001
Cont. lung	V _{10Gy} (%)	0.9 ± 1.7	0.8 ± 1.4	2.8 ± 4.1	0.4 ± 1	0.4 ± 0.7	1.4 ± 2	1.5 ± 2.1	1.9 ± 2.5	> 0.05
	V5 Gy (%)	$\begin{array}{c} 7.9 \pm \\ 6.6^{\mathrm{f},\mathrm{g},\mathrm{h}} \end{array}$	$8.4\pm6.1^{\rm f,g,h}$	10.8 ± 8	$6.6\pm7.6^{f,g,h}$	$7.4\pm7^{f,g,h}$	${18.9 \pm \atop {10.9^{a,b,d,e}}}$	$19 \pm 11.2^{a,b,d,e}$	$21\pm15.2^{\text{a,b,d,e}}$	< 0.01
Efficiency	MLC Motion (cm)	837 <u>+</u> 509	3170 <u>+</u> 1475 ^{a,c,d,e}	1279 <u>+</u> 563 ^b	1184 <u>+</u> 341 ^b	960 <u>+</u> 310 ^b	N/A	N/A	N/A	<0.00 1
	Monitor Units	$\frac{3823 \pm}{792^{b,c,d,f,g}}$	$\begin{array}{c} 4946 \pm \\ 1226^{a,c,e,f} \end{array}$	$\frac{8288 \pm}{3412^{a,b,d,e,f}}$	$\begin{array}{l} 4782 \pm \\ 655^{a,c,e,f} \end{array}$	$\begin{array}{l} 4023 \pm \\ 678^{b,c,d,f} \end{array}$	$\frac{11208 \pm}{1510^{a,b,c,d,e,h}}$	7047 ± 4407 ^a	$5457\pm3451^{\rm f}$	< 0.001
	Delivery time (min)	$2.5\pm0.3^{\ast}$	$3\pm0.5^{\ast}$	$\begin{array}{c} 4.4 \pm \\ 1.4^{a,b,d,e,f,g} \end{array}$	$\begin{array}{c} 2 \pm \\ 0.3^{a,b,c,f,g,h} \end{array}$	$\begin{array}{c} 1.9 \pm \\ 0.2^{a,b,c,f,g,h} \end{array}$	$\begin{array}{c} 13.2 \pm \\ 1.8^{a,b,c,d,e,h} \end{array}$	$\begin{array}{c} 8.3 \pm \\ 5.2^{a,b,c,d,e} \end{array}$	$6.4\pm4.1^{a,b,d,e,f}$	< 0.001

To further emphasize estimated treatment delivery time amongst all techniques, a significant increase was observed in all HT, and SS plans compared to SA; however, a statistically significant difference is not found between RA&SA (p=.393) (Figure 2-3).





In the overall MLC travel comparison, SS-HM required significantly more MLC motion than all other modalities compared, as shown in Figure 2-4. SA resulted in the lowest MLC travel time, and therefore, least amount of potential degradation on the MLC track, compared to all other techniques, albeit, significance was not detected.



Figure 2-4. Box plot of the total MLC traveled in each plan in millimeters for all treatment modalities compared. For each plot, the median is displayed by the central line, the upper and lower border of the rectangle represent the 75th and 25th percentile or interquartile range, and the whiskers represent the extreme data points not considered outliers. Outliers were illustrated by 'o' and significance was shown by '*.'

In the two VMAT techniques, RA displayed significantly superior D_{2cm} , dose fall-off parameter, to SA (p=0.011), whereas total monitor units significantly increased (p=0.043). However, VMAT showed improved overall treatment quality and efficiency compared to all other modalities with SA achieving optimum efficiency.

Further analysis to identify main differences amongst fixed beam, VMAT and HT was completed by grouping the SS-LM and SS-HM plans, RA and SA VMAT plans, and HT-2.5cm and HT-5cm plans (Table 2.3). SW and HM-1cm treatment plans were not included in this analysis based on poor performance in efficiency parameters, while dose distribution was not improved, as observed in Table 2.2. A significant reduction in maximum dose to the spinal cord was observed in the VMAT plans (p=0.017) compared to the SS. Although not statistically significant for the remainder of the parameters, a reduction was found between SS and VMAT (other than esophagus, bronchus and heart). When comparing SS

to HT, target conformality (CI_{95%}) significantly improved in the SS plans (p=0.015), at the cost of the target mean and maximum dose which was significantly reduced in the HT plans (p<0.001). Similarly, target mean and maximum dose (p<0.001) showed a significantly reduction in the HT plans compared to the VMAT plans while all three target conformality parameters significantly improved with VMAT (p<0.05 for all). In the DVH parameters, maximum dose to the trachea and normal lung, V_{10Gy} and V_{5Gy} , contralateral lung V_{5Gy} , and mean lung dose significantly reduced using both the SS and VMAT treatment planning compared to HT. These differences show that patients treated with SS or VMAT may be less susceptible to radiation-induced lung toxicities compared to HT treated patients. Estimated treatment delivery time was significantly reduced with VMAT plans compared to all other techniques (p<0.001).

Table 2-3. Significance for each parameter studied between grouped SS, VMAT, and HT (significance identified when p<0.05).

			p-value	
		SS & VMAT	SS & HT	VMAT & HT
PTV	D _{max} (Gy)	0.957	< 0.001	< 0.001
	Mean dose (Gy)	0.213	< 0.001	< 0.001
	D _{2cm} (%)	0.978	0.168	0.152
	CI95%	0.058	0.015	< 0.001
	CI _{80%}	0.117	0.055	< 0.001
	CI _{50%}	0.176	0.083	0.003
Cord	D _{max} (Gy)	0.017	0.507	0.323
Bronchus	D _{max} (Gy)	0.611	0.218	0.742
Esophagus	D _{max} (Gy)	0.686	0.993	0.755
Heart	D _{max} (Gy)	0.152	0.552	0.552
Trachea	D _{max} (Gy)	0.626	0.004	0.020
Total lung	MLD (Gy)	0.561	0.005	0.001
-	V _{50%} (cm ³)	0.779	0.369	0.113
	V _{50%} (%)	0.756	0.341	0.093

	$V_{20Gy}(\%)$	0.918	0.247	0.119
	V _{10Gy} (%)	0.990	0.002	0.002
	V _{5 Gy} (%)	0.898	< 0.001	< 0.001
Cont. lung	V _{10Gy} (%)	0.778	0.091	0.044
	V _{5 Gy} (%)	0.204	< 0.001	< 0.001
Efficiency	MLC Motion	0.123	N/A	N/A
	Monitor Units	0.607	0.516	0.787
	Delivery time (min)	< 0.001	< 0.001	< 0.001

2.4 Discussion

In this study, all 80 IMRT plans generated conformal dose distributions and provided clinically acceptable plans according to the guidelines of RTOG 0618 and our in-house protocol based on SABR-COMET. Various IMRT planning techniques for treating SABR were compared to conclude which IMRT modality is propitious by proving the most favorable dose conformality, DVH parameters and treatment efficiency. In this study, VMAT planning, RA and SA, provided for the optimal trade-off in treatment efficiency and dose coverage. The inherent rotational nature of VMAT and tomotherapy treatment planning optimization allows for greater degrees of freedom compared to fixed beam and, therefore, should lead to higher quality radiation therapy treatment plans. Furthermore, the application of a broad beam in VMAT compared to a thin fan beam in tomotherapy, led to significantly improved treatment delivery efficiency. In treatment planning studies, Pareto efficiency should be achieved using multi-criteria optimization to ensure accurate planning comparison²⁸. However, this technique was not available during the course of this study. To overcome the lack of multi-criteria optimization, each treatment plan was computed by a certified dosimetrist or by the application of a clinically acceptable protocol.

Several other studies have investigated the role of different IMRT treatment techniques in the treatment of early stage NSCLC with SABR to reduce lung toxicities^{29,30}. Kannarunimit et al.²⁹ compared three SABR treatment techniques robotic surgery, RA and HT plan for

treatment of central lung with SABR. They concluded that HT and VMAT provided more efficient treatment delivery and higher target dose homogeneity while robotic surgery and VMAT provided a lower risk of radiation-induced lung pneumonitis, with VMAT yielding the lowest risk in cases of large PTV coverage. During hypofractionated radiation treatment, sharp dose gradients outside the PTV are desirable, hot spots in the center of the PTV are invoked to aid a dose fall off outside the PTV^{25-27} . Alluding to dose homogeneity parameters not being included in the study, where traditionally HT planning excels. The findings on the reduction of radiation-induced pneumonitis during VMAT plans by Kannarunimit et al. were further supported by our study where RA and SA demonstrated the lowest risk of radiation pneumonitis by having the lowest MLD and V_{20Gy} values. A significant reduction in MLD was found when grouping both VMAT techniques and comparing to HT (p<0.001); however, no significant difference was found between the two VMAT techniques³¹. For further analysis of radiation-induced lung toxicity, our study investigated the reduction in the risk of fibrosis amongst the different treatment planning techniques ($V_{50\%}$); VMAT achieved reduced $V_{50\%}$ values. However, the differences in $V_{50\%}$ were not found to be statistically significant.

Weyh et al.³⁰ compared RA, HT and fixed beam for SABR treatment to lesions in the peripheral lung to conclude RA and fixed beam plans were equivalent but the reduction in treatment time with RA makes them more preferable. This study has supported their work and furthermore, our results demonstrate a decrease in all normal lung DVH parameters in RA and SA, albeit not significant. Weyh et al. executed their study in eight patients for a total of 24 treatment plans, whereas this study expands on validating different treatment methods within FB, VMAT and HT compromising of 80 treatment plans. Treatment plans, in both Weyh et al. ³⁰ and Kannarunimit et al. ²⁹, were generated using traditional beams with flattening filter (FF) and analytical anisotropic algorithm (AAA) dose calculation algorithm. Whereas in this study, FFF beams were utilized in all linear accelerator based plans. Studies have shown that FFF treatment planning provides equivalent dose distribution to FF beams while significantly reducing treatment delivery time and increasing dose distribution conformity¹⁶. AXB dose calculation algorithm, computed in this study for Eclipse treatment planning in RA and SW plans, has been shown to generate treatment plans comparable to x-ray voxel Monte Carlo (XVMC) developed by

BrainLab¹⁴. Moreover, AXB allows for faster computational time to XVMC, while maintaining higher accuracy when dealing with tissue heterogeneity in the lung compared to AAA.

An important parameter when considering IMRT treatment, degradation of the MLC carriage due to MLC motion required during treatment delivery. The jaw opening in the field sizes in all treatment plans ranged between 4-cm to 9-cm to surround the PTV but limit MLC motion. Even though a significance was only found when comparing each of the techniques to SS-HM, within the VMAT techniques, there was a reduction in MLC motion for the SA in nine of ten patients compared to RA. SA based treatment planning could result in a longer lifespan of the MLC carriage.

The limited number of patients used in this study may have led to insufficient statistical power to show significance between some of the parameters analyzed. The statistical power of 0.76 was measured using ANOVA repeated measures in G-power v. $3.1.9.2^{32}$.

Although other various treatment modality comparison studies have been conducted for the treatment of NSCLC with SABR, to the best of our knowledge, there are not any other studies comprehensively covering a wide range of different IMRT techniques from various commercial vendors. In this study, the most up to date treatment planning using FFF beams to reduce significantly treatment times was used for both fixed beam and VMAT planning.

2.5 Conclusion

In the treatment of early-stage NSCLC patients with SABR, this study has demonstrated VMAT treatment planning techniques to have the optimal trade-off between dose conformality and sparing normal tissue, and treatment efficiency. Although all plans were clinically acceptable, VMAT outperformed HT in all parameters measured, and statistical superiority was observed in 12 parameters when comparing grouped VMAT and HT techniques. In the comparison between SS and VMAT techniques, an increase in dose to the heart, esophagus and bronchus, was observed, although insignificant. VMAT was dosimetrically advantageous in all other parameters while providing significantly shorter treatment times than any other modality studied.

RA and SA VMAT techniques performed comparably; RA displayed significantly sharper dose fall off while SA optimization was statistically more efficient.

2.6 References

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Chapter 3

3 The potential for respiratory-gated VMAT to reduce normal lung toxicity in SBRT patients

This chapter is adapted from research paper entitled "Dosimetric planning study of respiratory-gated volumetric modulated arc therapy for early-stage lung cancer with stereotactic body radiation therapy" published in Practical Radiation Oncology vol. 5 (3): pp. 156-61 (2015) by Xhaferllari I, Chen JZ, MacFarlane M, Yu E, Gaede S.

3.1 Introduction

Non-small cell lung cancer (NSCLC) continues to be the leading cause of cancer death. Twenty percent of NSCLC diagnosed are in early-stage and it continues to rise due to better diagnostic techniques¹. Common treatments for early-stage NSCLC are surgery and radiation therapy. Patients undergo radiation therapy if they are inoperable or refuse surgery. To provide inoperable patients comparable treatment, early-stage lung tumors are treated with strereotactic ablative body radiotherapy (SABR), a technique of high precision radiation therapy where high doses (54 - 60 Gy) are delivered in fewer fractions (three to eight)². Studies have demonstrated SABR to have comparable local control and regional reoccurrence to surgery³. Local control in 3 years surpasses 90% and the 3-year survival is 84.7% for early-stage NSCLC patients treated with SABR⁴.

However, in lung cancer radiotherapy, respiratory motion may have large impact on the dose to both the tumour and the normal lung. Studies have shown the magnitude of motion is variable and unpredictable between patients and within a patient over treatment days^{5–9}. Respiratory motion, in conjunction with the complexity of intensity-modulated radiation therapy (IMRT) delivery, can lead to the interplay effect, caused by the asynchronous movement of the tumor and the multi-leaf collimator (MLC)^{10,11}. Beam-intensity gradients are defined by MLC and the target may move in and out of these gradients. This movement is not accounted for in the treatment planning systems.

In lung radiotherapy, a method of accounting for respiratory motion is to create a full motion encompassing margin called the internal tumor volume (ITV) with the aid of four-

dimensional computed tomography (4D-CT)¹². When motion is considered "significant", breathing motion management technique such as respiratory gating, abdominal compression, voluntary/involuntary breath hold technique, or tumor tracking can be used¹³.

In recent years, volumetric modulated arc therapy (VMAT) has been implemented in many centers for the treatment of SABR for early-stage NSCLC and has shown to provide better normal tissue sparing to critical organs while maintaining proper dose coverage to the target¹⁴. The Varian TrueBeamTM System (Varian Medical Systems, Palo Alto, CA) has an integrated respiratory gating and motion management system using an external surrogate, allowing for the delivery of respiratory gated VMAT. To increase treatment efficiency, respiratory-gated VMAT can be delivered with flattening filter free mode (FFF) for both 6 MV and 10 MV beams, allowing for dose rates four times greater than previously available. Another feature of the TrueBeamTM System is advanced image guidance, allowing for gated kV imaging before or during treatment. Typically, prior to respiratory gated VMAT treatment, a free breathing cone-beam CT is acquired for anatomical verification of patient setup, followed by orthogonal gated kV imaging to verify the gating window by comparison with the digital reconstructed radiographs produced during planning.

This paper investigates the potential dosimetric advantage of combining respiratory gating and VMAT using FFF beams for treating early-stage NSCLC with SABR.

3.2 Materials and Methods

3.2.1 Patient Selection

In this study, 4D-CT scans from twenty early-stage NSCLC patients with respiratory tumor motion greater than 5 mm peak-to-peak were randomly selected from recent patient data. Table 3-1 displays the patient demographics and the calculated centroid tumor motion.

	Tumor location	3D Motion (cm)			Free	Gated	
Patient		Sup/Inf	Ant/Post	Lat	ITV size (cm^3)	ITV size (cm ³)	Gating window
1	RLL^*	3.0	1.3	0.8	22.1	13.2	40% - 60%
2	RLL	3.0	1.3	0.0	17.2	5.6	40% - 70%
3	RLL	2.8	0.8	0.3	22.6	10.7	30% - 60%
4	RLL	2.6	0.7	0.6	4.8	1.6	40% - 70%
5	RLL	1.9	0.5	0.3	35.2	17.2	40% - 70%
6	LLL^\dagger	1.7	0.2	0.1	40.9	27.3	30% - 60%
7	RLL	1.6	0.9	0.1	27.7	16.8	40% - 70%
8	RLL	1.6	0.4	0.1	26.7	18.3	30% - 60%
9	LLL	1.4	0.3	0.2	143.1	113.0	30% - 60%
10	RLL	1.3	0.2	0.2	53.1	37.5	40% - 70%
11	RML§	1.2	0.1	0.2	16.2	9.9	40% - 70%
12	RUL [‡]	1.0	0.9	0.2	16.6	10.3	30% - 60%
13	RLL	1.0	0.2	0.2	17.3	11.6	30% - 60%
14	RLL	0.9	0.6	0.1	97.8	68.7	30% - 70%
15	RML	0.9	0.3	0.1	48.8	31.0	30% - 60%
16	LLL	0.6	0.2	0.2	10.2	6.1	40% - 70%
17	LUL	0.6	0.1	0.2	4.4	3.1	40% - 70%
18	LLL	0.5	0.2	0.1	3.9	2.7	30% - 60%
19	RUL	0.4	0.5	0.2	27.9	16.3	30% - 70%
20	LLL	0.3	0.2	0.7	3.4	2.1	40% - 70%

Table 3-1. Patient tumor location, motion, size, and the gating window used in the study.

Abbreviations: ^{*}RLL-Right Lower Lobe; [†]LLL-Left Lower Lobe; [§]RML-Right Middle Lobe; [‡]RUL-Right Upper Lobe; ^{II}LUL- Left Upper Lobe

3.2.2 Treatment planning

Each patient was retrospectively planned with gated and non-gated VMAT using SmartArc technique on Pinnacle treatment planning system version 9.0 (Philips Radiation Oncology, Fitchburg, MA) and the dose was calculated using collapsed cone convolution. SmartArc is a VMAT optimization system developed by Philips Radiation Oncology Systems in collaboration with RaySearch Laboratories AB (Stockholm, Sweden)¹⁵. The non-gated VMAT plans were generated using the average intensity projection CT images encompassed by the entire 4D-CT dataset. The ITV in the non-gated VMAT scenario was defined as the envelope of the GTV delineated in all 10 phases of the respiratory cycle. The gated VMAT plans were generated using a subset average of the intensity projection CT images encompassed by only those phases which lie within the intended gating window. The gating window was chosen based on the analysis of the 4D-CT images to provide the optimal trade-off between an increase in treatment time and a decrease in motion, keeping residual motion in the gating window within 3 mm. The gating window for each patient is listed in Table 3-1. The ITV, in the gated case, was defined as the envelope of the GTVs delineated in the phases defined by the subset average CT. For both gated and non-gated scenarios, a five millimeter margin was added to account for set-up uncertainties, defining the planning target volume (PTV).

Each VMAT plan consisted of two 225 degree arcs, one clockwise and one counterclockwise, with beam energy of 10X FFF and a maximum dose rate of 2400 MU/min. The dose prescription was based on the tumor location; for tumors near or adjacent to the chest wall, a dose of 55 Gy in 5 fractions was prescribed, whereas for all other cases, a dose of 54 Gy in 3 fractions was prescribed. The prescription was set according to RTOG 0618, 100% of the dose to 95% volume of the PTV. All dosimetric parameters satisfied the requirements of our in-house SABR protocol^{16–18}. In order to avoid dosimetry bias between the gated and non-gated plans, a Pinnacle planning script was generated and used to optimize all 40 plans. The planning script generated the beams required according to the location of the target, set IMRT optimization parameters, and then optimized using Pinnacle's direct machine parameter optimization (DMPO) for 25 iterations (Appendix A). After the plan was completed, minor adjustments were sometimes

necessary to satisfy limits of dose to normal structure and target. Any adjustments performed on one of the patient's plan were repeated for their other respective plan.

3.2.3 Statistical Analysis

The main normal lung parameters considered in this study were V_{20Gy} , the percent volume of the normal lung minus the ITV receiving at least 20 Gy and $V_{50\%}$, the absolute volume of lung minus the ITV receiving at least 50% of the prescription dose. In studies, V_{20Gy} has shown to be a predictive of pneumonitis¹⁹ while $V_{50\%}$ is an important parameter used to control the amount of intermediate dose spillage, and hence, the total volume of potential irreversible fibrosis^{16–18}. Other common lung parameters considered were: contralateral V_{5Gy} , the percent volume of contralateral lung receiving at least 5 Gy, MLD, mean normal lung dose and D_{2cm} , the maximum dose that is 2 cm away from the PTV. D_{2cm} is a useful parameter representing the extent of dose falloff outside the PTV, which is crucial for lung SABR¹⁸. The total number of monitor units (MU) necessary to deliver each plan was also compared. Other parameters compared were the maximum dose to nearby critical organs such as the cord, esophagus, heart, bronchus, and trachea, and the ITV and PTV size.

To test for significance, initially Shapiro-Wilk tests were done to check for normality. If the significance value is less than 0.05, then the null hypothesis is rejected and the parameter values were not normally distributed; whereas if it is above 0.05, the null hypothesis was accepted and the parameter was normally distributed. Based on the Shapiro-Wilk test, the volumes of the ITV and PTV, and the maximum dose to the trachea were not normally distributed. Consequently, tests of significance for these parameters were performed using the Wilcoxon–Mann–Whitney non-parametric test. Paired t-test was performed for all other parameters.

3.3 Results

For each plan, target coverage and organ sparing was achieved according to the requirements of our in-house SABR protocol by using a Pinnacle planning script with some adjustments. However, there were significant differences in the dose distributions due to

the differences in PTV sizes between the gated and non-gated VMAT plans. The dose distribution for both gated and non-gated VMAT plans for one patient are shown in Figure 3-1 in the transverse and coronal planes through the isocenter. The volume covered by the 100% of the prescription, 54 Gy, and 50% of the prescription, 27 Gy, is noticeably greater in the non-gated case than the gated case.



Non - Gated

Gated

Figure 3-1. Dose distribution for a non-gated VMAT plan (left) and gated VMAT plan (right) in the transverse and coronal planes. The isodose line of 54 Gy, and 27 Gy are shown in white and black respectively, while the planning target volume is the black contour.

Figure 3-2 compares V_{20Gy} amongst the 20 patients. The use of gating significantly reduced V_{20Gy} from (6.05 + 2.06)% to (5.21 + 1.75)% (p=0.00004).

Figure 3-3 compares V_{50%} amongst the 20 patients. The use of gating significantly reduced V_{50%} from (158.17 \pm 61.12) cm³ to (125.71 \pm 49.46) cm³ (p=0.00002).



Figure 3-2. Comparison of the percent of the lung volume receiving at least 20 Gy (V_{20Gy}) for both the non-gated and gated VMAT plans for all 20 patients.



Figure 3-3. Comparison of the volume of lung receiving 50% of the prescription dose between gated and non-gated VMAT plans for all 20 patients.

Table 3-2 compares each parameter considered in this study with their respective mean values and corresponding p-value. A decrease is seen in all the parameters between non-gated and gated VMAT plans. A significant p-value was found for the difference of each

parameter between gated and non-gated VMAT plans except for the maximum dose to critical structures.

Motrio	Non -	Catad	n voluo	Tests of Normality			
Metric	gated	Galeu	p-value	Shapi	Shapiro-Wilk		
				Gated	Non - gated		
ITV^*	32.00 cm^3	21.13 cm ³	< 0.001	0.000	0.000		
PTV^\dagger	71.61 cm ³	50.54 cm ³	< 0.001	0.000	0.001		
$D_{2cm}{}^{\ddagger}$	61.38%	59.27%	0.007	0.625	0.197		
$V_{20Gy}{}^{\$}$	6.05%	5.21%	< 0.001	0.178	0.292		
$\mathbf{V}_{50\%}{}^{ll}$	158.17 cm ³	125.71 cm ³	< 0.001	0.054	0.553		
$V_{5Gy}\P$	14.10%	11.59%	< 0.001	0.139	0.159		
Cord dose	11.35 Gy	11.19 Gy	0.895	0.006	0.904		
Esophagus dose	14.87 Gy	14.27 Gy	0.278	0.297	0.491		
Bronchus dose	15.59 Gy	15.44 Gy	0.814	0.115	0.039		
Trachea dose	3.83 Gy	3.44 Gy	0.059	0.000	0.000		
Heart dose	18.2 Gy	17.38 Gy	0.121	0.325	0.642		
MLD [#]	455.24 Gy	408.02 Gy	< 0.001	0.176	0.667		
MU**	3707.7	3434.9	0.003	0.981	0.942		

Table 3-2. Mean values and statistics for each of the parameters studied.

Abbreviations: ^{*}ITV - Internal Target Volume; [†]PTV - Planning Target Volume; [‡]D_{2cm} - Percent ratio of the dose 2 cm away from the PTV to the prescription; [§]V_{20Gy} - Percent volume of healthy lung receiving 20 Gy or more; ^{II}V_{50%} - Absolute volume of healthy lung receiving 50% of the prescription; [¶]V_{5Gy} - Percent volume of contralateral lung receiving 5 Gy or more; Critical organ dose – maximum dose to that organ; [#]MLD - Mean Lung Dose; ^{**}MU - Monitor Units

3.4 Discussion

Several studies have investigated the benefits of VMAT in providing accurate target dose while sparing normal tissue in lung radiotherapy ^{20,21}. However, one of the largest sources of dosimetric error in NSCLC treatment, including VMAT, is respiratory motion. Respiratory gating is one method of managing respiratory motion. Respiratory gated VMAT is now possible with TrueBeamTM and previous studies have shown that gated VMAT delivery with TruebeamTM can be performed accurately^{22,23}.

This study is demonstrating the potential clinical benefits of respiratory-gated VMAT with FFF beams in reducing lung toxicities associated with SABR for early stage lung cancer. Reducing margins of the target volume by using respiratory gating can aid in sparing of normal tissue while maintaining clinically feasible treatment times. A predictor for early toxicity seen in the lung, pneumonitis, is the percent volume of the lung receiving 20 Gy (V_{20Gy}) ; the lower the V_{20Gy} , the lower the risk. We have shown the use of respiratory-gated VMAT can significantly reduce V_{20Gy} and $V_{50\%}$ compared to non-gated VMAT, commonly used in clinics worldwide. It should be taken into account that the ITV in the non-gated case contains normal lung volume not accounted for in the calculation of $V_{50\%}$ and, therefore, the values received represent an underestimation of the true values in the non-gated case. Also, the volume of lung during full breathing cycle is greater than the volume of lungs in the end-exhale.

In Table 3-2, the max dose of other normal tissues such as cord, esophagus, heart, bronchus, and trachea decreased in respiratory gated VMAT compared to non-gated VMAT, albeit not significantly. A greater maximum dose reduction in critical organs was seen in cases where the tumor was proximal to these critical organs. In all other cases, the reduction in margin did not result in a significant difference. Otherwise, all the parameters studied have shown to be significantly decreased when gated VMAT planning is performed. In general, the doses to critical organs are expected to decrease with respiratory gating because of the reduction of the PTV volumes with gating. The dose falloff parameter, D_{2cm} , significantly decreased with gated VMAT, meaning less normal tissue being exposed to higher doses. Dose spillage or the percent of contralateral lung receiving at least 5 Gy, V_{5Gy} , significantly decreased with gated VMAT.

A disadvantage to respiratory gating is increase in the treatment time. However, FFF-based treatment reduces gated treatment times with higher dose rates. Treatment time was estimated based on the planning dosimetric values, monitor units, dose rate and gating window. On average, each non-gated VMAT treatment requires 1.5 minutes whereas gated VMAT treatment requires 4.7 minutes. However, based on the electronic treatment records for 30 fractions of patients treated clinically with 10X-FFF SABR VMAT, treatment time for respiratory gated VMAT was increased by a factor of 2.3 compared to non gated VMAT delivery. A study by Malinowski et al showed changes in the spatial relationship between tumour and surrogate marker occurred mostly in 30-minute treatment fractions; however, as we showed above, typical respiratory gated SABR VMAT treatments with FFF beams have significantly lower treatments times, a tenth of the values reported in the study²⁴.

Figure 3-2 and Figure 3-3 shows cases of patients, 16, 17, 18, and 20, where gated VMAT may not be necessary since there is only a slight difference in reduction of normal lung dose; the p-values for $V_{20 \text{ Gy}}$ and $V_{50\%}$ difference for these four patients are 0.286 and 0.040 respectively. This lack of reduction in normal lung dose may be due to the target in each of these plans not being located centrally in the lung. Also, the paucity of motion may contribute, in each of these cases, maximum target motion in any direction is less than 6 mm; there is only one other patient with motion of similar magnitude as seen in Table 1. The slight increase in sparing of lungs may not outweigh the increase in treatment time during gated treatment, inferring that gating is not necessary for all patients.

A weakness of this study was that treatment planning for non-gated cases was performed on the average intensity projection from the full 4D-CT dataset, and not using 4D dose accumulation. However, a study by Li et al showed that there was no significant difference in both the target and normal tissue dose distribution using 3D or 4D dose calculation²⁵. Also, since the definition of normal lung in this study was lung-ITV, we are actually underestimating the dose to the normal lung, as mentioned earlier, thereby increasing the necessity for motion management strategies such as respiratory gating.

3.5 Conclusion

This dosimetric planning study has shown that respiratory gated VMAT using flattening filter free technology has the potential to reduce dose to normal lung compared to free breathing VMAT, without greatly compromising treatment delivery time. There was a significant decrease in normal lung V_{20Gy} and $V_{50\%}$, both of which are important parameters to consider when minimizing the risk of radiation-induced lung toxicity.

3.6 References

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Chapter 4

4 The use of on-board kV imaging during respiratory gated VMAT delivery to evaluate the correlation between tumour motion and external surrogate motion in patientspecific waveforms

This chapter is based on a research paper entitled "The use of on-board kV imaging during respiratory gated VMAT delivery to evaluate the correlation between tumour motion and external surrogate motion in patient-specific waveforms" by Xhaferllari I, Stevens T, El-Sherif O, Gaede S to be submitted to the Medical Physics journal.

4.1 Introduction

Respiratory motion leads to significant uncertainties in the treatment of thoracic and abdominal tumors with radiation therapy¹. Respiratory gating is one method used to limit intra-fractional breathing motion, resulting in reduced target margins and radiation-induced lung toxicities^{2–4}. The gating window can be determined based on either the amplitude or phase of the periodic external surrogate motion waveform. The gating threshold in amplitude based gating is defined on motion displacement relative to the baseline, the mean motion at end-exhale calculated during the learning of the respiratory motion⁵. Whereas, gating thresholds in phase gating are defined as two angular positions of the respiratory waveform⁵. Of these two techniques, amplitude gating has demonstrated to be more reliable when tracking irregular respiratory motion over time^{6–8}. Phase gating assumes constant periodicity in respiratory breathing motion, and can lead to substantial targeting errors for irregular non-periodic waveforms⁹. Variabilities in respiratory waveform to the same phase during phase-based respiratory gating.

In respiratory gating, predictive filters are employed to control for irregular, non-periodic breathing by setting a threshold of periodicity for triggering the beam on¹⁰. The breathing waveform recorded during 4D-CT acquisition is used as a reference for radiation treatment. The threshold applied to the predictive filter aids in restricting inaccurate treatment
delivery by triggering the beam off when the motion does not match the 4D-CT reference within the specified threshold.

The main uncertainty in respiratory gated treatment lies in the assumption that an external surrogate can accurately predict the internal motion of the target. Respiratory gated treatments are susceptible to baseline changes during treatment and overall variability in intrafraction tumor motion⁹. Intrafraction motion variability may invoke a phase shift between the external trace and the internal target motion. In gated delivery of lung cancer, this can lead to discrepancies in dose delivery, with some target volumes being on the verge of under-dosage^{11,12}. Previous studies have investigated the correlation between the motion of external markers and internal targets during 4D-CT acquisition^{13–15}, before treatment^{16–18}, and with the use of ultrasound¹⁹ or fiducial markers^{18,20,21}.

Respiratory gated volumetric modulated arc therapy (VMAT) is a method used to treat early-stage non-small cell lung cancer (NSCLC) with stereotactic ablative body radiotherapy (SABR). However, the impact of multiple gantry "starts and stops" as well as multiple dose rate "ramp-ups and ramp-downs" during high dose rate respiratory-gated VMAT on the internal/external correlation and, subsequently, the dose to the target is unclear. The increase in treatment delivery complexity may cause latencies in machine response and recording external motion. The goal of this study is to examine the utility of using on-board kV imaging to: 1) determine the correlation of external surrogate motion and internal target motion during ungated, amplitude gated, and phase gated VMAT delivery using flattening filter free (FFF) beams ; and 2) identify known phase shifts between the internal and external trace.

4.2 Methods

4.2.1 Study subjects

From our institutional database, five previously treated early-stage NSCLC real patient breathing (RPB) traces were selected, along with a sinusoidal trace, to represent variable breathing patterns and a range of motion irregularity. For early-stage NSCLC patients, the breathing trace was acquired from the Real-Time Position Management (RPM) suite (Varian Medical Systems, Palo Alto, CA) during CT simulation. The RPM motion trace file specifies a flag indicating acquisition of 4D-CT imaging. The portion of the respiratory motion waveform represented by the 4D-CT acquisition flag was extracted. The gross target volume, (GTV), was contoured on all ten 4D-CT phases using MIM software version 6.3 (Mim Software Inc., Cleveland, OH). The centroid coordinates of the GTV contour were identified in each of the 4D-CT phase using MIM software, and the total motion of the GTV in the superior-inferior direction was calculated based on variability between phases. The respiratory breathing trace extracted from the RPM system was scaled to the total calculated motion of the GTV to represent the real-patient full respiratory cycle.

The variability in target displacement at consecutive end-exhalation phases was calculated in each RPB waveform to determine motion irregularity. High standard deviation in the end-exhale position represented irregular breathing while low standard deviation represented periodic, regular breathing. In addition to the five real-patient breathing traces, a sinusoidal waveform with 1.5 cm peak-to-peak motion, and four second period was included in the study (patient 6). Variability in motion pattern was defined as periodic for regular RPB and sinusoidal trace, exhibiting a baseline drift if the position of the baseline was slowly veering, and defined as baseline shift for patients exhibiting sudden changes in displacement of the baseline position. Table 4-1 demonstrates characteristics of the patients analyzed.

Patient	Centroid tumor motion (cm)	Standard Deviation (cm)		Motion	
		End-Inhale	End-exhale	Irregularities	
1	1.23	0.092	0.017	Periodic	
2	1.02	0.254	0.060	Baseline drift	
3	0.93	0.219	0.127	Baseline shift	
4	0.73	0.168	0.170	Baseline shift	
5	0.60	0.300	0.179	Baseline drift	
6	1.50			Periodic	

 Table 4-1. Selected subjects motion characteristics

4.2.2 Treatment planning and delivery

RPB traces were acquired corresponding to previously treated patients from our in-house respiratory gated SABR protocol. All treatment plans corresponding to these patients were optimized using SmartArc VMAT technique in Pinnacle Treatment Planning system v9.6 (Philips Medical Systems, Fitchburg, MA) and consisted of two 225⁰ arcs.

The Varian TrueBeam linac version 2.0 with the integrated respiratory gating system, operating in Research Mode (Varian Medical Systems, Palo Alto, CA), was used for treatment delivery due to its ability to design customized beam and imaging trajectories. Here, the axes of the treatment delivery, such as the gantry, collimator, couch, and MLC, and imaging points are user controlled and programmed as a function of cumulative control points. Research Mode trajectories were written in an extensible markup language (XML) and allowed for modification of the partial 225° arcs from the original VMAT treatment plans. Namely, simultaneous kV imaging was added to the VMAT arc. These plans were then delivered to the Quasar programmable respiratory motion phantom (Modus Medical Devices, London, ON). The Quasar programmable respiratory motion phantom contained a cedar insert with an embedded 3 cm delrin sphere, to simulate healthy lung with a tissuelike tumour. The internal trace was extracted from the superior-inferior motion of the insert. Meanwhile, the external trace was obtained from the respiratory gating box, placed on a platform stage with vertical motion (Figure 4-1). The phantom operates using a circular shaped cam for sinusoidal motion, and another cam for typical respiratory cycle to drive both the platform stage and insert. The Quasar motion phantom was programmed according to the real-patient one-dimensional breathing trace derived above.²²



Figure 4-1. Quasar programmable respiratory motion phantom, depicting the moving cedar insert with an embedded delrin sphere (internal motion) and the platform stage for the respiratory gating box (external motion).

Treatment delivery was performed under free breathing ungated, amplitude gated, and phase gated conditions. Free breathing ungated conditions encompassed 100% duty cycle via phase gating while respiratory gated conditions encompassed 40% duty cycle at end exhalation. The free breathing ungated delivery condition was used to test reproducibility of motion with variability in the phantom. Amplitude gating has shown to perform well with the lack of consistent periodicity in breathing^{6–8}, whereas phase gating has been shown to produce errors under irregular motion conditions that can lead to inconsistent triggering of the beam on and off ⁸.

The predictive filter defines a threshold within which the respiratory breathing trace should correspond to the reference breathing trace. Before treatment delivery, the predictive filter registers amplitude versus respiratory phase data points to define periodicity in the breathing trace. The threshold of the predictive filter, or quality of gating, applied during treatment allows the beam to trigger off if the breathing traces falls outside of these limits. We further investigated the impact of the predictive filter threshold on phase-based gating acquired with kV imaging. All respiratory phase gated deliveries were repeated with a predictive filter of 0, 2, 5, and 10% threshold, or as set in the XML treatment file with the gating quality of 0, 0.02, 0.05, and 0.1.

4.2.3 Image acquisition

On-board gated kV projections were acquired simultaneously during MV beam-on while inside the gating window. A dynamic gain fluoroscopy protocol, with an imaging frequency of 7 frames/second, was designed to maintain low kV dosage while attaining sufficient imaging data to establish an internal breathing trace. A head and neck clinical pre-treatment cone-beam CT protocol was used to define imaging parameters. The fluoroscopic imaging parameters were 100 kVp, 20 mA, with a 20 ms duration of the kV pulse. A full bow-tie filter was applied.

4.2.4 Analysis of the internal and external trace

The phantom was set-up under static breathing conditions such that the 3-cm delrin sphere was located at isocenter. The delrin sphere, embedded in cedar, exhibits one-dimensional motion in the superior-inferior direction or y-orientation in the kV projection. The location of the delrin sphere was determined by acquiring multiple line profiles from 1-cm left to 1-cm right of the center of the sphere (Figure 4-2). In all the line profiles, the noise and average intensity in the cedar were determined. The delrin sphere was identified as consecutive values in the line profile that deviate from the cedar. Profiles affected by the noise of MV degradation or obstructed from the treatment couch were removed if deviating by two standard deviations of the centroid mean position. The remaining profiles were averaged to determine the centroid in the kV projection. The internal trace was defined as the variability of the centroid position between consecutive projections. Afterward, the motion trace was manually inspected for projections, or centroid points, deviating from the programmed motion. These points were removed from further analysis if manual analysis revealed differing centroid values. The header of the imaging files enclosed the amplitude of the external surrogate box for each kV projection. The external trace was defined as the variability in amplitude of the external surrogate box from consecutive kV projections.



Figure 4-2. Quasar respiratory motion phantom depicting the moving cedar with the embedded delrin sphere. Centroid of the delrin sphere was calculated based on line profiles between the dashed lines.

Linear regression was used to compare the accuracy of the external surrogate trace in predicting the internal trace. Based on this model, correlation of determination, R^2 , was determined for all deliveries. The point-to-point root-mean-square-error (RMSE) was calculated over the waveform of the internal and external motion. The difference in correlation between free breathing ungated, phase gated, and amplitude gated conditions for each of the six breathing traces under varying predictive filters were investigated.

The data acquired from the on-board kV imaging was also used to examine the variations in the residual motion in amplitude and phase based respiratory gated during VMAT delivery. The length of gating window for the breathing cycle was calculated based on the time stamp associated with each projection. Displacements in the position at the start and end of the gating window was analyzed to investigate discrepancies in amplitude associated with the same phase. The amplitude value of the time stamp associated with the entering or exiting the gating window in amplitude and phase gating was measured.

4.2.5 Phase shift

A phase shift of the external surrogate can occur during treatment due to either patient specific physiology or system latency in machine response to recording the external data points and triggering respiratory gating. Unfortunately, the Quasar respiratory motion phantom is unable to decouple the external platform motion from the insert motion. Therefore, the ability of during treatment kV imaging to identify a phase shift between the internal and external trace, was investigated by using a second phantom, the Quasar programmable motion platform (Modus Medical Devices, London, ON), with independent motion. The external motion trace and, hence, the respiratory gating trigger, were obtained via the second phantom while the internal trace was obtained via on-board kV imaging of the Quasar programmable respiratory motion phantom. A sinusoidal motion pattern with a 2-cm peak-to-peak motion and 4 second period, was programmed for both phantoms with eight known shifts spaced 0.4 seconds apart. The correlation of determination coefficient in the linear regression statistical test was performed for each experimental set of respiratory traces. The observed phase shift was calculated by shifting the external trace, in time, until correlation was maximized.

4.3 Results

4.3.1 Correlation analysis

The calculated internal and external trace along with the programmed breathing pattern for the ungated, amplitude gated, and phase gated treatment delivery, is displayed in Figure 4-3 for the first 45 seconds of treatment of patient 1. This respiratory trace entailed repetitive RPB motion with low deviations in the end-exhale position. A correlation of $R^2 = 0.996$, 0.948, 0.973 was achieved for free-breathing ungated, amplitude gated, and phase gated, respectively.



Figure 4-3. Computer controlled respiratory breathing trace (solid line), and the internal target (circle symbol) and external surrogate trace (asterisk symbol) are shown for free-breathing ungated, end-exhale amplitude gated, and phase gated in the first 45 seconds of treatment delivery. Over the course of the treatment delivery, a correlation of $R^2 = 0.996$, 0.948, 0.973 was achieved for free-breathing ungated, amplitude, and phase gating, respectively.

The correlation observed in free breathing ungated treatment delivery, validates the Quasar motion phantom accuracy in reproducing the computer controlled real patient breathing

trace, and the automation technique in delineating the internal trace despite MV degradation, and obstruction from the acrylic of the phantom and treatment couch at some angles. Regardless of motion irregularities programmed, the correlation in the free breathing ungated scenario for all patients ranged between $R^2 = 0.950-0.997$ with a mean of 0.986, as shown in Figure 4-4A. Similarly, for amplitude gated and phase gated scenarios, correlation ranged between $R^2 = 0.919-0.987$ or a mean of 0.942, and $R^2 = 0.959-0.981$ or a mean of 0.974, respectively.

Different predictive filter thresholds were applied during respiratory phase gated delivery. The correlation coefficient for treatment deliveries with a predictive filter threshold of 0%, 2%, 5%, and 10% ranged between $R^2 = 0.959$ to 0.981, 0.938 to 0.976, 0.890 to 0.975, and 0.890 to 0.975, respectively (Figure 4-4B). The correlation was high for all scenarios including the sinusoidal case (patient 6) where no variability amongst treatment delivery techniques was observed. In RPB with high end-exhalation position variability, the MV and kV beams were not able to trigger due to the periodicity of motion remaining outside of the threshold. For these breathing traces, only a zero threshold could be used to allow the MV and kV beam to trigger. This can be observed by the lack of points in Figure 4-4B for patients 4 and 5.



Figure 4-4. The coefficient of determination, R^2 . (A) Free breathing ungated (circle symbol), amplitude-gated (asterisk symbol), and phase-gated (square symbol). (B) Phase-gating with different predictive filter thresholds applied of 0% threshold (circle symbol), 2% threshold (asterisk symbol), 5% threshold (square symbol), and 10% threshold.

The variety of RPB patterns traces is displayed in Figure 4-5 along with the corresponding linear regression analysis in the free breathing ungated, amplitude gated and phase gated scenario. Patient 1 (Figure 4-5A) represented a repetitive RPB waveform, patient 2 (Figure 4-5B) represented a baseline drift scenario, and patient 3 (Figure 4-5C) represented an RPB trace exhibiting baseline shift. The phase-based gated deliveries exhibited a greater range of motion, approaching the motion magnitude of the free-breathing in Figure 4-5C.



Figure 4-5. Different programmed motion traces and the corresponding linear regression analysis for free breathing ungated (circle), amplitude gated (asterisk), and phase gated (square). A) Patient 1 exhibited a repetitive breathing with a low standard deviation in the end-exhalation, b) patient 2 exhibited amplitude variation, and c) patient 3 exhibited a baseline shift and varying periodicity.

The calculated RMSE for the different treatment delivery techniques and the inclusions of various predictive filters are shown in Figure 4-6. Submillimeter accuracy was found in all deliveries. The free breathing ungated delivery, with the greatest motion magnitude,

resulted in the largest error at a range of 0.023 cm to 0.065 cm, whereas the error in the residual motion in amplitude gating and phase gating resulted in a range of 0.015 cm to 0.024 cm and 0.015 cm to 0.033 cm, respectively (Figure 4-6A). With various predictive filters the RMSE ranged between 0.015 cm to 0.033 cm, 0.014 cm to 0.026 cm, 0.014 cm to 0.026 cm, and 0.014 cm to 0.025 cm, for predictive thresholds of 0%, 2%, 5%, and 10%, respectively (Figure 4-6B).





4.3.2 Residual motion analysis

The length of the gating window during amplitude and phase gated deliveries is shown in Figure 4-7. The overall deviations with phase gating were lower than with amplitude gating at 0.276 seconds and 0.757 seconds, respectively.



Figure 4-7. Variation in the length of the duty cycle during amplitude (diamond) gated, and phase gated (circle) deliveries. The symbol represents the average while the whiskers represent the standard deviation.

Irregular, non-periodic motion has been shown to lead to significant variabilities in phase gating⁶. On board kV imaging was utilized to compare the amplitude displacement variability at the entrance and exit of the gating window during amplitude- and phase-based respiratory gated VMAT, as shown in Figure 4-8. On the contrary to the length of the gating window, the position variations in the entry and exit of the gating window were less in amplitude gating than phase gating, shown in Figure 4-8 by small whiskers in the mean position of amplitude gating. The mean position variations in exiting and entering the gating window were 0.024 cm and 0.131 cm in amplitude and phase gating, respectively.



Figure 4-8. The amplitude of motion at entry, left, and exit, right, the gating window in phase-gating. Diamond and circle symbol represents the mean amplitude when entering and exiting the gating window, while the whiskers represent the standard deviation.

4.3.3 Determining a phase shift

Known baseline phase shifts between the external surrogate trace and internal target trace were introduced to investigate the ability of kV imaging to detect such phase shifts. A second independently programmed phantom was used to trigger the kV and MV beam while the original phantom's trace was shifted at 0.4-second intervals. The correlation coefficient between the internal and external trace for each shift was 0.229 ± 0.14 . The external waveform was shifted until the correlation coefficient was maximized, resulting in a mean \pm standard deviation correlation of 0.974 ± 0.03 (Table 4-2).

Shift (se	conds)	Correlation of Determination (R ²)		
Programmed	Measured	Before shift	After shift	
0.4	0.364	0.026	0.915	
0.8	0.636	0.027	0.981	
1.2	1.182	0.166	0.993	
1.6	1.455	0.434	0.989	
-0.4	-0.455	0.007	0.994	
-0.8	-0.909	0.127	0.997	
-1.2	-1.200	0.269	0.995	
-1.6	-1.727	0.773	0.929	

Table 4-2. Programmed shifts between the internal target motion and the external surrogate marker were measured using the correlation coefficient. Their respective correlation values are shown.

The results indicated that the kV projections were able to accurately detect any phase shifts in phase respiratory gating, shown in Figure 4-9, where the programmed and measured shift are displayed. The correlation between the known shifts and the measured was determined to be 0.997. Ideally, the slope of the line between the measured and programmed data points should be one, and the y-intercept should be zero. However, the values achieved are within the resolution of the imaging, of 0.091 seconds per frame or 11 frames per second.



Figure 4-9. The programmed shift between the two independent phantoms, and the measured shift when maximizing the correlation.

4.4 Discussion

To the best of our knowledge, this is the first study that investigated kV imaging as a tool to evaluate internal target and external surrogate verification during gated VMAT treatment without the use of fiducial markers. This was accomplished by varying respiratory gating parameters such as the mode (free breathing ungated, amplitude and phase-gated), and the predictive filter threshold used in phase gated delivery.

Sinusoidal motion trace, 1.5 cm peak-to-peak and 4 second period, was tested, along with five RPB waveforms exhibiting repetitive motion, baseline drifts, and baseline shifts with differing end-exhale deviations. Decreasing correlation between the internal and external trace could be due to a time delay on the acquisition kV imaging inside the gating window and/or latencies in recording the external trace. Chugh et al. concluded time delays of over 100 ms can be expected in breathing waveform with period variations²³. In all treatment

delivery scenarios, a high correlation was observed despite increasing deviation in the endexhale and non-periodicity.

Despite a higher correlation between the external surrogate and internal target observed in phase gating compared to amplitude gating, in Figure 4-3, gated kV images appear to be acquired outside the end-exhalation during phase-based respiratory gating. Phase gating relies on sinusoidal approximation based on previous breathing periods. Learning period of four waveform periods is required to learn the characteristics of the respiratory trace, as discussed in section 1.5.3 of this thesis. In TrueBeam Research Mode, treatment delivery was initiated without learning the characteristics of the breathing trace. Consecutively, the beam triggered outside of the end-exhalation gating in the beginning of the trace, as observed in phase gating of Figure 4-3.

Clinically, the reference breathing trace recorded during 4D-CT acquisition is used to provide a histogram of displacement versus phase. This allows for calculations of the respiratory waveform periodicity. Malone et al. 2014 recommend the use of a 5%-40% predictive filter for reproducible treatment delivery¹⁰. In treatment delivery, a predictive filter threshold reduces the potential of triggering the MV beam when the patient is outside the limitations included in the 4D-CT acquisition, i.e. the patient coughs, takes a deeper breath, or exhibits a lack of periodicity. However, the addition of the predictive filter to treatment delivery increases treatment delivery complexity, along with high dose rate respiratory gated VMAT, which in turn can cause latencies in machine response. A strong correlation was observed in all deliveries where a predictive filter was included. In the selected group of waveforms analyzed, patients 4 and 5 had the greatest deviations in end-exhale position which inhibited the use of a predictive filter during respiratory gating. Patient 2 was the only study subject that required removal of one to four projections out of the total 278 - 368 projections acquired after manual verification. The poorer results of the internal trace can explain the lower correlation values seen in this patient.

Phase gating is susceptible to dosimetric uncertainties due to potentially long treatment times and due to potential drift occurring with the external surrogate which leads to phase shifts in the internal and external trace^{9,11}. In SABR treatments that use high dose rates,

capable with flattening filter free beams, the treatment time can be reduced to 3-4 minutes⁴ making these patients less vulnerable to baseline drifts. Shifting the external trace along the internal trace to maximize the correlation coefficient provided the ability to accurately observe phase shifts. Although only tested for sinusoidal motion, this method can still provide an approximation of more complex real patient breathing waveforms. Uncertainty in the phase shift experiment lies in the usage of two independently programmed phantoms, allowing the study to become prone to additional mechanical errors.

Previous studies have investigated the internal and external correlation via acquisition of the planning CT dataset^{13,14}, via pre-treatment image verification techniques^{16–18}, during treatment using fiducial markers and the Mitsubishi Real-Time Radiation Therapy system^{16,20,24} or via fluoroscopy in the CyberKnife system¹⁹. Most of these studies require additional imaging dose, but it is important to limit kV exposure time to limit skin dose²⁵. This study investigated computer customized kV images acquired at specific imaging points, and the imaging parameters maintained similar to pre-treatment CBCT protocol while capturing fewer projections.

During treatment, kV imaging can also provide verification of the gating window. The length of the gating window exhibits more variance in amplitude gating than phase gating because amplitude gating is based on a threshold for displacement, whereas phase gating relies on two angular phases in every breathing cycle. Variation in the baseline amplitude and length of the end-exhale will cause deviations in the length of each gating window in amplitude gating. Whereas the variations listed above, as well as periodicity of the respiratory signal, will influence the position of each breathing cycle in phase gating as shown in Figure 4-6 and Figure 4-7. Recently, studies have demonstrated the capability of during treatment verification using the on-board MV or kV imaging^{26–30}.

This study was limited to phantom experiments as it was completed using Research mode of Varian TrueBeam linear accelerators and does not investigate the correlation in patients during treatment. Patient-specific hysteresis may alter the relationship between the internal and external targets not accounted for during respiratory gated VMAT delivery³¹. However, the method investigated here can provide a tool to triage irregular RPM

waveforms to make clinical decisions on the use of respiratory gated motion management if there is a lack of correlation. Clinical use of kV-imaging during gated VMAT delivery could detect discrepancies in correlation and potentially be accounted for in subsequent treatment fractions.

4.5 Conclusions

In this study, on-board kV imaging has been validated as a tool that can verify the external surrogate motion and internal target motion correlation during respiratory gated VMAT. The technique examined RPB exhibiting regular and irregular motion with different breathing waveform patterns, considered various gating scenarios, and was able to accurately detect any phase shifts. Verification of respiratory-gated VMAT delivery is essential, especially for adaptive radiation therapy, which relies on accurate intrafraction knowledge of tumour position for accurate dose calculation.

4.6 Acknowledgments

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4.7 References

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Chapter 5

5 Investigation of image quality of intrafraction cone beam CT for 3D verification of respiratory-gated VMAT delivery

The contents of this chapter are in preparation for submission to Physics in Medicine and Biology entitled "Investigation of image quality of intrafraction cone beam CT for 3D verification of respiratory-gated VMAT delivery" by Xhaferllari I, Dekker K, Hajdok G, Gaede S.

5.1 Introduction

Respiratory motion causes a major challenge in the treatment of thoracic and abdominal cancers with radiation therapy^{1,2}. At the same time, the clinical implementation of stereotactic ablative body radiotherapy (SABR) in early-stage non-small cell lung cancer (NSCLC) has led to higher doses per fraction, requiring tight margins^{3–5}. Respiratory gating is a technique to manage respiratory motion by limiting the radiation beam to specific portions of the breathing cycle^{6,7}. As a result, high doses are delivered to the target, while limiting dose to normal tissue. One of the main limitations of respiratory gating is that it relies on the accuracy of an external surrogate to predict the internal motion of the target, despite intrafraction variations in respiratory motion^{8,9}. Therefore, treatment dose verification methods are required to ensure the planned dose distribution are accurately delivered during respiratory gated radiotherapy.

The application of image-guided radiation therapy (IGRT) improves tumour targeting¹⁰. On-board kV imaging and electronic portal imaging device (EPID) are widely used as a pre-treatment image-based verification method¹¹. Cone-beam CT (CBCT) can be reconstructed for volumetric verification when kV or MV planar images are acquired in an arc. Pre-treatment CBCT portrays patient anatomy before treatment and aids in reducing patient misalignments. However, CBCT acquired prior to treatment does not guarantee accurate dose delivery to the target during treatment delivery, especially for moving targets.

Continuous imaging through EPID in cine mode has been used for during treatment verification. However, EPID is limited in the investigation of anatomy alignments by the field-of-view (FOV) of the treatment beam, especially for SABR treatment delivery with small field sizes. Recently, intrafraction verification techniques using on-board kV projections have been investigated for treatment verification of SABR, including volumetric modulated arc therapy (VMAT)^{12–15}. The benefit of during VMAT imaging is the ability to reconstruct a volumetric CBCT. However, added imaging dose from the onboard kV unit should be maintained as low as possible¹⁶. For during treatment verification, the added imaging dose is reliant on the treatment session time and the imaging acquisition mode. Treatment session times are greater during respiratory gated SABR compared to ungated conventional radiation therapy, due to higher doses per fraction in SABR, and the restriction of radiation beam delivery to portions of the breathing cycle. The ability to compute gated-kV imaging concurrent with treatment can help reduce patient exposure and limit imaging dose for respiratory gated patients. Another limitation of intrafraction kV imaging is the potential degradation of the kV projections due to MV scatter hitting the kV detector^{17–19}.

The hypothesis of this study is that gated on-board kV CBCT can be used as a 3D method to validate the delivery of respiratory-gated VMAT using a programmable respiratory motion phantom. This was tested by evaluating imaging quality and target visualization capabilities of during treatment gated on-board kV CBCT while minimizing kV beam-on time.

5.2 Methods

5.2.1 Quasar Motion phantom

The Quasar programmable respiratory motion phantom (Modus Medical, London, ON) was used in all on-board kV CBCT reconstructions. It is a dynamic phantom with the ability to insert different moving components, useful for investigating the impact of motion on imaging and radiation delivery (Figure 5-1A). For the purpose of this study, a cedar cylindrical insert, representing lung equivalent electron density with embedded polystyrene

spheres, representing tumour equivalent electron densities, was added (Figure 5-1B, C). The polystyrenes spheres ranged in sizes of 3-cm, 2-cm, 1-cm, and 0.5-cm, best exemplifying detectability properties of different sized lesions typically seen in early-stage NSCLC treated with SABR. The cedar and polystyrene unit moves in the superior-inferior (SI) direction by the magnitude specified in the programmed motion trace.



Figure 5-1. Quasar programmable respiratory motion phantom (A). Moving insert composed of cedar, representing normal lung tissue, and embedded polystyrene spheres, representing tumour tissues (B). (C) Schematic of the moving insert with various sizes and locations of polystyrene spheres.

5.2.2 Imaging Acquisitions

Varian TrueBeam linear accelerator v.2.0 (Varian Medical System, Palo Alto, CA) in Research Mode was used to obtain on-board kV imaging simultaneous to the MV treatment beam. Research Mode allows for user defined imaging and treatment delivery protocols, and has the capability of synchronizing image acquisition to treatment delivery. On-board kV imaging was acquired concurrently to treatment beam delivery of a clinical SABR lung plan delivered in a 225° partial arc. Ungated and triggered gated kV acquisition projections were collected with a stationary and moving phantom, respectively. A full bow-tie filter and a titanium filter were added to compensate for greater attenuation of the x-ray beam at the center of the FOV by the phantom, and reduce low energy x-rays of the beam, respectively.

5.2.2.1 Imaging Parameters

5.2.2.1.1 Treatment Deliveries under static conditions

In the first set of measurements, static conditions were kept to investigate various imaging parameters on image quality and target detectability, in the absence of respiratory motion. This included reconstructing a pre-treatment on-board kV CBCT of the phantom in the absence of MV scatter, based on a current clinical protocol, acquired using a full 360° arc at 11 frames per second. A reference on-board kV CBCT, in the presence of MV scatter, was reconstructed using similar parameters to the pre-treatment on-board kV CBCT, but acquired at 7 frames per second. The acquisition parameters for the reference on-board kV CBCT were 100 kVp, 20 mA, 20 ms, 7 frames per second, during SABR VMAT with arc range of 225°, and a kV source to detector distance (SDD) of 150 cm. MV scatter was added using the SABR-VMAT clinical plan of a previously treated patient. We varied the energy, tube current, and SDD. All static deliveries and respective test numbers, referred throughout this paper, are summarized in Table 5-1.

Test #	Energy	Current	Pulse length	SDD	Frame rate	Arc range	MV
	(kVp)	(mA)	(ms)	(cm)	(fr/sec)	(degrees)	scatter
1	100	20	20	150	11	360	No
2	100	20	20	150	7	225	Yes
3	80	20	20	150	7	225	Yes
4	125	20	20	150	7	225	Yes
5	100	10	20	150	7	225	Yes
6	100	40	20	150	7	225	Yes
7	100	20	20	140	7	225	Yes
8	100	20	20	160	7	225	Yes

Table 5-1. Imaging parameters of static acquisitions. The reference acquisition has been bolded.

5.2.2.1.2 Treatment Deliveries under motion conditions

In the second set of experiments, the motion phantom was enabled during treatment delivery as kV projections were captured. Three real-patient breathing (RPB) traces were tested to represent various breathing patterns, depicted by a simplified sinusoidal waveform in Figure 5-2. The three RPB waveforms were extracted from CT-simulation of previous patients treated with respiratory gating. Each RPB trace was normalized to the total motion measured in the 4D-CT dataset. A fast, repetitive RPB trace (Figure 5-2A) with a peak-to-peak amplitude of 1.2 cm, was used to represent regular motion. RPB traces with irregular motion patterns were observed with a baseline drift²⁰ (Figure 5-2B) and a trace with a baseline shift²¹ (Figure 5-2C). The baseline drift motion displayed a veering position of the baseline with a peak-to-peak amplitude of 1.0 cm. Whereas the baseline shift trace displayed sudden changes in the baseline amplitude of motion, with a peak-to-peak motion of 0.9 cm. A set of projections were acquired under free breathing ungated conditions, using a 100% duty cycle, and amplitude- and phase-based gating using a 40% duty cycle for each RPB. The reference imaging parameters, from acquisition (2) in Table 5-1, were used for all acquisitions.



Figure 5-2. Schematic of the different waveforms in a simplified sinusoidal waveform. A) Fast, repetitive breathing, B) Baseline drift (shown by the red line), C) Baseline shift (shown by the red step).

5.2.2.2 CBCT reconstruction

In clinical practice, CBCT images are generally reconstructed using the Feldkamp-Davis-Kress (FDK) algorithm of filtered backprojections²². To simulate clinical application, all datasets in this study were reconstructed using the FDK algorithm with Hamming filter applied. Reconstructions were also computed using in-house CT projection code written in CUDA-C for GPU acceleration on a CPU with intel i7-2600 and GPU of NVIDIA GTX 780. The reconstructed matrix size was 512x512x384 pixels with isotropic voxel of 0.0517 cm. Therefore, the FOV was 26.5 cm by 26.5 cm. The number of projections per scan varies with gantry speed, frame rate, treatment modality, and the periodicity of the respiratory breathing trace. The gantry speed was limited to 6° per second, and the highest dose rate of 2400 monitor units per minute was used for the treatment beam. The number of projections acquired in the pre-treatment on-board kV CBCT was 662. The during treatment on-board kV CBCTs were acquired under static conditions with approximately 311 projections, due to shorter scanning angle and lower frame rate. The during treatment CBCTs acquired under respiratory motion conditions resulted in 311 projections for the ungated conditions, and 345 – 397 projections for gated conditions. Acquisitions with MV scatter resulted in fewer number of projections compared to the pre-treatment on-board kV CBCT, because a lower kV acquisition frame rate of 7 frames per second was used in acquisitions with MV scatter compared to 11 frames per second in pre-treatment on-board kV CBCT projections. CBCT acquired under gated conditions required greater projections than ungated conditions due to frequent ramp up and down of the dose rate limiting the gantry speed.

In datasets acquired using imaging parameters expected to lead to a decrease in image quality (e.g. low mA, low kVp) with respect to the reference acquisition, and the reference acquisition, [(2), (3), (5), (8)], were reconstructed using an iterative reconstruction technique to potentially increase image quality. The iterative algorithm applied, OSC- TV^{23} , combines ordered subsets convex (OSC) algorithm^{24,25} and the total variation minimization (TV) regularization technique²⁶.

5.2.3 Evaluation methods

5.2.3.1 Image Quality

The CBCT datasets were exported into 3D-SlicerRT program for analysis^{27,28}. 3D-Slicer is a multi-platform free, open source software for visualization and medical imaging computing. In the stationary phantom measurements, the polystyrene spheres and a 2-cm sphere region of interest (ROI) in the cedar, were delineated on the reference acquisition (2). These contours were imported onto the remaining static on-board kV CBCT datasets (1) - (6) to remove contouring bias in the analysis process. The contours for on-board kV CBCT datasets (7) and (8) were delineated separately as these datasets had different image acquisition geometries. For the respiratory motion induced CBCT datasets, the polystyrene spheres and the cedar ROI, were delineated individually based on the blur of motion observed.

Image quality was investigated for all CBCT datasets by calculating the contrast-to-noise ratio (CNR) between each of the polystyrene spheres and the ROI in the cedar²⁹.

$$CNR = \frac{\mu_p - \mu_c}{\sigma_p} \tag{1}$$

where μ_p and μ_c are the mean linear attenuation coefficients of the polystyrene spheres, and the cedar ROI, respectively, and σ_p is the standard deviation of the linear attenuation coefficient of each polystyrene sphere.

5.2.3.2 Target Delineation

In the static acquisitions, target detectability was identified by calculating the full-widthhalf-maximum (FWHM) for each of the polystyrene spheres. The central coronal slice, shown in the schematic of Figure 5-1C, displays the center through all four spheres. Based on the geometry of the cedar insert, profiles were calculated to obtain the FWHM.

In the motion induced acquisition, the region of interest delineated in 3D-Slicer was compared to the static CBCT targets by calculating the volume percent difference (VPD) for each region of interest¹².

$$VPD = \frac{|V_M \cup V_S - V_M \cap V_S|}{V_S} \times 100\%$$
(2)

where V_M represents the volume blur of the polystyrene sphere in the moving phantom acquisition, and V_S represents the respective polystyrene sphere in the stationary phantom delivery. All static and motion induced treatment deliveries were set-up at isocentre, inherently shifting the gated delivery targets to the end-exhalation extreme from the static

target. To limit registration error in the VPD calculation, the gated CBCT images were retrospectively shifted based on the number of pixels representing 40% of the total breathing motion.

Statistical analysis was performed using a one-way analysis of variance (ANOVA) followed by a Tukey's posthoc test in the statistics package of IBM SPSS v.20 (IBM SPSS Statistics for Windows, Armonk, NY).

5.3 Results

5.3.1 Effects of Acquisition Parameters on Image Quality

The on-board kV CBCT acquisitions with a static phantom were used to investigate image quality in the different sized polystyrene spheres. In Figure 5-3, the coronal slice from the isocentre of the static CBCT reconstructions is shown using the same window and level. The reconstruction volume was cropped to display only the moving cedar with the polystyrene spheres. The pretreatment CBCT (labelled no MV) (1) displayed the best visualization of the spheres. However, each polystyrene sphere was visible in all reconstructions, except for the 0.5-cm sphere in the 80 kVp (3) CBCT volume.



Figure 5-3. Coronal slice at isocenter in all the static deliveries. The corresponding numbers represent the imaging parameters described in the methods section. For visual purposes, the slice is cropped to only represent the moving insert. The same window level is used in all eight CBCT images.

The effect of MV scatter on on-board kV CBCT was investigated in polystyrene. Linear attenuation coefficients in the pre-treatment CBCT (1) and the reference acquisition (2) were compared by delineating the 2-cm polystyrene sphere. The difference in linear attenuation coefficient was investigated by subtracting the pre-treatment CBCT (1) from the reference acquisition (2), shown by the red histograms in Figure 5-4. In polystyrene, a decrease in the linear attenuation coefficient is observed, with a mean value of 0.027 cm⁻¹, and spread or standard deviation of 0.01 cm⁻¹. Previous studies have observed a significant effect of MV scatter on kV imaging^{18,30}, however, the field size in these studies was 10 cm by 10 cm or greater, whereas this study used a smaller field size of 4.5 cm by 4.2 cm, as observed in early-stage NSCLC SABR treatment.



Figure 5-4. Difference in linear attenuation coefficient (μ) values in the polystyrene ROI between the reference CBCT acquisition in the presence of MV scatter (2), and the pre-treatment CBCT acquisition in the absence of MV scatter (1). The difference in linear attenuation coefficient (μ) values is shown by the red histogram.

The CNR between each polystyrene sphere and cedar ROI displayed the lowest values for acquisitions with 80 kVp (3), where CNR ranged between 1.8, for the 0.5-cm sphere, to 2.2, for the 1-cm sphere, as shown in Figure 5-5. A significant reduction was found for volumes acquired with 80 kVp (3) (p = 0.002), and 10 mA (5) (p = 0.006), compared to the pre-treatment CBCT acquired without MV scatter (1). Similarly, a significant difference was observed when comparing CNR for 120 kVp (4) and 40 mA (6), to 80 kVp (3) and 10 mA (5) (p < 0.015). Otherwise, no significant difference was observed amongst other CBCT volumes. For volumes acquired with the reference MV scatter acquisition (2), compared to the pre-treatment on-board kV CBCT (1), increased tube voltage acquisition (125 kVp) (4), and increased current acquistion(40 mA) (6), there was a greater discrepancy between CNR in the larger spheres, 3-cm and 2-cm, compared to the CNR in the smaller spheres 1-cm, 0.5-cm. The 0.5-cm sphere CNR ranged between 2.9 to 4.0, whereas the CNR in the 3-cm sphere ranged between 3.7 to 6.4.



Figure 5-5. Contrast-to-noise ratio (CNR) between each of the polystyrene spheres and a region of interest in the cedar in CBCT in a stationary phantom.

Similarly, when comparing FWHM, the lower energy (80 kVp) (3) diminished the visibility of the 0.5-cm lesion (Figure 5-6). For the remaining CBCT datasets, the FWHM calculation for the 3-cm, 2-cm, 1-cm, and 0.5-cm spheres resulted in a range of 2.96 to 3.02 cm, 1.98 to 2.07 cm, 0.92 to 1.11 cm, and 0.47 to 0.58 cm, respectively. No significant differences were found amongst different acquisition parameters. On-board kV CBCT acquired during SABR treatment delivery, resulted in detectability of different sized lesions for all acquisition parameters explored in this study.



Figure 5-6. The full-width-half-maximum (FWHM) of all polystyrene spheres in the centroid slice of the CBCT dataset in a stationary phantom.

5.3.2 Comparison of CBCT reconstruction techniques

The FDK filtered backprojection algorithm is implemented clinically for pre-treatment CBCT reconstruction. All acquisitions were reconstructed using FDK filtered backprojection. Iterative reconstruction has recently been shown to improve imaging quality in lower dose acquisition modes, and in acquisitions with limited projections²³. The reference acquisition (2), projections acquired with a low energy of 80 kVp (3), low current of 10 mA (5), and 160 SDD (8), were reconstructed using the OSC-TV iterative algorithm. The coronal slice of the reconstruction in the centroid position comparing FDK to OSC-TV, is displayed in Figure 5-7.



Figure 5-7. Comparison of filtered backprojection (FDK algorithm) and iterative (OSC-TV algorithm) reconstruction displayed in the coronal slice at isocenter. The same window level was used in both datasets.

A significant increase (p<0.001) was observed in the CNR calculations with OSC-TV compared to FDK (Figure 5-8). The CNR increased by 2.6 times or more in the different polystyrene spheres for acquisitions with 80 kVp (3). The 0.5-cm sphere in the 80 kVp CBCT reconstruction (3) was visible and had a FWHM value of 0.53 cm. FWHM calculations on the iterative reconstructed CBCT datasets did not reveal significant differences (p>0.05) and all the ROIs were identified. The FWHM for the 3-cm, 2-cm, 1-cm, and 0.5-cm polystyrene spheres ranged from 2.97-3.00 cm, 1.98 – 2.01 cm, 0.94-1.01 cm, and 0.43 – 0.53 cm, respectively. Iterative reconstruction with OSC-TV demonstrates the potential to reduce imaging dose while maintaining detectability of various sized lesions.


Figure 5-8. Comparison of contrast-to-noise ratio (CNR) between filtered back projection (FDK algorithm) and iterative reconstruction (OSC-TV algorithm) for every polystyrene sphere.

5.3.3 Target Motion Analysis

Figure 5-9 demonstrates the coronal slice of the on-board kV CBCT for the static (reference imaging protocol), and the RPB trace exhibiting a baseline drift under free breathing ungated, amplitude and phase gated conditions. Blurring is observed among all polystyrene spheres in the free breathing ungated image, where the visualization for 0.5-cm and 1-cm spheres was difficult.



Figure 5-9. Coronal slice at isocenter comparing static, free breathing ungated, amplitude gated and phase gated delivery for the RPB waveform with a baseline drift

Image quality was quantified by the CNR between the delineated polystyrene spheres and a ROI in the cedar (Table 5-2). A significantly lower CNR was observed for the free breathing ungated conditions encompassing the full blur of motion, compared to amplitude gating (p=0.001) and phase gating (p<0.001). However, amplitude gating and phase gating did not reveal significant differences (p>0.05).

Detectability of different sized regions of interest was investigated by comparing the VPD between the motion induced acquisition and the static reference (2) on-board kV CBCT (Table 5-2). Similar to the CNR calculations, the VPD improved in respiratory gated deliveries compared to free breathing ungated conditions, albeit not significant (p>0.05). However, in the baseline drift RPB, the VPD decreased in the free breathing ungated conditions compared to gated conditions for the 0.5-cm sphere. The delineation of the 0.5-cm polystyrene sphere was difficult in all CBCT datasets due to respiratory motion artifacts. A significant decrease was observed when comparing the CNR of the 0.5-cm sphere to the 2-cm sphere (p = 0.014) and the 3-cm sphere (p=0.028). This resulted in a significant increase of the VPD for the 0.5-cm sphere compared to the remaining polystyrene spheres (p<0.05).

Table 5-2. Contrast-to-noise ratio (CNR), and volume percent difference (VPD) calculation for each polystyrene sphere amongst the different RPB traces and treatment delivery conditions.

Polystyrene	Motion Management	Fast, regular RPB trace		Baseline drift RPB		Baseline Shift RPB	
sphere		CNR	VPD	CNR	VPD	CNR	VPD
3-cm	Ungated	2.5	27.6	2.1	15.8	2.1	20.6
	Amplitude	3.0	16.6	3.8	15.8	3.0	9.2
	Phase	3.2	12.0	3.3	12.1	2.9	12.9
2-cm	Ungated	2.1	32.7	1.7	25.9	2.5	18.7
	Amplitude	2.9	24.8	3.7	18.5	3.2	15.3
	Phase	3.1	20.9	3.9	18.3	3.6	16.5

1-cm	Ungated	1.8	52.3	1.5	43.4	1.9	43.0
	Amplitude	2.3	34.8	2.1	38.5	2.7	22.0
	Phase	2.7	17.6	3.2	32.8	2.7	35.8
0.5-cm	Ungated	1.8	142.0	1.1	41.7	1.9	66.1
	Amplitude	1.9	85.6	2.7	78.8	2.5	48.9
	Phase	3.0	57.8	1.5	57.8	1.9	65.5

5.4 Discussion

Current clinical practice relies on on-board kV CBCT acquired prior to treatment for proper patient set-up and verification. However, early-stage NSCLC patients are susceptible to intrafraction motion variations not accounted for in pre-treatment verification^{8,9}. The objective of this study was to evaluate imaging quality and target visibility of intrafraction on-board kV CBCT, and to investigate the influence of respiratory motion on gated and free breathing CBCT in a respiratory motion phantom study. High visibility and imaging quality is required to allow for usability of on-board kV CBCT acquired during treatment. Despite results in literature regarding the negative effects of MV scatter from the treatment beam on during treatment kV-CBCT reconstruction^{18,30}, we observed no significant differences in image quality and target visibility in CBCTs reconstructed in the presence of MV scatter compared to pre-treatment CBCT. Smaller field sizes in SABR treatment delivery minimize degradation in on-board kV CBCT from MV scatter, compared to studies where field sizes of 10 cm x 10 cm or greater were used.

Respiratory motion artifacts were minimized through the use of gated on-board kV CBCT acquisition. This acquisition mode, restricts on-board kV acquisition to specific portions of motion in the phantom, limiting imaging dose. A significant decrease was observed in CNR between the free breathing ungated and respiratory gated on-board kV CBCT. For very small targets, respiratory motion, introduced motion artifacts in both gated and ungated CBCT, causing uncertainty in delineating the 0.5-cm spheres. A limitation in this

study was potential retrospective registration misalignment between the gated and static on-board kV CBCT calculations introducing uncertainties in the VPD calculations. These registration errors can be reduced by acquiring a subset average 4D-CT dataset to represent the gating window used during treatment delivery. The subset average 4D-CT can be applied to verify respiratory gated treatment delivery.

Li et al. described a clinical application of gated on-board kV CBCT in patients by acquiring kV fluoroscopy during a treatment session, and retrospectively removing all projections acquired while the treatment beam is turned off¹⁵. This significantly increases imaging dose due to the increased length of a respiratory gated treatment session. Kincaid et al. investigated gated CBCT acquisition as a method to remove target blurring by limiting the MV exposure and shifting the treatment jaws to block the MV beam³¹. The CNR values reported were comparable to the measurements in this study. Our study evaluated image quality while maintaining low imaging dose exposure with 124 mAs in the free breathing ungated acquisition, and a range of 138 mAs to 159 mAs in the respiratory gated on-board kV CBCT, compared to 1478 mAs reported by Kincaid et al.³¹. The application of iterative reconstruction in on-board kV CBCT can further increase image quality and target detectability. In this study, various real patient breathing motion irregularities investigated did not lead to a significant difference amongst CNR and VPD, as expected during gated delivery.

Imaging dose and potential wear-and-tear on the on-board kV unit was limited by acquiring kV projections as triggered gated acquisitions in TrueBeam Research Mode. This modality is currently not available in clinical mode but potential implementation could easily allow translation to gated on-board kV CBCT to early-stage NSCLC patients. In this patient group, gated CBCT will reduce motion artifacts, and limit imaging dose and MV degradation. Future work will investigate the role of intrafraction CBCT for usability in adaptive radiotherapy.

5.5 Conclusions

Intrafraction on-board kV CBCT acquired during gated VMAT SABR treatment can provide during treatment verification. In this study, CBCT potentially tarnished by MV

scatter during a partial arc delivery was observed to show insignificant differences compared to CBCT acquired without MV scatter using similar imaging parameters. In a motion induced thoracic phantom, intrafraction respiratory gated CBCT quality was significantly improved compared to free breathing ungated CBCT. This intrafraction treatment verification method can positively impact adaptive radiotherapy applications.

5.6 Acknowledgments

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Chapter 6

"It always seems impossible until it is done" – Nelson Mandela

6 Summary, Conclusion, and Future Work

6.1 Summary

The overall goal of this thesis was to optimize radiation therapy planning and delivery of respiratory gated IMRT and VMAT for early-stage NSCLC patients treated with SABR. This goal led to the formulation of the following research objectives:

- To compare different IMRT treatment delivery techniques to deduce the most optimal trade-off between treatment efficiency, tumour dose conformality and healthy tissue sparing when treating early-stage NSCLC with SABR.
- To evaluate the potential reduction of radiation induced lung toxicity through the use of respiratory gated VMAT, when treating patients that exhibit significant respiratory-induced tumour motion.
- To determine if on-board kV imaging can be used as a tool to validate respiratory gated VMAT delivery by investigating the correlation of the external surrogate motion to the internal target motion, and by determining potential phase shifts.
- To optimize imaging parameters of volumetric CBCT acquired by synchronizing kV imaging with respiratory-gated VMAT delivery to provide 3D verification of correct tumour targeting

In the following subsections, an overview of Chapters 2-5 of the thesis will be provided, along with resulting conclusions from each study and impact on the above objectives.

6.1.1 Dosimetric planning comparison of IMRT techniques for early stage non-small cell lung cancer treated by SABR

In Chapter 2, various IMRT techniques were compared for the treatment of early-stage NSCLC with SABR. This was accomplished by retrospectively planning ten patients with three fixed beam techniques (step-and-shoot low and high modulation, and sliding

window), two VMAT techniques (SmartArc and RapidArc), and Helical Tomotherapy with three different fan beam widths (1-cm, 2.5-cm, and 5-cm). The Eclipse v11.3 treatment planning system employed the Acuros XB dose calculation algorithm and was used to compute sliding window fixed beam IMRT and RapidArc VMAT. High and low modulation step-and-shoot fixed beam plans and SmartArc VMAT were computed with Pinnacle v9.1 treatment planning system that uses collapsed cone convolution dose calculation algorithm. All HT treatment plans were planned in TomoPlan v.3.1.1, which employs a convolution/superposition dose calculation algorithm. Fixed-beam and VMAT plans were generated using 10MV FFF x-ray beams with a maximum dose rate of 2400 MU/min, while HT plans were generated with 6MV beams with a maximum dose rate of 600 MU/min. A comprehensive analysis was completed by comparing various parameters grouped into tumour dose conformality, dose volume histograms and indices, and treatment efficiency (i.e. minimization of MUs, MLC travel distance, treatment time delivery).

VMAT treatment plans resulted in significantly lower contralateral lung V_{5Gy} (p ≤ 0.05) compared to the HT plans, and significantly lower mean lung dose (p<0.006) compared to HT-5cm treatment plans. Increased MLC leaf travel used to form intensity gradients in the beam can lead to potential degradation of the MLC carriage over time. SmartArc resulted in the least MLC leaf travel, while a significant difference was found between high modulation step-and-shoot and the remainder of the delivery techniques. Treatment efficiency was evaluated by calculating treatment delivery "beam on" time and a significant difference was found amongst HT and fixed-beam plans compared to VMAT modalities (p<0.001).

Further comparison was completed by grouping the most efficient techniques from each modality, both step-and-shoot plans, VMAT plans, and HT 2.5-cm and 5-cm. VMAT outperformed HT, with statistical superiority observed in 11 parameters. In the comparison between step-and-shoot and VMAT techniques, an increase in dose to the heart, esophagus and bronchus was observed in the VMAT plans, although insignificant. VMAT showed significantly improved treatment efficiency and was dosimetrically advantageous for all other parameters.

In the comparison between the two VMAT techniques, SmartArc resulted in a significant reduction in the total monitor units (p = 0.05), whereas a significant decrease was observed in the dose fall-off parameter, D_{2cm} , (p=0.05), in RapidArc treatment plans. Otherwise, RapidArc and SmartArc performed comparably. Although all techniques had clinically acceptable treatment plans, VMAT was dosimetrically advantageous in treating early-stage NSCLC with SABR as it provided the optimal trade-off between dose conformality and sparing of normal tissue, and treatment efficiency. Based on the results of this study, VMAT is recommended in treatment planning of early-stage NSCLC patients treated by SABR.

6.1.2 Assessing the potential to reduce normal lung toxicity in SABR patients using respiratory-gated VMAT

In Chapter 3, VMAT enhanced by respiratory gating was assessed for tumour motion of 5 mm or more, identified as significant by the AAPM task group 76¹. Twenty patients were retrospectively planned using both the free breathing "untagged average" CT scan and the "subset average" 4D-CT data set, to represent non-gated and respiratory gated scenarios, respectively. The ITV in the non-gated plans was defined as the envelope of the GTVs delineated in all 10 phases of the respiratory cycle. In the gated plans, ITV encompassed only end-exhalation phases included in the subset average. Treatment planning was computed with 10MV-FFF x-ray beams using Pinnacle v.9.0 treatment planning software. Pinnacle scripts were developed to optimize all 40 plans in order to minimize dosimetric bias in treatment planning. Minor adjustments were sometimes necessary to fulfill dose limits to critical structures. The main parameters analyzed were V_{20Gy} , predictive of radiation induced pneumonitis in healthy lung tissue², and $V_{50\%}$, parameter used to control intermediate dose spillage and total volume of potential irreversible fibrosis³⁻⁵.

There was a significant decrease in V_{20Gy}, from (6.05 +/- 2.06)% to (5.25 +/- 1.75)% (p=0.00009) and V_{50%} from (158.17 +/- 61.12) cm³ to (125.71 +/- 49.46) cm³ (p=0.00002) in the gated plans. Also, there was a significant decrease in contralateral lung V_{5Gy}, D_{2cm}, MLD and total MU. However, non-centrally located lesions with motion less than 6 mm did not result in a significant difference in V_{20Gy} (p=0.286) whilst a significant reduction was observed for V_{50%} (p=0.04). Respiratory gated treatment delivery increased treatment

time by approximately a factor of 2.3 compared to non-gated VMAT delivery, and the application of respiratory gating should be limited only to patients with significant motion.

The results of this study affirmed significant reduction of potential radiation induced lung toxicity, whilst previous studies resulted in safe delivery of respiratory gated VMAT in TrueBeam linacs^{6,7}. This provides the foreground information to enable the clinical introduction of respiratory gated VMAT in the clinic for tumours with significant respiratory motion.

6.1.3 On-board kV imaging during respiratory gated VMAT delivery to verify the correlation between internal tumour motion and external surrogate motion in patient-specific waveforms

In Chapter 4, a method to investigate respiratory gated delivery uncertainties was evaluated. Respiratory gated delivery relies on the accuracy of the external surrogate marker to predict the correct internal target motion. Challenges arise when the internal motion is out of phase with the external surrogate motion, or when there are latencies in machine response or recording of the external motion. Several other studies have investigated the correlation in respiratory gating during 4D-CT acquisition⁸⁻¹⁰, before treatment¹¹⁻¹³, and with the use of ultrasound¹⁴ or fiducial markers^{13,15,16}. Treatment delivery complexity is enhanced by combining respiratory gating with high dose rate VMAT, due to additional degrees of freedom, such as varying dose rates, and multiple pauses of the gantry motion. The goal was to evaluate on-board kV imaging as a tool to determine the internal and external correlation, and to detect phase shifts during respiratory gated VMAT delivery. The Quasar respiratory motion phantom, which contains a hollow body and drives a 3-cm delrin "tumour" sphere embedded in a cedar cylinder, was utilized to represent a tumour surrounded by normal lung tissue. This study was completed in TrueBeam Research Mode v.2.0 software to allow for computer customized kV fluoroscopy that was triggered only within the treatment beam gating window. VMAT treatment plans were delivered whilst the phantom motion was programmed using a simple sinusoidal conditions and five real-patient breathing conditions exhibiting variable respiratory motion, as characterized during 4D-CT acquisition. Treatment delivery was performed under free breathing non-gated, amplitude gated, and phase gated conditions.

For phase gating, the impact of various motion predictive algorithms was evaluated. The moving delrin target was automatically delineated in all kV projections and compared to the external platform (surrogate) motion integrated into the Quasar phantom. The external and internal correlation was evaluated by linear regression analysis; highest discrepancy ($R^2 = 0.919$), however still a high correlation, was observed during amplitude-based gating for waveforms exhibiting amplitude variations. High correlation coefficients were observed in all deliveries, with a range of $R^2 = 0.950-0.997$, 0.919-0.987, and 0.959-0.981 in non-gated, amplitude and phase gated, respectively. Similarly, the correlation coefficient for treatment deliveries with a predictive filter threshold of 0%, 2%, 5%, and 10% ranged between $R^2 = 0.959$ to 0.981, 0.938 to 0.976, 0.890 to 0.975, and 0.890 to 0.975, respectively. Submillimeter accuracy was found amongst the external and internal trace in all deliveries. During treatment on-board kV imaging provides for a tool to verify respiratory gated treatment.

Two independently programmed phantoms were used to determine if on-board kV imaging technique can accurately identify known artificial phase shifts. The motion of the external surrogate, from the second phantom, was shifted at intervals of 0.4 seconds in a sinusoidal waveform with a four second period, to the internal motion of the Quasar motion phantom. Retrospectively, shifts were measured by maximising the correlation coefficient. The mean correlation increased from 0.229 ± 0.14 to 0.974 ± 0.03 after shifting the respiratory trace of the original phantom. The measured and known shifts did not reveal a significant difference (p=0.899, R²=0.997).

This study was completed using TrueBeam Research Mode, and was limited to respiratory motion phantoms. However, real-patient breathing waveforms of various irregularity and various gated treatment delivery modes were programmed and assessed. In all scenarios, during treatment on-board kV imaging method was validated as a way to determine the correlation between the internal tumour motion and external marker motion during gated VMAT delivery. It can also be used to determine potential phase shifts between the motions of the tumour and the external surrogate marker.

Intrafraction on-board kV imaging will be useful in daily triaging of patients and allow for clinical decisions to be made on the use of respiratory gated motion management on a patient-specific basis. Also, clinical use of kV-imaging during gated VMAT delivery could be used for adaptive radiation therapy where any discrepancy detected in a daily beam delivery may be accounted for in subsequent treatment fractions.

6.1.4 Investigation of image quality of intrafraction cone beam CT for 3D verification of respiratory-gated VMAT delivery

Chapter 4 provided a two-dimensional verification of respiratory gated delivery, whereas in Chapter 5, intra- treatment CBCT was assessed as a three-dimensional treatment verification tool. The main goal of this study was to assess detection of different size targets, and image quality in intrafraction CBCT that is influenced by MV scatter. The range of the targets examined, 0.5-cm to 3-cm in diameter, coincide with typical lesion size in early-stage NSCLC patients. A "reference" CBCT of a stationary phantom was reconstructed using on-board kV-projections acquired simultaneously during MV treatment delivery of a 225° partial arc VMAT SABR treatment, using imaging parameters of 100 kVp, 20 mA, 20 ms and source to detector distance of 150 cm. Image quality and detectability were compared between this CBCT, and CBCT acquisition using a 360° arc acquired without MV scatter degradation. Then, imaging parameters were varied in order to evaluate image quality and detection of the targets while reducing imaging dose. For the static phantom, variable energy (80 kVp and 125 kVp), current (10 mA and 40 mA), and the source to detector distance (140 cm and 160 cm) were considered. Each acquisition was reconstructed using filtered back projection with a hamming filter. Imaging quality was defined as the improvement in the contrast-to-noise ratio (CNR), whereas detectability was defined by calculating the full-width-half-maximum (FWHM) of each of the spherical targets.

A significant reduction in image quality was found in reconstructed CBCTs with 80 kVp and 10 mA compared to the CBCT acquired without MV scatter contribution, the high energy of 125 kVp acquisition, and high current 40 mA acquisition. However, no significant difference was observed in image quality between the CBCT acquired with the reference imaging parameters with and without MV scatter. All targets were identified with

the exception of the 0.5-cm sphere in the 80 kVp acquisition. The reference acquisition, along with three sets of acquisitions obtained using low energy (80 kVp), low current (10 mA), and the greatest distance between the kV source and the detector (160 cm), were reconstructed using OSC-TV algorithm for iterative CT reconstruction. CNR significantly improved in all deliveries reconstructed with iterative reconstruction. No significant difference was observed in image detectability with all targets accurately identified.

Real patient breathing traces with periodic motion, motion exhibiting a baseline drift, and motion with a baseline shift were programmed on the Quasar motion phantom with cedar insert embedded with polystyrene "tumour" spheres. For each motion scenario, projections were acquired using the reference imaging parameters during a free breathing non-gated, amplitude gated, and phase gated VMAT delivery during SABR. Respiratory motion induced artifacts in the detection of the different targets and image quality were examined. Detection of the target was identified as the volume percent difference (VPD) between respiratory motion targets, and static targets obtained with reference imaging parameters. A significantly lower CNR was measured in free breathing ungated conditions encompassing the full blur of motion, compared to amplitude gating (p=0.001) and phase gating (p<0.001), whereas, amplitude gating and phase gating did not reveal significant differences (p>0.05).

This study has provided for verification of respiratory gated CBCT during treatment delivery. In most of the CBCT reconstructions, the smallest target at 0.5-cm remained visible, despite MV degradation on the acquired projections. Tarnished visibility was observed in free-breathing ungated on-board kV CBCT, but triggered respiratory gated on-board kV CBCT reduced motion artifact. Intrafraction volumetric datasets can be applied to respiratory gated SABR patients with potential applicability in adaptive radiotherapy. Adapting treatment dose distribution based on intrafraction CBCT will allow for accurate presentation of the true anatomy.

6.2 Future work

6.2.1 Simultaneous kV and MV imaging during treatment

6.2.1.1 Three dimensional motion calculation during respiratory gated delivery

In Chapter 4, internal and external correlation was investigated using only on-board kV imaging in two-dimensions. Interlaced MV imaging can provide for a three dimensional tracking of the respiratory trace during respiratory gated VMAT delivery. The EPID detector is located perpendicular to the kV detector and can acquire imaging at 90° simultaneous to on-board kV imaging. Customized kV imaging points can be triggered as a function of cumulative dose, while simultaneously, cine MV imaging can be acquired. Real patient breathing is predominantly in the superior-inferior (SI) direction, however in 40% of the treatments, motion is dominant in the anterior-posterior (AP) direction or the right-left (RL) direction¹⁷. Simultaneous kV and MV imaging, will provide a three dimensional position of the target in space. Consecutive acquisitions can be used to extract the respiratory trace in the SI, AP, and RL of the internal target to compare to the external surrogate box location in respiratory gated treatment delivery.

6.2.1.2 Simultaneous portal dosimetry and image verification

The synchronous kV and MV imaging technique described above can be used for any treatment verification, and is not limited to respiratory gating based delivery. The on-board kV imaging allows for an anatomical verification to ensure patients are properly aligned, whereas, the interlaced MV imaging permits for a dosimetric verification of the true dose delivered to the target. In TrueBeam Research Mode, continuous MV can be acquired in dosimetry mode, while kV radiographic projections are programmed every 1° of gantry rotation. The integrated MV image is a beams-eye-view (BEV) overlap of the exit fluence. Portal images can be calibrated as defined by 1 calibrated unit (CU) is equal to 1 Gy for 10x10 cm field size at 100 cm source-to-imager-distance¹⁸. The MV portal images can be compared to treatment dose distribution for variations in treatment dose delivery. Whereas, the simultaneous kV projections can be reconstructed, as described in Chapter 5, to allow for anatomical verification to the planning CT.

Ren et al¹⁹ discussed the combination of kV and MV imaging as a target verification tool by reconstructing volumetric imaging during treatment by the use of a priori information. The technique described increased the number of projections acquired, leading to improved image contrast while maintaining low imaging dose low in a non-clinical format. Whereas, the study being suggested here, includes the combination of kV and MV imaging for a dosimetric and anatomical intrafraction verification.

6.2.2 MV scatter characterization during kV acquisition

Chapters 4 and 5 exploit kV imaging as an intrafraction treatment verification method. However, the implementation of kV imaging, simultaneous with active MV treatment beams, cannot ignore the impact of the MV scatter and potential head leakage to the kV detector and, hence, the resulting image degradation. Wallace et al. investigated the kV signal to the kV detector as a ratio to the MV signal scattered to the kV detector in various frequencies of the kV source, and patient sizes²⁰. We have performed preliminary work to quantify the scattered dose to the kV detector from the MV source. A 10X FFF beam with 8 cm by 8 cm field size was used to deliver 3000 MU while the kV source to detector distance was 100 cm, located perpendicular to the MV beam. Transmission of the kV source was reduced by placing a lead block in the path of kV source and limiting the imaging parameters to 40 kVp, and 0.4 mA. Patient scatter of the treatment beam was simulated using the Quasar motion phantom (Modus Medical Devices, London, ON). Scattered dose was measured using ten optically stimulated luminescence dosimeters (OSLD), placed linearly along the on-board kV detector (Figure 6-1).



Figure 6-1. Scattered dose to the kV detector experimental setup.

The exposed OSLD were read using microStar InLight Reader (Landauer Inc, Glenwood, IL). The dose measured to the OSLD ranged between 1.04 cGy at the top of the detector, to 3.55 cGy at the bottom of the kV detector, with the center of the detector receiving 2.75 cGy, Figure 6-2.



Figure 6-2. Scattered dose to the kV detector ranged between 1.04 at the top, to 3.55 cGy at the bottom of the detector.

In Appendix B, a theoretical calculation of the estimated fraction of dose detected by a pixel in the kV detector was presented. According to the calculations, 3000 MU delivery will lead to 0.52 cGy to the kV detector at the centroid pixel, approximately 5 times less than measured in the OSLD experiment, 2.75 cGy. Despite the discrepancy between the calculated and measured values, both are low in comparison to the dose at isocentre, 3000 MU. The scattering volume in the measurements was a phantom composed of different density material, such as acrylic, cedar, and delrin, whereas the calculations were based on mimicking beam calibration by using a water phantom with isocentre at 5-cm depth. Also, in the calculated value of Appendix B, charged particle equilibrium was assumed, and in the measured values, the OSLD were placed directly on the kV detector without a build-up layer. Other potential sources for discrepancy in the measured values are head scatter, secondary scatter of photons, OSLD energy dependence, and backscatter from the treatment couch.

Although this preliminary work provides an estimation, a more accurate Monte Carlo calculation that accounts for the different spectra of kV energies and MV energies is required. The MV scatter can be characterized based on the kV detector material and thickness, and the kV and MV beam pulse rate. This information may be used to retrospectively remove MV scatter from kV projections and improve image quality. Studies have investigated removing the MV scatter by the read-out of unexposed frames between kV exposures through external hardware^{21,22}, interlacing kV projections in Research Mode without impact from the MV beam²³, and by using a lead collimator on the kV source to estimate MV scatter²⁴.

6.2.3 Clinical implementation of intrafraction kV imaging

A main clinical limitation in results of chapters 4 and 5 is the inability to trigger kV imaging solely in the gating window in clinical operation mode. Both studies were completed using TrueBeam Research mode only, which allows for user defined imaging trajectories but is not approved for clinical use.

Current clinical implementation of intrafraction kV imaging can be achieved through single projection images triggered at the entry or exit of the gating window, or fluoroscopy

throughout the entire treatment session, regardless of MV beam-on or -off. Triggered kV imaging at the entry or exit of the gating window will not supply a treatment verification simultaneous to the treatment MV beam, whereas, kV fluoroscopy will. However, the current kV fluoroscopy mode does not decipher between MV beam-on or -off with kV imaging continuously acquiring. Therefore, the imaging dose in kV fluoroscopy could be unacceptably high during respiratory gated delivery depending on the treatment time and the duty cycle. Also, projections acquired outside of the gating window are not useful for intrafraction verification but could be utilized to deduce accurate volumetric reconstructions absent of MV degradation.

6.2.3.1 Adaptive radiotherapy application

Future upgrades to include advanced imaging in clinical mode by allowing respiratory gated triggered kV will permit the implementation of methods examined in Chapters 4 and 5 to be translated into intrafraction verifications for early-stage SABR patients. Early-stage NSCLC patients treated with VMAT will be enrolled in the study, and will undergo respiratory gated kV imaging. Based on the projections, the external marker motion will be retrospectively correlated to the internal target motion. This analysis will provide a respiratory gated treatment verification. The kV projections acquired, will be reconstruct into during treatment gated-CBCT. Gated-CBCT and the planned dose distribution can be overlapped to certify accurate dose delivery throughout a treatment course. CBCT acquired for all treatments will monitor day-to-day variations and provide a dataset to re-optimize treatment planning for subsequent treatments. This process can help eliminate the need to re-acquire 4D-CT simulation for treatment planning.

6.2.3.2 Radiation induced lung toxicities in respiratory gated SABR patients

Chapters 3 of this thesis discussed potential reduction in radiation induced lung toxicity using respiratory gated VMAT. While in Chapter 5, image quality and target detectability of intrafraction gated and ungated CBCT was investigated. During gated treatment, CBCTs can be used for retrospective dose calculation to provide accurate dose-volume parameters for clinical outcomes research. Occurrence of radiation induced pneumonitis and

irreversible fibrosis can be investigated in these patients by acquiring CT scans at 3 months, 6 months, 12 months, and 24 months following radiation therapy. A future study in earlystage NSCLC patients can involve correlating volumes of pneumonitis and irreversible fibrosis observed in follow-up scans and respective doses to these volumes in the intrafraction CBCT.

6.2.3.3 Modelling on-board kV imaging in treatment planning system

The pitfalls of intratreatment kV imaging is the additional dose to the patient and the wear and tear on the kV tube and detector. Currently, acceptance testing and commissioning is computed during the installation of the on-board kV imaging unit to determine localization, and imaging quality for different anatomical sites²⁵. Quality assurance is performed at frequency dependent on the test to ensure the imaging unit operates safely and reproducibly²⁵. In this future works study, the spectrum of kV energies will be modelled based on acquisition of protocols for various anatomical sites. The half value layer will be measured using Unfors RaySafe Xi Mam detector (Unfors RaySafe Inc. Cleveland, OH) while the computed tomography dose index (CTDI) will be measured using Unfors RaySafe Xi transparent detector. The treatment planning system can be adapted for low energy kernels to allow accurate dose calculation through the beam characteristics in the anatomical site of kV imaging protocols. Modelling the kV beam in the treatment planning system will allow for the imaging dose to be accounted for. This will, in turn, result in adaptation of the treatment plan accordingly.

6.3 Conclusions

The main findings of this thesis are summarized as follows

 VMAT, RapidArc and SmartArc, are dosimetrically advantageous in treating earlystage NSCLC with SABR compared to fixed-beam and helical tomotherapy while providing significantly shorter treatment times.

- Respiratory-gated VMAT using flattening filter free technology has the potential to reduce the dose to normal lung, and lower the potential for inducing pneumonitis, and irreversible fibrotic volume when respiratory motion is a concern.
- On-board kV imaging was used to verify the external surrogate motion and internal target motion correlation during respiratory gated VMAT delivery. The technique was used in real-patient breathing traces exhibiting regular and irregular motion, and in a sinusoidal trace. All treatment deliveries resulted in a high correlation coefficient. Known artificial phase shifts were also accurately identified with on-board kV imaging.
- Intrafraction CBCT can provide high quality images and detectability despite the presence of MV scatter. Respiratory gated CBCT, acquired by customized kV imaging synchronously to respiratory-gated VMAT delivery, increases image quality by reducing the blur of motion compared to free breathing ungated CBCT.

The results of this thesis will provide the application of respiratory gated on-board kV imaging simultaneous to treatment beam delivery as a method to validate respiratory gated VMAT delivery while potentially enhancing clinical benefits of respiratory gating in early-stage NSCLC patients.

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Appendices

A. Appendix A – Automated IMRT planning

Treatment plans in Chapter 1 and 2 optimized in Pinnacle treatment planning systems (Philips Radiation Oncology, Fitchburg, USA) were computed using planning scripts to remove bias and optimize efficiency. Planning scripts produced for early-stage NSCLC are based on previous scripts written for different sites, such as head and neck. This appendix is adapted from previous publication titled "Automated IMRT planning with regional optimization using planning scripts" published in the in the Journal of Applied Clinical Medical Physics vol 14(1):4052 (2013) by Xhaferllari I, Wong E, Bzdusek K, Lock M, and Chen J.

A.1. Introduction

Intensity-modulated radiation therapy (IMRT) has become a standard technique in radiation therapy to provide more conformal dose distribution to improve tumor control probability and/or to reduce radiation toxicities. Currently, more than half of every disease site uses IMRT¹⁻⁴. For some simple cases, such as localized prostate cancer or whole breast irradiation, various class solutions or protocols can be developed to generate an IMRT plan efficiently⁵. However, for complicated cases such as some of head and neck cancers, it is still time-consuming to generate optimized IMRT plans. Besides requirements of accurate delineations of various target volumes and organs at risk (OAR), it is often required to generate additional IMRT optimization structures such as dose limiting ring structures, manually selecting beam directions and energies, IMRT objectives and associated weights. These parameters are generally adjusted manually during the optimization process with trial and error approach, including adding additional IMRT objectives to reduce various cold and hot spots in the dose distribution.

There are on-going research activities to find more efficient ways for IMRT planning^{6–12}. Multicriteria optimization technique^{13–20} has been introduced into IMRT planning in order to help solve issues faced with single objective planning where a weight for each objective needs to be set before the plan can be optimized. However, currently, it is still time-consuming with multicriteria optimization to generate and navigate through a large number

of plans in Pareto surface. Recently, multicriteria optimization has been commercialized in RaySearch Laboratories planning system (RaySearch Laboratories, Stockholm, Sweden)²¹.

Regional optimization²² is an effective way to improve IMRT plans by emphasizing specific region of interests to help create high-dose gradients between target volumes and critical structures during optimization using relatively high importance factors on small region of interests. In this study, we present an iterative method that can be incorporated in clinical process to improve IMRT plan quality and efficiency. Specifically, we have implemented regional optimization in a simple iterative algorithm in a commercial treatment planning system (Pinnacle, Philips Radiation Oncology, Fitchburg, MA). The regional optimization we implemented is based on region of interest (ROI), and is not voxel-based, as in the original paper²². Our method is based on automatically generated cold and hot regions in the plan. In this work, we demonstrate that such an iterative algorithm is applicable to clinical sites that are generally more challenging in IMRT planning. The method was applied to three clinical sites: head and neck, prostate with pelvic nodes, and anal canal cancers, where we evaluated its efficacies and time savings. In principal, this method can also be used for other sites to automate IMRT planning processes using planning scripts in treatment planning systems.

A.2. Material and Methods

A.2.1. Overview

For each clinical site, a class solution was first developed manually based on a group of clinical cases. The class solution provides standard beam parameters such as number of beams, their energies, directions, collimator angles, jaw positions, and initial IMRT objectives and corresponding weights. After a class solution was developed for a clinical site, the entire optimization process was incorporated in a planning script. The planning script includes the major activities shown in Figure A-1. For the purpose of providing concrete methodologies, we will explain each of the optimization steps using the National Cancer Institute of Canada Clinical Trials Group head and neck clinical protocol (NCIC

CTG HN.6) as an example. This is a good clinical site to illustrate how to automate regional IMRT optimization with many OARs and multiple target volumes.



Figure A 1. An overview of the steps completed by each script for a clinical site

A.2.2. Check required regions of interest

The IMRT scripts require basic regions of interests (ROIs) to be defined, such as all clinical target volumes (CTVs) and all organs at risk (OARs). For example, for the NCIC CTG HN.6, the following ROIs are required: CTV70, CTV63 and/or CTV56, where 70, 63, and 56 are the prescription dose in units of Gray for each volume, with intended doses delivered in 35 fractions. Other required ROIs are: cord, brain_stem, right parotid (rt_parotid), left parotid (lt_parotid), larynx, mandible, rt_cochlea, lt_cochlea, oral_cavity, and one for the body contour (external). Standard nomenclature is required by the script.

It is important to ensure all the required ROIs are present, so that the script can set proper IMRT objectives for these ROIs. The script will check for the required dose matrix and ROIs. If any of the ROIs are missing, it will display names of missing ROIs, in order for a user to add or correct the names of required ROIs. If all the required ROIs are present, the script will set standard colors for ROIs to facilitate quality assurance.

A.2.3. Generate additional contours

After checking for the required ROIs, the iterative algorithm will generate various derived contours such as planning target volume (PTV) for each CTV, planning organ-at-risk volumes (PRVs) for required OARs, and various dose-limiting ring structures for IMRT optimization purpose. For the head and neck IMRT clinical trial, Table A-1 gives a summary of all the contours generated.

Contour name	Explanations	Contour name	Explanations
PTV70	Planning target volumes for	TPTV	Total sum of all PTVs
PTV63	70, 63 and 56 Gy prescription	cord_prv	Planning risk volumes for cord
PTV56	doses	brainstem_prv	and brainstem with a 5 cm
			uniform margin
modPTV70	PTVs that exclude cord_prv,	rt_parotid_opt	Parotid volumes avoiding PTVs
modPTV63	brainstem_prv and not closer	lt_parotid_opt	
modPTV56	to the external contour by 5	external_5mm	Body contour with a 5 mm margin
	mm		
optPTV63	Optimization PTVs, avoiding	ring70	1 cm ring around PTV70
optPTV56	overlap volumes with higher	ring63	1 cm ring around ring70, and
	prescription doses		PTV63
optPTV63_m	Optimization PTVs, avoiding	ring56	1 cm ring around ring63, and
	overlap volumes with higher		PTV56
optPTV56_m	prescription doses with a 1 cm	ring50	1 cm ring around ring56
	margin		

Table A-1. Summary of all the contours generate for HN6 clinical trial

The script generates derived ROIs for OARs, such as cord_prv and brainstem_prv with 5 mm margin from cord and brain stem, respectively. Other generated PTVs are modPTV70, modPTV63, and/or modPTV56 that exclude cord_prv, brainstem_prv, and are away from skin by a 5 mm margin. Their purposes are to limit the dose to spinal cord and brain stem to within tolerance and reducing skin dose. Also, it generates optPTV63 and/or optPTV56 that avoids overlapping with higher dose PTVs, such as optPTV63 = modPTV63 - modPTV70 for optimization purpose. Rings with 1 cm uniform margin around PTVs and/or other rings, such as ring70, ring63, and/or ring56, are created for creating a more conformal dose distribution by specifying a maximum dose in each ring structure. In order

to reduce dose to critical structures such as the parotids, rt_parotid_opt and lt_parotid_opt are generated that avoid the PTVs so that more realistic objectives for IMRT optimization can be set. Total sum of the PTVs, TPTV, is generated in order to help define optimal beam geometries.

A.2.4. Add beams

A summary of the six different fields used for HN.6 with their respective couch, gantry, and collimator angles is given in Table A-2. Beams are added according to the class solution with fixed jaw sizes based on the PTV coverage and OAR sparing to reduce local minimum problem in IMRT optimization and to improve delivery accuracy and efficiency. TPTV (defined previously) is used to adjust beam geometry that covers the desired volumes. Beam geometry is set by setting the collimator, gantry, and couch angles, and setting the jaw sizes. The jaw sizes for LAO and RAO fields in Table A-2 were set to cover the total PTV with 8 mm margin, but it is limited to less than 14.5 cm in order to avoid beam splitting on Varian linacs. Thus, only the side of TPTV where beam direction is along the boundary of TPTV and parotids is made sure to be covered by the fields so that the field edge can provide higher dose gradient between TPTV and parotids. This jaw size is also set to avoid junction of the multileaf collimator (MLC) inside the fields to reduce delivery uncertainty. However, two noncoplanar beams, LSAO and RSAO, are added to cover the whole TPTV with fixed jaw size to avoid beam splitting and to provide dose gradients required for both sides of TPTV. The use of noncoplanar beams is to cover lower neck nodes but avoid irradiation to shoulders. The advantage of using fixed jaw size for large IMRT target volumes in the head and neck was discussed in a recent publication²³. As shown in Figure A-2, two posterior oblique fields cover the PTVs only from one side and shield part of the post neck region with only 2 cm jaw position from central axis for easier MLC segmentation to reduce dose to spinal cord and brain stem.

After the beam geometry is defined, the proper dose prescription is set. In the case of HN.6, the prescription dose is 70 Gy in 35 fractions to a reference point at the center of GTV. The script will check for the position of the isocenter; this isocenter will be used in all beams. The isodose lines will also be set using standard percentages of prescription with standard colors.

A similar procedure was carried out to implement class solutions for the high risk prostate cancer and anal canal cancer cases.

	Gantry angle	Collimator	Couch angle
		angle	
LSAO (left superior anterior oblique)	75 °	0 °	15 °
LAO (left anterior oblique)	15 °	15 °	0 °
LPO (left posterior oblique)	148°	350 °	0 °
RPO (right posterior oblique)	218 °	10 °	0 °
RAO (right anterior oblique)	285 °	0 °	345 °
RSAO (right superior anterior	345 °	350 °	0 °
oblique)			

Table A-2. Summary of beams generated for HN. 6



Figure A 2. Jaw positions for IMRT fields are fixed in the scripts to reduce probability of local minimum to avoid beam splitting for more accurate and efficient radiation delivery

A.2.5. Initial optimization

IMRT parameters are set in the script, including the maximum number of iterations, the maximum number of control points, minimum segment MU, and area. Then, IMRT objectives and their respective weights are set for the initial optimization using direct machine parameter optimization (DMPO) in Pinnacle. The IMRT objectives used for HN.6 are given in Table A-3. Higher weights are given to minimum dose of CTVs and modified or optimization PTVs (modPTV70, optPTV63. and optPTV56) to ensure proper dose coverage of CTVs and PTVs that are away from skin by 5 mm. However, we specified lower maximum doses with low weights to the original PTVs to ensure that MLC will open around PTVs, since part of PTVs may be too close or outside patient skin. This will ensure sufficient skin flashing without unnecessary high skin dose. If any CTV is right on the skin, bolus will be used to make sure proper dose coverage. After IMRT objectives are specified, the dose is calculated and the first optimization is then started.

ROI name	Objective type	Dose (cGy)	Weight
CTV56	Minimum dose	5700	100
CTV63	Minimum dose	6350	100
CTV70	Minimum dose	7100	10
modPTV70	Maximum dose	7690	100
modPTV70	Minimum dose	7000	65
optPTV63	Maximum dose	6720	70
optPTV63	Minimum dose	6450	80
optPTV63_m	Uniform dose	6550	5
optPTV56	Minimum dose	5700	100
optPTV56_m	Maximum dose	6125	100
optPTV56_m	Uniform dose	5650	1
PTV56	Minimum dose	2800	1
PTV63	Minimum dose	3200	1
PTV70	Minimum dose	3000	30
brainstem	Maximum dose	5000	100

Table A-3. Some of the IMRT objectives set for the first optimization for HN.6

brainstem_prv	Maximum dose	5500	33
cord	Maximum dose	4000	100
cord_prv	Maximum dose	4500	70
mandible	Maximum dose	7000	100
lt_parotid_opt	Maximum EUD	2350	20
ring50	Maximum dose	5000	10
ring56	Maximum dose	5600	100
ring63	Maximum dose	6300	50
ring70	Maximum dose	7000	100

A.2.6. Regional optimization

We implemented the regional optimization to reduce hot and cold spots in IMRT dose distributions automatically in a simple iterative manner.

A.2.6.1. Generating regional cold and hot spots

After initial IMRT optimization and the final dose calculation using collapsed cone convolution for the first pass, various isodose lines related to the minimum doses to PTVs, maximum doses inside or outside PTVs are converted to contours in the iterative algorithm. Then, the corresponding cold or hot spots in each region are generated, such as in HN.6, cold56, cold63, cold70 for cold spot in optTV56, optPTV63, and modPTV70, respectively. Each cold spot is automatically generated in the script by subtracting the required minimum isodose line (converted to contour) from the target volume. For example, cold70 = modPTV70 - 70 Gy isodose line. Similarly, hot56, hot63, hot70, hot_out_70 is the hot spot in optPTV56, optPTV63, PTV70, and outside PTV70, respectively, and they are generated automatically by the script. For example, hot63 = maximum isodose line allowed in PTV63 - PTV70 - ring70. The reason to subtract higher dose ring ROIs is to avoid conflict with minimum dose coverage of higher dose PTVs. The regional cold and hot spots for HN.6 clinical protocol are listed in Table A-4 with their relations to various ROIs and isodose lines. Similar cold and hot spots based on the prescription of each PTV are added for prostate with pelvic nodes and anal canal cases.

ROI name	Relation to ROI of isodose lines		
hot_out_70	70 Gy isodose line – PTV70 – ring70		
hot63	69.3 Gy isodose line – PTV70 – ring70		
hot56	61.6 Gy isodose line – PTV70 – PTV63 – ring70 – ring 63		
hot70	75.6 Gy isodose line		
cold70	modPTV70 – 70 Gy isodose line		
cold63	optPTV63 - 63 Gy isodose line		
cold56	optPTV56 - 56 Gy isodose line		

Table A-4. Summary of regional cold and hot spots for HN.6 clinical protocol.

A.2.6.2. Iterative optimization with regional cold and hot spots

IMRT objectives for these cold and hot spots are then added for regional optimization in the scripts — for example, objectives listed in Table A-5 for HN.6 protocol. The IMRT plan is then continually optimized with these added regional objectives based on previously optimized and segmented plan using DMPO. In this re-optimization, only MLC segment shape and weights are re-optimized. The HN.6 script uses 20 iterations. The generation of various hot or cold spots and re-optimization can be repeated multiple times until an optimal plan is achieved.

Table A-5. Summary of objectives set for the regional optimization for HN.6 clinical protocol

Objective type	Dose (cGy)	Weight
Maximum dose	6800	100
Maximum dose	6650	50
Maximum dose	5880	5
Maximum dose	7350	1
Minimum dose	700	100
Minimum dose	6300	50
Minimum dose	5600	10
	Objective type Maximum dose Maximum dose Maximum dose Maximum dose Minimum dose Minimum dose	Objective typeDose (cGy)Maximum dose6800Maximum dose6650Maximum dose5880Maximum dose7350Minimum dose700Minimum dose6300Minimum dose5600

A.3. Results

The method has been implemented and tested for three clinical sites: a clinical trial protocol for head and neck cancer, prostate cancer with pelvic nodes, and anal canal cancer. Figure A-3 shows DVH comparison for a head and neck case between a previously manually optimized clinical plan and the automatically optimized IMRT plan using the automatic iterative method. A manually optimized plan was used for comparison in this study and the plan was previously optimized by an experienced dosimetrist for clinical use. As shown in Figure A-3, the automatically generated plan has lower dose to the three most sensitive critical structures: brainstem, spinal cord, and the left and right parotids with similar PTV coverage. The comparison of dose distributions on an axial slice is shown in Figure A-4, showing fewer hot spots in the automatically optimized plan.

As an example, the effect of regional optimization is shown in Figure A-5 for comparison of dose distributions before and after regional optimization using the cold and hot spots for a head and neck case.



Figure A-3. DVH comparison for a head and neck case between manually (dashed line) and automatically generated plans (solid line).



Manually generated plan

Automatically generated plan

Figure A-4. Comparison of dose distribution on a transverse slice for a head and neck case between manually generated IMRT plan and automatically generated IMRT plan using the iterative method. Red shaded volume is PTV70 covered by 70 Gy isodose line in blue, and green shaded volume is PTV63 covered by 63 Gy isodose line in black.



Figure A-5. Comparison of dose distribution on the coronal slice for a head and neck case before (left) and after (right) automated regional optimization. Shaded volumes are PTV70 (blue), PTV63 (green), and PTV56 (red), respectively.

	Manual Planning	Automated Planning
Head and Neck	> 4 hours	~ 8 minutes
Anal Canal	> 2 hours	~ 6 minutes
Prostate with pelvic nodes	> 1.5 hours	~ 6 minutes

Table A-6. Estimated time required to generate IMRT plans

The time required to run the planning script on a Pinnacle thin client using computation server with 4 quad core 2.9 GHz CPU is listed in Table A-6. The estimated minimum time required for manual planning includes time needed to generate various derived contours, set up beams, dose prescription, manually and repeatedly adjust IMRT objectives, and running IMRT optimization. It shows that the iterative method implemented here as a script can save significant time in IMRT planning. These IMRT planning scripts are used clinically in our center for more than 500 clinical cases since they were implemented clinically in 2010. They include at least 300 head and neck cases, 180 prostate cases, and 20 anal canal cases. It should be noted that after using automated planning scripts, most cases will be tweaked by dosimetrists to see if further improvements can be made. However, most tweaking just needs a few more passes of the continuous optimization that usually take less than an hour. The estimated time saved in planning for each case is at least 2 hours for head and neck, and 1 hour for anal canal or prostate with pelvic nodes, depending on the experience of the planner.

A.4. Discussion

The present work implemented planning scripts for complex IMRT cases that automated most aspects of plan optimization which otherwise required continual manual input by a planner. We used Pinnacle planning script to automate the regional optimization in an iterative manner; however, the concept can be used in other planning systems, as well. Automated IMRT planning script was recently published for optimization of breast radiotherapy with tangential beams⁵. Here, we present an automated planning process for more complicated head and neck, prostate with pelvic nodes, and anal canal cases. It also includes the method to automatically reduce various cold and hot spots in the optimization

process. To our knowledge, such implementation for more complex IMRT cases has not been published before. Since the focus of this paper is on the methodology, we only present one example for each clinical site, even though the scripts have been used clinically for more than 500 cases. The thorough statistical analysis of these clinical cases will be presented in a separate paper.

Since many IMRT planning steps are included in our IMRT planning scripts, they generally save many hours in the IMRT planning process. It also helps implement clinical protocols, in-house standards, using standard dose prescriptions, standard margin for PTVs, standard derived region of interests (ROIs), such as modPTVs, optPTVs, cord_prv, and brainstem_prv, as well as standard color scheme for ROIs and isodose lines. The planning script can reduce variations of plan quality due to different experience of planners. The planning scripts can be improved during clinical use, incorporating new techniques learned in practice.

For many complicated cases, the IMRT planning scripts provide only a good starting point; an optimal plan still requires a planner to fine-tune the automatically generated plan to adapt the plan for individual situation. Also, the class solution does not consider geometry variations across patients; therefore, it requires fine-tuning for each individual patient. Such fine-tuning includes modifying IMRT objectives and their weights. Occasionally, beam parameters may also need to be modified, such as gantry or collimator angles. In future work we will investigate the impact of adjusting IMRT objectives and weights during the iterative optimization process. The regional optimization method presented in this paper may also be combined with priority-based IMRT optimization method²⁴.

A.5. Conclusions

We have developed IMRT planning scripts for a few clinical sites to automate most of IMRT planning process. In particular, regional optimization has been implemented in an iterative algorithm to reduce hot or cold spots during the optimization process, especially important for complex cases. We demonstrated that this is particularly useful in IMRT planning for head and neck and prostate with pelvic nodes. We have shown that automated iterative inverse planning improves IMRT planning efficiency substantially.
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B. Appendix B - Estimation of MV scatter contribution to kV detector

The dose due to the scattered MV beam at a voxel of the kV detector was characterized based on theory from a paper titled "Compton scatter imaging of a transverse scatter and attenuations" by Battista JJ, Santon LW, and Bronskill MJ published in Physics in Medicine and Biology, 1977, vol. 22 (2), pp 229-244¹.





The dose scattered to 3 sample voxels (a,b,c) of the cesium iodide array scintillator on the amorphous silicon flat panel detector was calculated for a non-divergent beam incident on a cubic water phantom[.] The geometry of the setup mimics beam calibration of monitor

units to dose at 100 cm source-to-axis distance (SAD), with a 10 cm x 10 cm field size at 5 cm depth in water:

$$D_{iso} = MU \times \frac{1.00 \ cGy}{MU}$$

Voxel 'P', located at the center of the phantom, was used to represent a typical scattering element of the scattering volume (blue). The scattering contribution was calculated at voxels on the kV detector located in the center (a), top center (b), and bottom center (c), as shown in Figure B.1.

The fluence of photons (i.e. per cm^2) scattered by a voxel at P with area, a, and thickness, z, then arrive at a pixel area (d²) on the kV detector panel was deduced as follows:

$$\Phi_{det}^{voxel} = \frac{\Phi_{iso} \frac{d\sigma}{d\Omega} d\Omega \ \rho_e \ da \ dz \ f_2}{d^2} \tag{1}$$

where, assuming charge particle equilibrium (CPE), the isocentric fluence is:

$$\Phi_{iso} = \frac{D_{iso}}{E_0} \left(\frac{\mu_{en}}{\rho} \right)_{H_2O}$$
(2)

The scattering Compton cross section is given by (Attix et al. 1986, equation 7.14)²:

$$\frac{d\sigma}{d\Omega} = \frac{r_0^2}{2} \left(\frac{E_1}{E_0}\right)^2 \left(\frac{E_0}{E_1} + \frac{E_1}{E_0} - \sin^2\phi\right)$$
(3)

Where (Attix et al. 1986, equation 7.8)²:

$$E_1 = \frac{E_0}{1 + (E_0/m_0 c^2)(1 - \cos\phi)} \tag{4}$$

The solid angle subtended by a detector pixel of size d at distance L from isocentre is:

$$d\Omega = \left(\frac{d^2}{L^2}\right) \tag{5}$$

The attenuation factor of the scattered photons is:

$$f_2 = \exp\left[-\int \mu(E_1, l) \, dl\right] \tag{6}$$

Next we consider the radiation scattered by all the voxels (like P) contained in the exposed region of the water phantom. We make the simplifying assumption that they are all well represented by the typical voxel at P. In reality, each scattering point has a different primary attenuation, scattering angle, solid angle, and secondary attenuation. We *estimate* the total scattered fluence reaching the detector pixel as follows:

$$\Phi_{det}^{volume} = \Phi_{det}^{voxel} \frac{dA \, dZ}{da \, dz} \tag{7}$$

where dA is the non-divergent beam's cross-sectional area and dZ is the phantom overall thickness.

Assuming the detector material (det) is thick enough to achieve CPE, the absorbed dose at the detector voxel, related to pixel signal, is then given by:

$$D_{det} = \left(\frac{\mu_{en}}{\rho}\right)_{det} \Phi_{det}^{volume} E_1 \tag{8}$$

Our ultimate step is to determine the "scatter-to-primary" ratio between the dose absorbed by pixels of the kV detector (assuming enough thickness to achieve CPE) and the isocentric reference dose:

$$\frac{D_{det}}{D_{iso}} = E_1 \left(\frac{\mu_{en}}{\rho}\right)_{det} \frac{d\sigma}{d\Omega} d\Omega \rho_e f_2 dA dZ / E_0 \left(\frac{\mu_{en}}{\rho}\right)_{H_2O} d^2$$
(9)

All parameters and units used in the calculation are summarized below:

 Φ_{det}^{voxel} Photon fluence due to scatter events originating in a small voxel at P (cm⁻²).

 Φ_{det}^{volume} Photon fluence due to scatter events originating from all P-like voxels in the exposed phantom volume (cm⁻²).

- da Cross sectional area of the voxel P (cm²). Assumption: Area 1 cm x 1 cm.
- *dz* Thickness of the voxel P (cm). Assumption: 1 cm.

Cross sectional area of the incident beam (cm^2) .

- Assumption: field size 10 cm x 10 cm of a non-divergent beam.
- *dZ* Thickness of the scattering phantom volume (cm). Assumption: 10 cm.
- Φ_0 Photon fluence rate at isocenter of the incident beam (cm⁻²).
- D_{iso} Dose to water at isocenter (cGy).

dA

Energy of incident photons. Assumption: 10 MV x-ray beam. Assumption: Effective monoenergetic source, with mean energy was calculated: $10 \times \frac{1}{3} = 3.333 \, MeV$

 $\left(\frac{\mu}{\rho}\right)_{H_2O}$ Mass attenuation coefficient of water (cm²/g).

- D_{det} Dose at the kV detector voxel (cGy).
- E_1 Energy of scattered photon.

 $\left(\frac{\mu_{en}}{\rho}\right)_{det}$ Mass energy absorption coefficient of the cesium iodide scintillator on the kV detector (cm²/g).

 f_2 Scattered beam attenuation factor.

l Scattered photon path length in the phantom (cm). For the central voxel (a) of the detector, l = 5 cm, whereas for the top (b) and bottom (c) voxel, calculated based on the size of the kV detector, D, and scattering angle, ϕ .

 $\frac{d\sigma}{d\Omega}$ Klein-Nishina differential cross-section for the incident beam (cm² e⁻¹ sr⁻¹).

$$r_0$$
 Classical electron radius: $r_0 = \frac{e^2}{m_0 c^2} = 2.818 \ x \ 10^{-13} \ \text{cm}.$

 ϕ Photon scattering angle (radians). For the central voxel (a) of the detector, $\phi = \frac{\pi}{2}$, whereas for the top (b) and bottom (c) voxel, calculated based on the size of the kV detector, D, and the distance from to kV detector, L: $\phi = tan^{-1} {D/2 / L}$

 $m_0 c^2$ Rest energy of an electron is 0.511 MeV

 $d\Omega$ Solid angle to the kV detector (sr).

d Size of the height, width, or thickness of the voxel at the kV detector (cm)

L Scattered photon path length to the voxel in the kV detector (cm).

 ρ_e Electron density of water:

$$\begin{split} \rho_e &= 3.343 \ x \ 10^{-23} (e \ g^{-1}) (e \ g^{-1}) \times 0.9982 \ (g \ cm^{-3}) \\ &= 3.337 \ x \ 10^{-23} 3370 \ (e \ cm^{-3}) \end{split}$$

The dose scattered to the central voxel (a), top voxel (b), and bottom voxel (c) on the kV detector per unit isocentric dose was 1.74×10^{-4} , 1.73×10^{-4} , 1.54×10^{-4} , respectively, or 0.0174%, 0.0173%, and 0.0154%. This calculation provided for an estimation of the dose ratio to the kV detector. Intra-fractional imaging synchronous to the MV beam, as investigated in Chapters 3 and 4 of this thesis, is tarnished by the MV scatter acquired at the kV detector. Further analysis to characterize the MV scatter in the kV detector, as described in Section 6.2.2 of Chapter 6, can aid in improving image quality in during treatment imaging.

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Appendix D - Curriculum Vitae

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Publications:

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