Comparing Volumetric Modulated Arc Therapy to Intensity Modulated Radiation Therapy for the Treatment of Early Stage Prostate Cancer

By

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Doctor of Philosophy
(Medical Radiation Science)

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Statement of Originality:

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University’s Digital Repository, subject to the provisions of the Copyright Act 1968.

Craig Elith

Declaration:

I hereby certify that this thesis is in the form of a series of published papers of which I am the primary author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Craig Elith
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List of Abbreviated Terms:

1A Volumetric Modulated Arc Therapy Using One Arc
1A+PA Volumetric Modulated Arc Therapy Using One Arc Plus a Partial Arc
2A Volumetric Modulated Arc Therapy Using Two Arcs
2D Two Dimensional
3D Three Dimensional
3DCRT Three Dimensional Conformal Radiation Therapy
AAA Anisotropic Analytical Algorithm
BC British Columbia
BCCA British Columbia Cancer Agency
Bladder opti Optimization Structures for the bladder
CAMRT Canadian Association of Medical Radiation Technologists
CCW Counter Clockwise
CW Clockwise
CN Conformity Number
CT Computed Tomography
CTCAE Common Terminology Criteria for Adverse Events
CTV Clinical Target Volume
D_n The Dose Covering n % of the Target Volume
DVH Dose Volume Histogram
DRE Digital Rectal Examination
DNA Deoxyribonucleic Acid
EBRT External Beam Radiation Therapy
EMR Electronic Medical Record
ERSPC European Randomised Study of Screening for Prostate Cancer
FVC Fraser Valley Centre
Fx Fraction
CAMRT Canadian Association of Medical Radiation Technologists
Gy Gray
HI Homogeneity Index
IGRT Image Guided Radiation Therapy
IMAT Intensity Modulated Arc Therapy
IMRT Intensity Modulated Radiation Therapy
LHRH Luteinising Hormone Releasing Hormone
Linac Linear Accelerator
min Minutes
MLC Multi-Leaf Collimators
MRI Magnetic Resonance Imaging
<table>
<thead>
<tr>
<th>Term</th>
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<tbody>
<tr>
<td>MRT</td>
<td>Medical Radiation Technologists</td>
</tr>
<tr>
<td>MUs</td>
<td>Monitor Units</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>OAR</td>
<td>Organs at Risk</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PA</td>
<td>Volumetric Modulated Arc Therapy Using a Partial Arc</td>
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<tr>
<td>PBC</td>
<td>Pencil Beam Convolution</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PLCO</td>
<td>Prostate, Lung, Colorectal, and Ovarian Cancer</td>
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<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
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<td>PTV__opti</td>
<td>Optimization Structures for the PTV</td>
</tr>
<tr>
<td>PRO</td>
<td>Progressive Resolution Optimiser Algorithm</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>Rectum__opti</td>
<td>Optimization Structures for the Rectum</td>
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<tr>
<td>RT</td>
<td>Radiation Therapy</td>
</tr>
<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiation Therapy</td>
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<tr>
<td>SIB</td>
<td>Simultaneous Integrated Boost</td>
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<tr>
<td>SSD</td>
<td>Source to Skin Distance</td>
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<tr>
<td>TPS</td>
<td>Treatment Planning System</td>
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<tr>
<td>TV</td>
<td>Target Volume</td>
</tr>
<tr>
<td>v8.6</td>
<td>Version 8.6</td>
</tr>
<tr>
<td>v10.0</td>
<td>Version 10.0</td>
</tr>
<tr>
<td>V__n</td>
<td>Percentage Volume (V) of an Organ Receiving n Dose</td>
</tr>
<tr>
<td>V__pres</td>
<td>The Total Volume Receiving the Prescription</td>
</tr>
<tr>
<td>V__TPres</td>
<td>The Target Volume Covered by the Prescription</td>
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<tr>
<td>VMAT</td>
<td>Volumetric Modulated Arc Therapy</td>
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<tr>
<td>VMAT-1A</td>
<td>Volumetric Modulated Arc Therapy Using One Arc</td>
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<td>VMAT-1A+PA</td>
<td>Volumetric Modulated Arc Therapy Using One Arc Plus a Partial Arc</td>
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<td>VMAT-2A</td>
<td>Volumetric Modulated Arc Therapy Using Two Arcs</td>
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<td>Volumetric Modulated Arc Therapy Using a Partial Arc</td>
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Abstract:

A series of five studies are presented that when pieced together describe the transition from an innovative concept through to the clinical implementation of the radiation therapy treatment technique, Volumetric Modulated Arc Therapy (VMAT) for the treatment of early stage prostate cancer.

At the outset of the research, Intensity Modulated Radiation Therapy (IMRT) was the standard modality for the treatment of early stage prostate cancer at Fraser Valley Centre (FVC). The initial studies of this research retrospectively compared IMRT to the innovative VMAT technique, specifically examining the quality of the plans produced and the impact of each technique on the departments planning and treatment resources. It was demonstrated that VMAT offered a treatment plan of similar quality to the IMRT technique yet VMAT had the definite advantage of being able to deliver treatment in significantly less time and also required significantly fewer monitor units to deliver a treatment fraction.

Having demonstrated an advantage of using VMAT, it was next investigated which VMAT beam arrangement would be best suited for the treatment of early stage prostate cancer. Four VMAT beam arrangements were considered; and ultimately it was decided that for FVC VMAT using one arc provided the best compromise between plan quality and delivery efficiency.

The increased complexity of VMAT planning and treatment dictates that patient specific quality assurance (QA) is required to ensure accurate dose delivery. A section of this thesis is dedicated to considering VMAT plan QA.

The final study presented here compares the acute side effects experienced by patients being treated with either IMRT or VMAT. VMAT has not only been demonstrated to be a safe alternative to IMRT for the treatment of early stage prostate cancer, in a world first VMAT has also been demonstrated to significantly reduce the incidence of the acute toxicities dermatitis, fatigue, pain and urinary frequency during treatment compared to IMRT.
Chapter One
Introduction and Overview
1.1 Overview:

This thesis by publication compares the innovative radiation therapy (RT) technique, Volumetric Modulated Arc Therapy (VMAT) with the standard treatment delivery technique, Intensity Modulated Radiation Therapy (IMRT), for the treatment of early stage prostate cancer. This research was performed at the Fraser Valley Centre (FVC) of the British Columbia Cancer Agency (BCCA), British Columbia (BC), Canada, in collaboration with the University of Newcastle, Australia.

It was decided to pilot VMAT on prostate cancer treatment at FVC for two reasons. Firstly, prostate cases account for a large portion of the workload at FVC (approximately 10 percent of workload in 2010). Therefore, any potential benefits of reduced treatment time using VMAT for prostate cases could have a significant impact on patient throughput in the department. Secondly, it was considered that using a less complex site to plan and treat, such as the prostate, would provide the best experience when using VMAT for the first time.

The thesis details the progression of VMAT from concept through to clinical implementation.

1.2 Outline:

Chapter 1: Introduction

Chapter 1 introduces the background and rationale of the research project as well as discussing the project aims and specific objectives. An overview of the thesis is provided together with an outline for each chapter/publication. The significance of the research is highlighted and the limitations of the project discussed. Reference is given to the ethics approval needed to perform this body of research.

Chapter 2: Literature Review (Paper 1)

Chapter 2 is a literature review designed to give the reader an introduction to IMRT, VMAT and another RT treatment technique not investigated in this thesis, Tomotherapy. The contents of chapter two were published as a directed reading article in the Canadian Association of Medical Radiation Technologists’ (CAMRT) journal, the Journal of Medical Imaging and Radiation Sciences. The literature review individually...
introduces IMRT, VMAT and Tomotherapy before a discussion section that compares advantages and disadvantages of the three treatment modalities.

Chapter 3: Paper 2

This chapter presents the first of two studies examining the quality of prostate treatment plans generated using either IMRT or VMAT, and the impact of these techniques on the departments planning and treatment resources. This research was performed using version 8.6 (v8.6) of Varian Medical Systems (Palo Alto, CA, USA) RapidArc software.

Chapter 4: Paper 3

In October 2011, FVC upgraded to version 10.0 (v10.0) of Varian Medical Systems RapidArc software. The study presented in chapter 3 using v8.6 of the software was then repeated using the new v10.0 of the RapidArc software. Again the quality of prostate treatment plans generated using either IMRT or VMAT was assessed together with the impact of these techniques on the departments planning and treatment resources. The results obtained using v10.0 of the software was compared to the data obtained using v8.6 (Chapter 3/Paper 2).

Chapter 5: Paper 4

Chapter 5 presents research specifically designed to determine which VMAT beam arrangement makes the best use of the department’s planning and treatment resources while still providing high quality treatment plans.

Chapter 6: Paper 5

It is widely accepted that IMRT and VMAT treatments are extremely complex and require patient specific quality assurance (QA) to be performed. The QA procedure ensures the dose predicted to be delivered in the treatment planning system (TPS) is the dose being delivered to the patient at the treatment unit. This chapter is dedicated to comparing two commercial systems to perform QA on the prostate VMAT plans. Specifically ArcCHECK, a linac measurement based QA system is compared with IMSure, a computer based QA software.
Chapter 7: Paper 6

Chapter 7 presents a study that examines the treatment related side effects experienced by patients treated with IMRT and patients treated with VMAT for early stage prostate cancer. The intent of this research is to ensure that VMAT treatments cause no additional toxicities than IMRT treatments.

Chapter 8: Conclusion

A summary of the research contributing to this thesis is provided here. The validity of the research is discussed as well as possible future directions.

1.3 Background:

1.3.1 What is Cancer?

Cancer is a disease of the body's cells.¹ Our bodies are made up of millions of cells, grouped together to form tissues, including muscles and bones, as well as organs such as the brain, heart and lungs. Normal cells have a life cycle. They reproduce themselves throughout the body to replace worn out tissue, to heal wounds and to maintain healthy organs. Genes inside each cell order it to grow, work, reproduce and die.²

Cancer cell growth is different from normal cell growth. Cancer begins when cells that would normally be dying, start to grow out of control and form a mass called a tumour. Some tumours grow only at the site where they begin (locally). These are called benign tumours. Other tumours grow locally but may invade and destroy the surrounding normal tissue or they may spread to distant parts of the body. These tumours are called malignant tumours or cancers.³ Untreated cancers can cause serious illness and death.

1.3.2 What Causes Cancer?

Most cancers occur by chance as the result of damage to cell genes at the deoxyribonucleic acid (DNA) level. DNA is in every cell and it directs all cell actions. In a normal cell, when DNA becomes damaged, the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, and the cell doesn't die.
Instead, the cell makes new cells the body does not need. These new cells all have the same abnormal DNA as the first cell does.⁴

People can inherit abnormal DNA, but most DNA damage is caused by mistakes that happen while the normal cell is reproducing. Alternatively, damage may be caused by environmental factors such as cigarette smoking, exposure to the sun, chemicals, radiation, or hormones.³,⁴

It is rare to know exactly what caused any one person’s cancer yet there is literature to support over half of all cancers can be prevented by quitting smoking, regular exercise and by eating a healthy diet.³,⁴

1.3.3 How Cancer Spreads:

Cancer cells often travel to other parts of the body where they begin to grow and form new tumours. This happens when the cancer cells get into the body’s bloodstream or lymph vessels. Over time, the tumour takes the place of normal tissue. The process of cancer spreading is called metastasis.⁴

1.3.4 Types of Cancer:

Cancers are named after the part of the body where they start. For example, breast cancer start within cells of breast tissue. The most common cancers in Australia (excluding non-melanoma skin cancer) are prostate, colorectal (bowel), breast, melanoma and lung cancer. These five cancers account for over 60 percent of all cancers diagnosed in Australia.¹

In Canada, lung, breast, colorectal and prostate cancer are the four most common types of cancer (excluding non-melanoma skin cancer). These cancers account for over half (52 percent) of all new cancer cases and prostate cancer accounts for about one-quarter (26 percent) of all new cancer cases in men.²

This thesis presents a series of studies exploring radiation therapy treatment options for prostate cancer, therefore further discussions on cancer will be limited to prostate cancer only.
1.3.5 Prostate Cancer:

Prostate cancer starts in the cells of the prostate gland in men. The prostate is part of the male reproductive system (Figure 1-1). The prostate's function is to make part of the liquid (seminal fluid) that mixes with sperm from the testicles to make semen. Semen is ejaculated during sex.

The prostate is a walnut-sized gland just below the bladder and in front of the rectum. It surrounds part of the urethra, the tube that carries urine and semen through the penis.5

![Diagram of the male reproductive system showing the position of the prostate.]

Figure 1-1: The male reproductive system showing the position of the prostate.5

Prostate cancer is the most common type of malignant disease in men.6 In 2009, over 19,400 new cases of prostate cancer were diagnosed in Australia. This represents more than 30 percent of all cancers diagnosed in Australian men. The risk of being diagnosed with prostate cancer by age of 85 is one in five men. In 2007, there were 2,938 deaths caused by prostate cancer, accounting for 13 percent of all cancer deaths in Australian men.7

In Canada it is estimated that in 2013, 23,600 men will be diagnosed with prostate cancer. This represents 25 percent of all new cancer cases in men in 2013; 3,900 men will die from prostate cancer representing 10 percent of all cancer deaths in men in 2013.5
The incidence of prostate cancer increases with age, it is very unusual under the age of 50 and men over 70 are at increased risk. The exact cause of prostate cancer is unknown. The symptoms of prostate cancer are associated with the prostate becoming enlarged. Symptoms may include:

- starting or stopping urination is a problem.
- slow stream.
- painful urination or ejaculation.
- dribbling.
- frequent urination.
- loss of urinary control.
- blood in urine or ejaculate.
- night-time voiding.

In advanced cases of prostate cancer, symptoms can include:

- Weight loss.
- Fatigue.
- Backache or sciatica-like pain, or swelling of the legs that doesn’t go away.

Prostate Cancer is usually detected through routine physical examination. A digital rectal examination (DRE) may find an enlarged prostate or a blood test may indicate elevated levels of prostate specific antigen (PSA).

Once diagnosed, prostate cancer is staged according to the TNM classification system (Table 1-1). The TNM classification system is used as the standard around the world. In general a lower number in each category means a better prognosis.

Standard treatments for prostate cancer includes observation, surgery and/or radiation therapy and/or hormone therapy. The type of treatment is influenced by the patient's age, medical condition and personal desires.

Low-grade disease confined to the prostate may be ‘observed’ (regular surveillance by doctor) if not causing symptoms.

Surgery with curative intent removes the whole prostate (radical prostatectomy). The main side effects are impotence and incontinence. Radical radiotherapy can also be used with curative intent, either with external beam radiation therapy (EBRT) or by implanting radioactive seeds (brachytherapy). Side effects are similar to surgery, however bowel problems may also occur.
Table 1-1: The TNM classification System for Prostate Cancer.8

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>T1</td>
<td>can’t feel the tumour during a digital rectal exam</td>
</tr>
<tr>
<td>T2</td>
<td>a nodule that can be felt on rectal examination</td>
</tr>
<tr>
<td>T2a</td>
<td>the tumour is small, on one side of the prostate only</td>
</tr>
<tr>
<td>T2b</td>
<td>on both sides but confined to prostate</td>
</tr>
<tr>
<td>T3</td>
<td>extends through the capsule of the prostate</td>
</tr>
<tr>
<td>T4 or N+</td>
<td>tumour is touching or attached to other organs, or cancer has escaped to lymph nodes or beyond</td>
</tr>
<tr>
<td>M+</td>
<td>metastatic (spread) to other organs, e.g. bone</td>
</tr>
</tbody>
</table>

For widespread disease, hormone therapy reduces the stimulus of the male hormones. Removing the testis or injecting luteinising hormone releasing hormone (LHRH), or anti-androgen hormones, can hold the disease for three to four years and may improve outcomes if given early with radiation in high risk patients.7

As this thesis examines different techniques used to deliver EBRT treatment to the prostate, further discussion will be limited to this treatment modality only.

1.3.6 External Beam Radiation Therapy (EBRT) for Prostate Cancer:

The central dogma of radiation therapy is to deliver a prescribed therapeutic dose of radiation to the target volume while minimising the dose to the surrounding tissues and vital organs to reduce radiation treatment related morbidities.

In EBRT for prostate cancer, a linear accelerator (linac) is used to carefully direct beams of radiation at the prostate target. The patient lies on the treatment couch while the gantry of the linear accelerator moves around them and delivers the radiation from many angles (Figure 1-2). The organs at risk (OAR) surrounding the prostate include the rectum, bladder and heads of femur (Figure 1-1). It is essential to limit the dose being delivered to the OAR to reduce the radiation treatment related morbidities outlined in Table 1-2.
Chapter 1: Introduction and Overview

Table 1-2: Common side effects of radiation therapy treatment to the prostate; listed by the surrounding tissue or vital organs receiving dose.

<table>
<thead>
<tr>
<th>Surrounding Tissue/Vital Organ</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>- Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>- Proctitis (inflammation of the anus and the lining of the rectum)</td>
</tr>
<tr>
<td>Bladder</td>
<td>- Increased urinary frequency</td>
</tr>
<tr>
<td></td>
<td>- Increased urinary retention</td>
</tr>
<tr>
<td></td>
<td>- Urinary tract pain</td>
</tr>
<tr>
<td>Heads of Femur</td>
<td>- Necrosis (cell death that can reduce bone strength and lead possible fracture)</td>
</tr>
</tbody>
</table>

Since the early 1990s, three dimensional conformal radiotherapy (3DCRT) has been the standard technique to deliver EBRT to the prostate.\textsuperscript{10} 3DCRT generally uses four or more beam directions that are shaped by multi-leaf collimators (MLC) to conform the radiation dose to the prostate target volume while shielding the surrounding normal tissues (Figure 1-3). In 3DCRT treatment, a uniform dose is delivered to a 3D target volume. Importantly, the dose delivered to the surrounding tissues and vital organs is limited therefore reducing radiation induced side effects.

IMRT was introduced in the mid-late 1990s and represented a major shift in modern radiotherapy over the pre-existing 3DCRT technique.\textsuperscript{11} The reported advantages of IMRT over 3DCRT include that IMRT can provide increased dose conformity throughout target volumes.\textsuperscript{12-15} Also, IMRT is capable of generating dose distributions that can be tailored to fit complex three dimensional (3D) target volume shapes and provides for rapid dose fall-off and the deliberate sparing of surrounding critical structures from unnecessary radiation dose.\textsuperscript{12-15} In summary, IMRT treatment plans are more conformal than 3DCRT plans and deliver lower doses to the OAR.\textsuperscript{16}
Figure 1-2: A Linear Accelerator (Linac) which is used to deliver external beam radiation therapy treatments.

a) A linac being demonstrated by the PhD candidate, Craig Elith, to local dignitaries at the Fraser Valley Centre of the British Columbia Cancer Agency. (Published in the Abbotsford Times 2007)

b) A schematic diagram of a linear accelerator delivering a treatment beam to the prostate.
On a linear accelerator, IMRT is typically delivered at fixed gantry angles by either step-and-shoot IMRT or sliding window IMRT. Step-and-shoot IMRT is achieved by delivering separate multiple field segments as part of a single treatment field which together supply an intensity modulated beam. In the sliding window technique, the MLC move constantly across a treatment field at a varying rate to deliver the dose modulated beam.\(^ {17}\)

Since 2008, FVC has used a five field IMRT technique to deliver RT treatment for early stage prostate cancer. Prior to the implementation of the IMRT technique, FVC used 3DCRT to treat prostate cancer. Specifically, the Bedford technique was used to deliver the 3DCRT treatment.\(^ {18}\) As supported by available literature, the FVC experience has been that IMRT produces RT treatment plans that improve the dose conformity to the target volume and deliver a reduced dose to surrounding tissues and vital organs (Figure 1-4).\(^ {12-15}\)

While the clinical applications of IMRT are numerous, IMRT has a large potential to benefit those cases where the target volume surrounds or partially surrounds an OAR of radiation injury. For example, in prostate cancer where the planning target volume (PTV) can wrap around the rectum and tumours of the head and neck where the PTV may surround the spinal cord.\(^ {11}\)

The improved dose distribution achieved using IMRT when coupled with Image Guided Radiation Therapy (IGRT) allows for accurate target localisation at the time of treatment delivery. Improved localisation may permit dose escalation to the target volume and increase the potential for a greater tumour control probability. Previous studies have demonstrated that dose escalation used in IMRT treatments for prostate cancer and locally advanced non-small cell lung cancer cases achieved improvements not only in local control, but in clinical survival.\(^ {20}\)

Despite the advantages offered by IMRT, it does have some disadvantages. IMRT treatments of the prostate typically utilise five to nine treatment angles and as such require more time to deliver a single treatment fraction compared with 3DCRT.\(^ {14,17}\) The increased treatment time using IMRT increases the likelihood of patient movement during treatment that may result in a geographical miss of the treatment target. Longer treatment times also reduce patient throughput in an RT department potentially increasing waitlists.
Figure 1-3: An example of a Multi-Leaf Collimator (MLC) system utilised to shape the linear accelerator treatment beams. (Varian Medical System’s MLC-120)

a) The MLC housed in the gantry head of the linear accelerator.\textsuperscript{19}

b) A beam’s eye view of the MLC.\textsuperscript{19}
Figure 1-4: Radiation therapy treatment plans comparing the dose distribution achieved using;

a) a Three Dimensional Radiation Therapy (3DCRT) *Bedford* technique and
b) a 5-field Intensity Modulated Radiation Therapy (IMRT) technique for the treatment of prostate cancer.

NB: The planning target volume (PTV) is outlined in red.
When using IMRT, a larger volume of normal tissue receives a low dose of radiation, compared with 3DCRT. This is due in part to a larger number of beams and beam directions used when treating with IMRT. Also, compared with 3DCRT, IMRT requires a significantly larger number of monitor units (MUs) to deliver a comparable prescription dose. This results in an increase to the whole body dose as a result of scatter and leakage radiation. Therefore, IMRT may result in an increased rate of radiation induced secondary malignancies due to the larger volume of normal tissues being irradiated to lower radiation doses and higher whole body dose.

In 2008, Otto reported a novel form of IMRT called Volumetric Modulated Arc Therapy (VMAT). In VMAT, treatment is delivered using a cone beam that continuously rotates around the patient. The cone beam is modulated by the intertwining of dynamic MLC, variable dose rates, and variable gantry speeds to generate IMRT quality dose distributions in a single optimised arc around the patient. Using VMAT, clinicians can now deliver a continuously modulated dose to the entire tumour volume while sparing normal, healthy tissue.

The primary advantage of VMAT compared with conventional IMRT is that the treatment delivery times are significantly reduced. Faster treatment times increase patient comfort, reducing the risk of patient movement during treatment and therefore limiting the risk of geographical target miss. Also, a reduced treatment time has the potential to reduce RT waiting lists. Another advantage of VMAT treatment over IMRT is that fewer MUs are required to deliver a treatment fraction. The reduction in MUs needed for treatment reduces the amount of low dose radiation delivered to a patient through scatter and leakage radiation that in turn reduces the theoretical risk of radiation induced secondary malignancies.

Since being introduced in 2008, VMAT has quickly attained widespread use in RT departments thought the world. There are now several variations of VMAT available commercially. These include; RapidArc (Varian Medical Systems, Palo Alto, CA, USA), Elekta VMAT (Elekta AB, Stockholm, Sweden) and Phillips SmartArc (Phillips, Inc, Andover, MA, USA).

In mid 2010, FVC upgraded its infrastructure to be able to deliver VMAT treatments using Varian Medical Systems RapidArc system. This thesis presents research performed at FVC during the transition from IMRT to VMAT for the treatment of early stage prostate cancer.
1.4 Aim:

The overall aim of the research presented here is to compare the innovative technique, VMAT, with the current standard technique, IMRT, for the treatment of early stage prostate cancer at FVC.

1.5 Objectives:

The specific objectives of the research are;

i. To compare the quality of the dose distributions generated using IMRT and VMAT for the RT treatment of early stage prostate cancer.

ii. To compare the time needed in RT planning to generate an acceptable dose distribution for the treatment of early stage prostate cancer using IMRT and VMAT

iii. To compare the time required on a linear accelerator to deliver a single treatment fraction for prostate cancer using IMRT and VMAT

iv. To compare the number of MUs needed to deliver a single fraction of treatment for prostate cancer using either IMRT and VMAT

v. To develop the best VMAT technique for the treatment of early stage prostate cancer that makes the best use departmental resources at FVC.

vi. To compare the usability of IMSure, a plan quality assurance software, with ArcCHECK, a linac measurement based method for the quality assurance (QA) check of VMAT treatment plans

vii. To monitor the clinical implementation of VMAT for the treatment early stage prostate cancer compared with IMRT by comparing the acute side effects.

1.6 Ethics:

Each component of the research presented here received ethics approval.

The retrospective planning analyses presented in Chapters 3-6 received approval from the University of Newcastle, Australia, Human Research Ethics Committee (approval number: H-2011-0073), and the British Columbia Cancer Agency, Canada, Research Ethics Board (approval number: H11-00108). This encompassed objectives i – vi.
In order to conduct the analysis of recorded acute side effects presented in Chapter 7, a request for variation was made to, and approved by, the University of Newcastle, Australia, Human Research Ethics Committee (approval number: H-2011-0073). Approval was also granted by the British Columbia Cancer Agency, Canada, Research Ethics Board (approval number H13-02127). This variation encompassed objective vii.

1.7 Limitations of the Thesis:

A limitation of this research is that only 20 cases were used in each of the retrospective planning studies that constitute Chapters 2-4 of the thesis. A study population of 20 was deliberately chosen to create a balance between having a reasonable number of cases to allow meaningful statistical analysis and ensuring the studies were completed in a reasonable time frame.

Another limitation is observed in Chapter 7 (study 5) where the treatment related morbidities associated with prostate cancer treatment using VMAT were compared with those observed using IMRT. The data used in this study was collected from patients treated with IMRT at FVC and patients treated with VMAT at the BCCA’s Centre for the North (CN), in Prince George, BC, Canada. A limitation of this research is that the dose tolerance applied to the rectum and bladder during planning was slightly different for the VMAT plans at CN and IMRT plans at FVC. It is possible to justify comparing these VMAT and IMRT cases when considering the intent of this study. The aim of the research presented in Chapter 7 is to demonstrate that VMAT treatments for prostate cancer cause no additional toxicities to the patient than IMRT treatments. The dose constraints applied to the VMAT plans were tighter than those using IMRT. In theory, this translates to less dose being delivered to the rectal tissues and therefore a reduced risk of rectal and bladder toxicities when using VMAT. In an attempt to validate that any observed differences in toxicities could be attributed to the treatment technique, IMRT and VMAT, an endeavour was made to ensure that the two groups of patients were similar for a range of personal and cancer data that included age, stage, PSA and Gleeson score.

A second limitation to the research presented in Chapter 7 (study 5) is that the treatment related side effects using VMAT and IMRT were recorded at two different centres of the BCCA. It is possible there was some variability in how the side effects were interpreted at the two centres. To minimise this risk, the treatment related
Chapter 1: Introduction and Overview

Morbidities were recorded according to a National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) toxicity scale which provides clear definitions on how to grade toxicities appropriately.

1.8 Assumptions:

The following assumptions are made during the research.

- All dosimetric calculations performed in chapters three to six were performed by the candidate. It is assumed the same planning performed by others would require the same or similar time to produce plans of equivalent quality.
- The time needed to produce a treatment plan is constant irrespective of planner experience. That is, the time measured to produce a treatment plan does not decrease as an individual planner gains experience with VMAT.
- The 20 data sets used in all retrospective planning analyses are representative of the greater population.
- An IMRT or VMAT dose distribution optimal for treatment is achieved at the first attempt.
- The time needed to set-up a patient for treatment is the same for both the IMRT and VMAT techniques.
- The 40 IMRT and 32 VMAT cases assessed for actual toxicities are representative of the greater population.
- The IMRT plans produced at FVC are of similar quality to the VMAT plans generated at CN.
- Radiation therapists interpret patient toxicity assessment using the National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) toxicity scale in the same way.
1.9 Clinical Significance:

Depending on the outcomes of the research performed here, there could be several clinically significant findings.

1.9.1 Faster Treatment Times Using VMAT:

Based on available literature it is hypothesised that VMAT compared with IMRT will take less time to deliver a single fraction of prostate cancer treatment. If this hypothesis is proven true the potential benefits may include;

- Improving patient comfort during treatment reducing the risk of patient movement and missing the treatment target.
- Allow more cancer patients to receive radiation therapy treatments daily and therefore reduce waiting lists.
- Provide extra time on a treatment unit to implement advanced image-guided radiation therapy (IGRT) protocols without increasing waiting lists.
- Provide additional time to implement advanced treatment techniques for other treatment sites that require longer treatment times without increasing waiting lists.
- Provide a biological advantage. Evidence has shown that the radiation survival is not only a function of the total dose delivered, but is also dependent on the duration that the radiation is delivered.\(^{26,27}\) There is a potential tumour cell killing benefit to deliver radiation doses in a shorter time.\(^{28}\)

1.9.2 Less Monitor Units Required to Deliver VMAT Treatment:

It is hypothesised each fraction of treatment using VMAT will require fewer MUs to deliver a treatment compared with IMRT. If this is proven true, the decrease in MUs required for VMAT treatments reduces a patient’s exposure to scatter and leakage radiation, reducing the risk of developing secondary cancers.\(^{21,22}\) Secondary malignancy induction is an important consideration for cancers such as prostate cancer where ongoing technical improvements in cancer diagnosis and treatment are improving the survival of patients being treated with radiation.\(^{29}\)
1.9.3 Improved Conformity May Allow Dose Escalation:

It is well established that high-dose radical radiation therapy for localised prostate cancer improves disease control.\textsuperscript{30-33} Others have reported that conformity of the prescription dose to the target volume is improved when using VMAT when compared with IMRT.\textsuperscript{34} If VMAT is demonstrated to improve conformity compared with IMRT, VMAT may be used to escalate the dose being delivered to the prostate, therefore improving disease control, without increasing treatment-related morbidities associated with radiation exposure to surrounding tissues.

1.9.4 Quality Assurance (QA):

It will be tested if the \textit{IMSure} planning QA software is as effective as \textit{ArcCHECK}, a linac measurement based QA system, for the QA of prostate VMAT treatment plans. If demonstrated to be as effective as the linac measurement based system, using a planning software to perform the QA will significantly reduce the workload of the medical physicist and eliminate the need to use linac time to perform the QA, time that could be used to treat more cancer patients.

1.9.5 Side Effects:

The acute radiation related side effects observed during radiation therapy treatment of early stage prostate cancer using either IMRT and VMAT will be compared. If VMAT is demonstrated to causes no additional harm than IMRT, it would be recommended that VMAT becomes the new standard of treatment at FVC to takes advantage of the possible faster treatment times and reduction in monitor units. It also possible VMAT reduces the incidence of acute radiation induced toxicities. If this is proven true, VMAT could be used for dose escalation as described in 1.9.3 above.
1.10 Chapter References:


11. Nutting C. Intensity-modulated radiotherapy (IMRT): the most important advance in radiotherapy since the linear accelerator?. *Br J Radiol* 2003;76(910):673.


Chapter Two

Literature Review

Publication(s) contained within Chapter:

2.1 An Introduction to the Intensity Modulated Radiation Therapy (IMRT) Techniques, Tomotherapy and VMAT

Primary Author: Craig Elith a,b

Co-Authors: Shane E Dempsey, b Naomi Findlay, b and Helen Warren-Forward b

a British Columbia Cancer Agency, Fraser Valley Centre, BC, Canada
b School of Health Sciences, University of Newcastle, Australia.


2.2 Preface:

This literature review was published as a directed reading article in the Canadian Association of Medical Radiation Technologists (CAMRT’s) *Journal of Medical Imaging and Radiation Sciences*. The paper is intended for an audience of all medical radiation technologists (MRTs) which includes radiation therapists, diagnostic radiographers, nuclear medicine technologists, magnetic resonance imaging (MRI) technologist and sonographers. The paper provides an introduction to the two radiation therapy treatment techniques which form the basis of the PhD research presented here, that is, Intensity Modulated Radiation Therapy (IMRT) and the innovative technique, Volumetric Modulated Arc Therapy (VMAT). The article also introduces another innovative technique, Tomotherapy. At the time this article was written, VMAT and tomotherapy were rivalling, newly emerging technologies which provide IMRT quality treatments units using a rotational delivery technique.

In order for the MRTs to achieve CAMRT continuous professional development credits for reading the directed reading article, there is a requirement to answer the multiple choice questions provided at the end of this chapter. These multiple choice questions were developed by the primary author.
2.3 Statement of Contribution of Others:

The first draft of this literature review was written in its entirety by the candidate, Craig Elith. The co-authors of this paper are the candidate’s PhD supervisors who provided feedback on the draft version of this paper. Craig Elith was then responsible for the preparation of the final version and journal submission.

2.3.1 Co-author Statements:

I attest that Research Higher Degree candidate, Craig Elith, made significant contribution to the paper/publication entitled An Introduction to the Intensity Modulated Radiation Therapy (IMRT) Techniques, Tomotherapy and VMAT. Independently, Craig performed the literature review and was responsible for preparation of the manuscript. Craig also prepared the multiple choice questions that formed the directed reading quiz.

(Signature of Co-Author)  (Signature of Co-Author)
Shane Dempsey             Naomi Findlay
Date:                     Date:

(Signature of Co-Author)  (Signature of Candidate)
Helen Warren-Forward      Craig Elith
Date:                     Date: July 2 2014

(Signature of Assistant Dean Research Training (ADRT))

(Full Name of ADRT)
Date:
Chapter 2: Literature Review

Directed Reading Article

An Introduction to the Intensity-Modulated Radiation Therapy (IMRT) Techniques, Tomotherapy, and VMAT

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ABSTRACT

The goal of radiation therapy is to administer a therapeutic dose of radiation to a target while limiting the side effects caused by delivering the dose to surrounding tissues and vital organs. The ongoing pursuit to achieve an optimal dose distribution has prompted the radiation therapy profession to develop new techniques that incorporate advances in technology. In radiation therapy today, modern techniques that include three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) are routinely used in the treatment of cancers. Compared with 3D-CRT, IMRT is capable of producing dose distributions that conform to the planning treatment volume and deliver a reduced dose to surrounding tissues and vital organs. This has come with the cost of increased treatment time and a larger volume of normal tissue receiving low radiation doses. Most recently, there has been considerable interest in the rotating gantry IMRT techniques, tomotherapy and volumetric-modulated arc therapy (VMAT).

Tomotherapy is a dedicated treatment system that is best described as a combination of a computed tomography scanner and a linear accelerator. In tomotherapy, treatment is delivered using a rotating fan beam. A therapeutic dose is delivered when a patient is translated smoothly through the bore of the machine as its gantry continuously rotates. Tomotherapy is capable of producing high-quality plans that increasingly spare dose to surrounding organs at risk. In VMAT, treatment is delivered on a linear accelerator using a cone beam that rotates around the patient. The cone beam is modulated by dynamic multileaf collimation, variable dose rate and variable gantry speed to generate IMRT-quality dose distributions in a single optimized arc around the patient. VMAT treatments can significantly reduce the time and monitor units required to deliver a patient’s treatment. Conventional IMRT, tomotherapy and VMAT typically produce dose distributions of similar quality. Which technique is most suited to treat a patient will depend on considerations such as the availability of the specific treatment type and its impact on the utilization of departmental planning and treatment resources.

RÉSUMÉ

Sous l’impulsion principale des avancées technologiques, la radiothérapie a progressé à un point tel que la radiothérapie conformale 3D (3DCRT) et la radiothérapie à modulation de dose (IMRT) sont utilisées couramment dans le traitement du cancer. Comparativement à la 3DCRT, l’IMRT conventionnelle permet de produire une distribution de dose conforme au PTV et une dose réduite aux tissus et aux organes environnants. Ceci s’est toutefois accompagné d’une augmentation de la durée des traitements et d’un plus grand volume de tissus normaux recevant de faibles doses de rayonnement. Récemment, les techniques IMRT utilisant un portique rotatif, la tomothérapie et l’irradiation dynamique VMAT ont suscité beaucoup d’intérêt. La tomothérapie fait appel à un système spécialisé qu’on peu décrire comme une combinaison d’unité de tomodensitométrie et d’accélérateur linéaire. En tomothérapie, la dose est administrée à l’aide d’un faisceau à cone rotatif. La dose thérapeutique est administrée pendant que le patient est lentement déplacé par l’ouverture de la machine et que le portique tourne. La tomothérapie permet de produire des plans de grande qualité tout en épargnant de plus en plus les organes à risque environnants. Le cone de rayonnement est module par MLC dynamique, taux de dose variable et vitesse variable du portique de manière à produire des distributions de dose de qualité IMRT dans un arc optimisé unique autour du patient. Les traitements VMAT peuvent diminuer de façon marquée le temps et les unités de surveillance requises pour assurer le traitement du patient. L’IMRT conventionnelle, la tomothérapie et l’irradiation dynamique VMAT produisent habituellement des distributions de dose de qualité similaires. La technique la plus appropriée pour un patient dépend de considérations comme la disponibilité d’un type particulier de traitement et son effet sur l’utilisation des ressources de planification et de traitement du service.

Introduction

Within one year of Roentgen’s discovery of X-rays in 1895, radiation was being used for the treatment of various malignant diseases [1].
From the 1950s to the late 1980s the approach to radiation therapy was largely a two-dimensional (2D) approach. In 2D radiation therapy:

- Image acquisition relied on the use of a conventional X-ray simulator to generate planar radiographs on which bony anatomy landmarks could be visualized and used as cues for volumes of interest.
- Plans were created on a limited range of images and standardized beam arrangement techniques were used [2].
- On treatment, rectangular and symmetrical collimation was used with manually applied shielding blocks collimating a beam.

The central dogma of curative intent radiation therapy had been largely realized; that is, radiation therapy aims to deliver a prescribed dose across a target volume, while keeping dose to the surrounding tissues and vital organs to a minimum. However, one restriction was still the doses received by surrounding organs.

Technological advances since the early 1990s have changed the practice of radiation therapy significantly, and radiation therapy transitioned from the 2D method to a three-dimensional (3D) highly conformal approach.

In the 3D paradigm:

- Image acquisition included imaging technologies such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). These imaging modalities provide a full 3D anatomical model of the cancer patient. This permits more accurate identification of tumor volumes and their spatial relationship with other tissues [3].
- Advances in computing technology allowed treatment planning systems to incorporate these new imaging technologies to generate and calibrate treatment plans in 3D.
- The multileaf collimator (MLC) system was developed which allows precise shaping of the treatment beam to the target volume in beams-eye view.

These technological advances combined led to the development of 3D conformal radiation therapy (3D-CRT). 3D-CRT generally uses an increased number of fields that are shaped by MLC to conform the dose to the target volume while shielding normal tissues. Therefore, in 3D-CRT treatment, a more uniform dose is delivered to a 3D target volume and the dose received by the surrounding tissues and vital organs is reduced.

With 3D-CRT came a review of the 2D dogma. It was now possible and easy to give the tumor high doses. Perhaps the dogma had now changed to ensuring a high and homogenous dose to the target while avoiding doses to all other structures.

The improved levels of dose conformity achieved by 3D-CRT increased the chance of a geometric miss during radiation therapy treatment. The consequence of missing the target encouraged the development of improved imaging capabilities at the time of treatment. Imaging in the treatment room during a course of radiation therapy, with decisions made on the basis of the imaging, is referred to as image-guided radiation therapy (IGRT) [4]. IGRT focuses heavily on the potential benefit of advanced imaging and image registration to improve precision, thus reducing the volume of healthy tissue irradiated and potentially allowing for dose escalation [5].

Since the mid-1990s and early 2000s, there has been an explosion in the development of an advanced form of radiation therapy called intensity modulated radiation therapy (IMRT). IMRT represents a major shift in the practice of modern radiation therapy [6]. Notably, IMRT can provide an improved dose distribution and increased dose homogeneity when compared with 3D-CRT. IMRT itself has taken many forms including step-and-shoot IMRT, sliding window IMRT, tomotherapy, volumetric-modulated arc therapy (VMAT), stereotactic body radiation therapy, cyberknife and proton therapy. It is beyond the scope of this article to discuss each of these IMRT technologies in detail. Instead, this article will introduce the concepts behind IMRT and the most commonly used techniques: step-and-shoot and sliding window IMRT. The discussion will then focus on the IMRT methods that arguably are of most interest currently, the rotating gantry IMRT techniques, tomotherapy and VMAT.

**IMRT**

IMRT is the delivery of radiation to the patient via fields that have non-uniform radiation fluence [2]. The introduction of IMRT creates the possibility of generating dramatically improved dose distributions that could be tailored to fit complex shapes.

IMRT improves on the dose distributions achieved using 3D-CRT. 3D-CRT beams are fashioned with tight margins to conform to a target volume. A major limitation of 3D-CRT is that it is unable to account for indentations in the target where critical structures invaginate into the target volume. IMRT addresses this shortcoming of 3D-CRT in that IMRT offers great flexibility in sculpting the dose to complex-shaped targets [7].

The complex shapes achieved using IMRT are made possible in that IMRT considers each radiation beam as multiple rays, or beamlets, and assigns different beam strengths to the individual rays. These beamlets treat small areas of tissue, called voxels, which are a cubic millimetre of space. The beamlets are designated to satisfy the predetermined dose specifications to the tumor site and surrounding normal tissues. By modulating both the number of treatment fields and the intensity within each field, there is a greater control of dose distribution around the target and the dose...
homogeneity within the target [8].

A new feature of IMRT that is not normally associated with previous planning techniques is the inverse-planning process. Both 2D conventional and 3D-CRT rely on forward-planning to create radiation dose distributions. In forward-planning, after the radiation treatment fields are designated by the physician, a physicist or dosimetrist defines the number, direction, beam weighting and shapes of the radiation beams that make up the plan. Based on these decisions and inputs, a treatment plan is produced and a judgement is made on how well the plan meets the prescription.

An IMRT plan is typically created with inverse planning (also referred to as reverse planning). In inverse planning, the physician will outline the target on the CT simulation images. Because of the potential of IMRT to sculpt radiation dose around and between volumes, the CT simulation data- sets can be fused with PET or MRI images to more accurately define the target volume and surrounding normal structures. The treatment planner will then enter the desired dose limits for the tumor as well as the dose constraints for the surrounding normal tissues. Inverse-planning software, using a dose-optimizing algorithm, determines the radiation beam characteristics (e.g., shape, weight) most likely to meet the prescription requirements designated at the start of the treatment planning process. After numerous beam-modifying iterations where size, shape and dose profiles of individual beams are constantly modified by the software, the planning system generates the optimum treatment plan that delivers the closest adherence to the dose limits applied to the target and surrounding normal tissues [9]. To increase the potential for producing a better plan, IMRT generally requires more beams than 3D-CRT and often five to nine beams are used for each fraction [10].

On a conventional linear accelerator, it is the MLC that is key to altering the beam fluence, thus making IMRT possible. On a linac, IMRT is typically delivered at fixed gantry angles by either step-and-shoot IMRT or sliding window IMRT. Step-and-Shoot IMRT can be achieved by delivering multiple static dose segments within each field (beamlets of dose) that together produce an intensity-modulated field. In the sliding window technique, the leaf pairs move constantly across the field at varying rates to deliver the modulated dose for that beam. This approach has been widely used in the treatment of patients with prostate, head and neck, and breast cancers with excellent results [3].

There are many advantages for IMRT over 2D and 3D-CRT techniques. As previously mentioned, IMRT is capable of sculpting dose distributions to a complex target volume involving concave and convex portions [2]. The technology of IMRT also allows for rapid dose falloff sparing surrounding critical structures [11].

Improved protection of the surrounding tissues using IMRT has decreased the side effects in comparison to 3D-CRT methods in virtually every type of cancer treated [8]. For example, a steep dose gradient in the head and neck region can potentially spare the function of surrounding normal tissues. Many studies have specifically assessed the benefit of IMRT in sparing the parotid glands as xerostomia has been problematic for patients treated with conventional radiation. Salivary flow reduction causes a number of problems for head and neck cancer patients including difficulty chewing, tooth decay, dysphagia, taste loss and altered speech. These manifestations of reduced salivary function can impact quality of life for head and neck cancer patients after treatment [11]. Parotid sparing and quality of life have been significantly improved in patients who had received IMRT as compared with patients who underwent conventional radiation [12].

The improved dose distribution achieved using IMRT when coupled with IGRT (that allows accurate target localization at the time of treatment delivery) permits dose escalation to the target volume. Numerous studies have demonstrated that dose escalation achieved in IMRT treatments of patients with locally advanced non-small-cell lung cancer and prostate cancer, achieved improvement not only in local control, but also clinically meaningful improvement in survival [8].

Another advantage of IMRT is that it allows a simultaneous integrated boost, which allows the delivery of a higher dose per fraction to areas considered at high risk of disease while prescribing a lower dose per fraction to lower risk regions [13]. Despite the many advantages of IMRT, the technique does have some negatives. The greatest concern is that IMRT increases the integral dose received by a patient. It is true that an IMRT plan does result in an overall reduction in the volume of normal tissues receiving a high dose. However, there is a larger volume of normal tissues that is radiated to lower radiation doses [14, 15]. This is due in part to the larger number of beams and beam directions used when treating with IMRT. Also, compared with 2D and 3D-CRT, IMRT requires a significantly larger number of MUs to deliver a comparable prescription dose. This results in an increase in the whole body dose as a result of scatter and leakage radiation. Thus IMRT may result in an increased rate of secondary malignancies because of the larger volume of normal tissues being irradiated to lower radiation doses and higher whole body dose [3].

Another criticism of IMRT is that it relies heavily on the target volume being determined by the physician. A sharp dose gradient ensures that minimal radiation is delivered to areas that are not designated at risk by the contours specified. The physician responsible for defining a target volume must have knowledge of clinical and radiographic anatomy and the potential route of spread to avoid a marginal miss [11]. Another consideration for IMRT is that it does come with increased financial and logistical costs [11]. These costs include hardware/software upgrades, training costs as well as
Tomotherapy

Tomotherapy, literally meaning “slice therapy,” is one of the earliest forms of IMRT [16]. Tomotherapy delivers radiation using a rotating intensity modulated fan beam. Serial, or axial, tomotherapy dose distributions are delivered slice by slice, with patients being sequentially translated through the linac gantry rotational plane between slices. Helical tomotherapy distributions are delivered without interruption. Patients are translated smoothly through the bore of the machine as its gantry continuously rotates [17].

Serial tomotherapy was implemented in 1994. In serial tomotherapy, a binary collimator is attached to the head of a conventional 6-MV linear accelerator. The collimator comprises two banks of 20 MLC leaves, which are pneumatically driven to lie either within or outside the fan beam produced by the linear accelerator. The fan beam is modulated by arranging the MLC to lie within the radiation field for varying intervals. The width of the fan beam can be set to 2 or 4 cm projected at the isocenter and the width of each leaf is 1 cm at the isocenter. If the target length is greater than the fan beam width, the patient must be irradiated using multiple adjacent arcs [17].

In the mid- to late 1990s, the focus on IMRT development shifted toward the now more widely used fixed gantry techniques (step-and-shoot, sliding window IMRT). However, in 2002, TomoTherapy Inc (Madison, WI), developed the Hi-Art machine, specifically designed to deliver helical tomotherapy [16]. The release of the Hi-Art treatment machine renewed interest in tomotherapy.

The helical tomotherapy unit has the appearance of a large CT unit and is essentially the fusion of a CT scanner and a therapeutic linear accelerator [18]. The Hi-Art system is a fully integrated system that includes treatment planning computational capability, a 6-MV photon accelerator, a binary collimator mounted on a ring gantry, synchronized patient treatment couch and an MV CT imaging system [3]. As in a CT scanner, the radiation source and the collimator continuously revolve around the patient. Radiation is applied as a fan beam by the rotating gantry and is modulated by a fast pneumatically driven binary collimator. During treatment the patient is moved through the gantry bore resulting in helical dose application [19].

The MLC of the Hi-Art system is equipped with 64 leaves with a 0.625-cm width at the isocenter, thus providing a fan beam length of 40 cm. The fan beam width is held constant during treatment, generally at 1, 2.5, or 5 cm projected at the isocenter (the smaller the field width, the longer the treatment time). During treatment, the gantry rotates at a constant speed while MLC open 51 times per rotation and close entirely between different projections. Therefore, a tomotherapy treatment consists of 51 projections per rotation. As the gantry rotates, the treatment couch translates the patient through the beam by a constant fraction of the fan beam width. This fraction is known as the pitch and typically lies somewhere between 0.2 and 0.5 [17].

Tomotherapy has demonstrated an advantage over fixed-gantry IMRT techniques in that it is capable of producing highly conformal dose to a planning target volume (PTV) while increasingly sparing dose to organs at risk [20]. This potential of tomotherapy is best understood when considering the number of beamlets associated with a tomotherapy plan. In tomotherapy, as the fan beam rotates around the patient, it is modulated by the MLC. One leaf of the MLC is considered to have 51 beamlets associated with it during each rotation. Because there are a total of 64 leaves, it follows that the treatment may have tens of thousands of beamlets associated with it. Thus tomotherapy is a complex rotational method of treatment delivery that may improve the dose conformity of a treatment plan compared with the fixed gantry method of IMRT that uses a limited number of beam directions [21].

An advantage of tomotherapy is that fields of up to 160 cm in length are able to be treated without the need for junctions. The maximum field size on a conventional linac is 40 cm x 40 cm. Larger fields for IMRT require junctioning or extended SSD [17].

An important consideration for tomotherapy is the time needed to complete a treatment. In axial tomotherapy, typically an arc takes 2 minutes to deliver with approximately 1 minute required between arcs to increment the treatment couch a distance of one slice thickness. The treatment time for a seven arc delivery is around 20 minutes. In helical tomotherapy, treatment times are significantly reduced when compared with the serial technique. Helical treatment times are dependent on the prescribed dose per fraction, the length of the target, the depth of the target in the patient, and the maximum degree of beam modulation used. A 2 Gy per fraction prostate plan typically takes around 5 minutes to deliver [17]. For longer treatment times, there is a need for excellent immobilization to limit intrafractional patient movement [21].

VMAT

Intensity modulated arc therapy (IMAT) was proposed by Yu in 1995. IMAT is a radiation delivery technique in which rotational IMRT is delivered on a conventional linear accelerator using conventional MLC [22]. There has been renewed interest in IMAT because of the introduction of linear accelerator delivery control systems that are able to vary the MLC leaf positions, dose rate and gantry rotation speeds during the
delivery of arc based IMRT. There has also been a move toward the delivery of rotational IMRT using a single arc [23].

A major advance in IMAT was realized when a novel form of arc therapy called VMAT was reported [24]. VMAT is similar to tomotherapy in that a full 360° of beam directions are available. However, it is fundamentally different in that the dose can be delivered to the entire PTV in a single arc rotation [25]. In VMAT, treatment is delivered on a linear accelerator using a cone beam that continuously rotates around the patient. The cone beam is modulated by dynamic MLC, variable dose rate and variable gantry speed to generate IMRT-quality dose distributions in a single optimized arc around the patient. Clinicians can now use a linear accelerator to deliver continuously modulated dose to the entire tumor volume while sparing normal, healthy tissue [26].

There are several variations of VMAT that are available commercially: RapidArc (Varian Medical Systems, Palo Alto, CA), Elekta VMAT (Elekta AB, Stockholm, Sweden) and Phillips SmartArc (Phillips, Inc, Andover, MA) [10]. Key to the success of VMAT is the optimization algorithm, which was introduced in 2008 [24]. Let us consider the optimization process for Varian Medical Systems RapidArc. Briefly, RapidArc consists of optimizing a dose distribution from dose volume objectives. To achieve the desired level of modulation, the optimizer is enabled to continuously vary the dose rate, MLC positions, as well as the gantry speed. The optimization process begins with a small number of control points, gradually increasing them to a sufficient number to ensure dose calculation accuracy [27, 28]. The entire gantry rotation is described in the optimization process by a sequence of 177 control points, i.e., one approximately every 0° [29]. Early results suggest that plans generated with VMAT exhibit a dose distribution equivalent or superior to fixed gantry IMRT [24]. Compared with fixed gantry IMRT, the potential advantages of VMAT include a large reduction in treatment time and concomitant reduction in the number of MUs required to deliver a given fraction size [25]. The significance of this is discussed in more detail in the following section.

Discussion

Comparing Fixed-gantry IMRT, Tomotherapy, and VMAT

Several publications exist that compare fixed gantry IMRT, tomotherapy and VMAT. These publications are usually planning studies that should be interpreted with some caution. In these types of studies, the differences in the quality of the plans produced by the modalities are likely to reflect the areas of expertise of the people performing the dosimetry. Also, there may be intrinsic difference between the planning modalities. Finally, it is possible that the author has a bias toward one technique over another.

In the studies comparing fixed gantry IMRT, tomotherapy and/or VMAT, it is typically reported that each of these IMRT approaches yield treatment plans of improved quality when compared to 3D-CRT [20]. It is also commonly observed that there are differences in the plans produced using these IMRT techniques. The differences are typically seen in indicators such as conformity index, homogeneity index and PTV conformation. It is important to realize that despite the differences, each technique is capable of producing adequate plans for treatment. In fact, results have demonstrated that the plan quality achieved using fixed-gantry IMRT, tomotherapy and VMAT are of comparable quality [23]. The absolute difference observed in dose are small in most cases, thus the clinical significance is unclear. More long-term studies are needed to determine if the differences in dose distribution observed are of any real long-term significance. Each technique has its own advantages and disadvantages, which will be discussed.

A study by Oliver et al. directly compared the planning performance of sliding window IMRT, VMAT and tomotherapy. The study was performed on four phantoms designed to represent different anatomical treatment sites, including the pelvis, and head and neck. Their results suggest tomotherapy is capable of meeting most of their planning objectives and can provide the most uniform dose to the PTV. The tradeoff for using tomotherapy was that it had the longest planning time, longer estimated treatment time, lower conformity index and higher integral dose. Single- and dual-arc VMAT plans were delivered in the shortest period and were able to provide the most conformal delivery to the PTV. The study demonstrated that five and nine-field sliding window IMRT was able to be planned in the shortest time and could be delivered with the lowest integral dose [30].

Like tomotherapy, VMAT plans take longer than fixed-gantry IMRT plans to generate. Yoo et al. reported that optimization and dose calculation took 2 and 5 minutes for conventional IMRT and approximately 15–20 minutes and 5 minutes for VMAT, respectively. VMAT planning systems are still in the early stages of clinical application. Further improvement of the optimization and dose calculation process will continue to advance the planning process [31].

An important consideration of plan quality is integral dose. As previously discussed, when using fixed-gantry IMRT techniques, the volume of tissues receiving a low dose is increased when compared to 3D-CRT. Similar observations have also been reported for both tomotherapy and VMAT. Reports are conflicting as to which technique produces the greater integral doses. The higher integral doses reported in the three IMRT techniques discussed here could increase the chance of radiation-induced secondary malignancies [31]. An advantage that both tomotherapy and VMAT have over the fixed-gantry technique is that in the rotating gantry techniques, the uncertainty in selecting the optimal gantry
angles for treatment is eliminated. In the fixed-gantry technique, the most effective gantry angle may not be obvious. This can result in loss of useful directions before the initiation of optimization. In tomotherapy and VMAT, the optimizer can have full access to $360^\circ$ of rotation [32].

It has been suggested that VMAT holds an advantage over tomotherapy in that VMAT is able to deliver non-coplanar arcs [24, 27]. Similarly, fixed-gantry IMRT techniques are also capable of delivering non-coplanar fields. For some intra-cranial and head and neck tumors, the use of non-coplanar arcs can provide significant dosimetric benefits because of preferential sparing of adjacent sensitive structures [32]. Supporters of tomotherapy would argue that range of beam angles possible using fixed-gantry IMRT or VMAT is limited by the need to avoid collision between the linac head with the patient or couch. Also, the time required to deliver non-coplanar IMRT would be increased by the need to repeatedly adjust the couch rotation, a maneuver that also has the potential to disturb the patient setup [17]. Tomotherapy is not capable of delivering non-coplanar fields. However, tomotherapy employs hundreds of thousands of beamlets, which can overcome much of this limitation, even in very complex targets adjacent to sensitive structures [32].

When considering fixed-gantry techniques and tomotherapy, these two IMRT methods have increased treatment time compared with 3D-CRT. This combined with improvements in patient care achieved through IGRT and plan adaption has resulted in an increase in overall treatment times. For a radiation therapy department to maintain patient throughput, it is necessary to increase the treatment efficiency of IMRT techniques. This is where VMAT has an advantage. Compared with both fixed-gantry IMRT and tomotherapy, treatment times are significantly reduced for VMAT [24].

The treatment times using VMAT are reduced because fewer MUs are required to deliver the therapeutic dose distribution via a single arc [24]. Such a reduction in beam-on time can have a strong impact on clinical throughput (i.e., patients treated per day and waitlist reduction). Also, if a patient spends less time on the treatment couch, the chance of geometrical miss due to intra-fractional movement is reduced [29]. The time saved by reducing beam-on time could be used to implement more online imaging technologies without increasing the total time in the treatment room [25].

The decrease in MUs achieved using VMAT, partly addresses one of the major concerns of conventional IMRT, the hypothesized risk of secondary malignancies. As previously discussed, a larger number of MUs results in an increase to the whole body dose as a result of scatter and leakage radiation [3]. Because VMAT uses fewer MUs to deliver a dose, the chances of secondary malignancies must also be reduced. The risk of generating secondary malignancies after radiation therapy is not only dependent on the scatter dose and MUs, but also on the volume of tissue receiving a low dose. As with conventional IMRT and tomotherapy, VMAT also delivers low dose to a larger volume on normal tissue than 3D-CRT. Therefore, the theoretical risk of secondary malignancies is not eliminated with VMAT [25].

As the implementation of VMAT continues, a realization has developed that optimal dose distributions for complex target volumes can require the use of two or more arcs. When more than one arc is used in VMAT treatments, the benefits of reduced treatment times and a reduction in the possibility of introducing secondary malignancies are reduced [33].

Besides their impact on departmental planning and treatment resources, another important consideration is the availability of the IMRT modalities. Fixed-gantry IMRT is routinely used in clinics around the world and is easily the most readily available form of IMRT. VMAT treatments can be performed on any linear accelerator that has had the necessary upgrades to the planning and treatment delivery systems. Such upgrades require financial, training and quality assurance considerations [33]. That conventional IMRT and VMAT can be performed on general purpose linear accelerators allows for more clinical flexibility [27]. For some patients, the delivery of 3D-CRT treatment on a linear accelerator provides a more efficient solution than IMRT techniques. Linacs also provide the ability to deliver electron fields which are a better choice for some treatments such as superficial targets [32]. Tomotherapy requires a dedicated treatment unit and cannot match the versatility of a linac [32]. Consequently, tomotherapy is not as available or widely used as either conventional IMRT or VMAT.

A future direction for both tomotherapy and VMAT is adaptive therapy. Adaptive therapy is a strategy for adapting the progression of the treatments when deviations from that plan are detected. Linear accelerators and the tomotherapy unit are already equipped with imaging technology that allows for CT scans to be recorded for daily treatment. At present, these scans are commonly used within the IGRT process to confirm isocenter positioning before daily treatment. In adaptive therapy, the patient’s treatment plan could be computed on the scans obtained routinely at treatment. The accumulated dose from all fractions may be used to track how closely the treatment is following that planned. Interventional steps could be taken at any stage to ensure the final dose delivered to a patient is true to that intended [16].

Conclusion

The concepts and values behind tomotherapy and VMAT have been introduced here. How these new rotating-gantry IMRT techniques relate to conventional fixed-gantry IMRT and 3D-CRT has also been examined.

Compared with 3D-CRT, fixed-gantry IMRT is capable of producing dose distributions that conform to the PTV and
deliver a significantly reduced dose to surrounding tissues and vital organs. This has come with the cost of increased treatment time and larger volume of normal tissue receiving low radiation doses.

Tomotherapy is a dedicated treatment system that delivers treatment using a rotating intensity modulated fan beam. A therapeutic dose is delivered when a patient is translated smoothly through the bore of the machine as its gantry continuously rotates. Tomotherapy is capable of producing high-quality plans that increasingly spare dose to surrounding organs at risk.

In VMAT, treatment is delivered on a linear accelerator using a cone beam that continuously rotates around the patient. The cone beam is modulated by dynamic MLC, variable dose rate and variable gantry speed to generate IMRT-quality dose distributions in a single optimized arc around the patient. VMAT has the advantage of significantly reducing the time and monitor units required to deliver a patient’s treatment.

Each of these IMRT techniques produces plans of similar quality. Which technique is most suited to treat a patient will depend on considerations such as the availability of the specific treatment type and its impact on the utilization of departmental planning and treatment resources.

References


Chapter 2: Literature Review

Directed Reading—Evaluation Quiz

Multiple Choice Questions

1) The following statement best defines —:
“... whereby a conventional x-ray simulator to generate planar radiographs on which bony anatomy landmarks can be visualized and used as cues for designing beam portals for standardized beam arrangement techniques.”
   a) Two-dimensional radiation therapy (2D-RT)
   b) Three-dimension conformal radiation therapy (3D-CRT)
   c) Intensity-modulated radiation therapy (IMRT)
   d) Volumetric-modulated arc therapy (VMAT)

2) Which of the following technological advances contributed to the development of 3D-CRT?
   a) Imaging technologies such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)
   b) Advances in computing planning systems
   c) Development of multileaf collimator (MLC) systems
   d) All of the above

3) Imaging in the treatment room during a course of radiation therapy, with decisions made on the basis of the imaging, is referred to as
   a) 3D-CRT
   b) Image-guided radiation therapy (IGRT)
   c) Tomotherapy
   d) IMRT

4) IMRT has the advantage over 3D-CRT in that IMRT
   a) Reduces integral dose to the patient
   b) Requires less MUs to deliver a therapeutic dose
   c) Is capable of achieving dose distributions that could be tailored to fit complex shapes.
   d) Uses a lower number of beam directions

5) An IMRT plan is typically created using
   a) Forward planning
   b) Inverse planning
   c) Hand planning
   d) None of the above

6) Which IMRT treatment delivery system can be described as a fusion of a CT scanner and a therapeutic linear accelerator?
   a) VMAT
   b) Cyberknife
   c) Tomotherapy
   d) 3D-CRT

7) Which IMRT technique does not allow the treatment of non-coplanar fields?
   a) VMAT
   b) Step-and-shoot
   c) Sliding window
   d) Tomotherapy

8) What is the maximum field length achievable in helical tomotherapy?
   a) 160 cm
   b) 40 cm
   c) 35 cm
   d) 100 cm

9) In helical tomotherapy, as the gantry rotates, the treatment couch translates the patient through the beam by a constant fraction of the fan beam width. This fraction is known as the
   a) Roll
   b) Pitch
   c) Wavelength
   d) Speed

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10) Which of the following does not influence the treatment time in tomotherapy?
   a) The length of the target
   b) The length of the patient
   c) The maximum degree of modulation used
   d) The depth of the target in a patient

11) Which of the following IMRT delivery techniques uses a fan beam?
   a) Tomotherapy
   b) VMAT
   c) Step-and-shoot
   d) Sliding window

12) Which of the following treatment techniques may be considered rotating gantry IMRT?
   a) Step-and-shoot and sliding window
   b) Step-and-shoot and tomotherapy
   c) VMAT and sliding window
   d) VMAT and tomotherapy

13) What is the name of the technique that is capable of producing IMRT quality dose distributions in a single optimized arc around the patient?
   a) VMAT
   b) Tomotherapy
   c) IGRT
   d) Cyberknife

14) In VMAT, modulation is achieved by
   a) Dynamic MLC
   b) Variable dose rate
   c) Variable gantry speed
   d) All of the above

15) In tomotherapy, how many projections are achieved per rotation?
   a) 360
   b) 177
   c) One every 2°
   d) 51

16) The commercially available versions of VMAT are
   a) RapidArc
   b) Elekta VMAT
   c) Philips SmartArc
   d) All of the above.

17) In the Varian version of VMAT (RapidArc), how many projections are achieved per rotation?
   a) 360
   b) 177
   c) 180
   d) 51

18) A conventional linear accelerator is not capable of performing which of the following treatments?
   a) VMAT
   b) Conventional IMRT
   c) Tomotherapy
   d) Electron treatment

19) Which of the following is not an IMRT technique?
   a) Tomotherapy
   b) VMAT
   c) IGRT
   d) None of these

20) Which of the following IMRT techniques has been reported here to have the shortest treatment times?
   a) Tomotherapy
   b) VMAT
   c) Step-and-shoot
   d) Sliding window

21) IMRT techniques typically require more MUs when compared with 3D-CRT; therefore, compared with 3D-CRT, IMRT has the potential to
   a) Increase the risk of secondary malignancies
   b) Reduce overall treatment times
   c) Reduce departmental waitlist
   d) Reduce intrafractional movement
Chapter 2: Literature Review

22) Compared with 3D-CRT, IMRT has a disadvantage in that it
   a) Increases integral dose to the patient
   b) Increases planning time
   c) Increases treatment time
   d) All of the above

23) The following statement best describes a systems strategy for adapting the progression of the treatments when deviations from that plan are detected.
   a) IMRT
   b) IGRT
   c) Adaptive therapy
   d) 3D-CRT

24) Which IMRT technique produces plans of significantly improved quality?
   a) VMAT
   b) Tomotherapy
   c) Fixed-angle IMRT
   d) Each of these IMRT techniques produce plans of adequate quality.

25) When choosing which IMRT technique is best suited for a patient’s treatment and departmental needs, which of the following may be considered?
   a) The availability of the specific treatment type
   b) The impact on the utilization of departmental planning resources
   c) The impact on the utilization of departmental treatment resources
   d) All of the above

This article is a Directed Reading and provides 2 hours of Category “A” RCEEM credits that may be applied to your professional development credit program. To access the quiz questions, please activate your online access to the journal at www.jmirx.org. You will receive an automatically generated certificate if a minimum grade of 75% is achieved on the quiz.
Evaluation Quiz Answers

1. a  
2. d  
3. b  
4. c  
5. b  
6. c  
7. d  
8. a  
9. b  
10. b  
11. a  
12. d  
13. a  
14. d  
15. d  
16. d  
17. b  
18. c  
19. c  
20. b  
21. a  
22. d  
23. c  
24. d  
25. d
Chapter Three
Study One

This chapter contains the published paper

Elith CA, Cao F, Dempsey SE, Findlay N, Warren-Forward H.
3.1 A Retrospective Planning Analysis Comparing Volumetric Modulated Arc Therapy (VMAT) to Intensity Modulated Radiation Therapy (IMRT) for Radiotherapy Treatment of Prostate Cancer

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Journal: Journal of Medical Imaging and Radiation Sciences, 2013; 44:79-86

3.2 Preface:

After performing the literature review it was decided to explore the effectiveness of VMAT on the treatment of early stage prostate cancer. Prostate cancer was specifically selected for two reasons. Firstly, the prostate is considered a relatively simple anatomical site on which to perform dosimetry, so it was considered prostate cancer would provide the best opportunity to gain early experience with using VMAT for treatment planning. Secondly, and more importantly, treatment of early stage prostate cancers accounted for a high volume of work at FVC (approximately 10 percent of workload in 2010). If VMAT was demonstrated to reduce treatment times as reported in the available literature, VMAT treatment of prostate cancers could have the greatest potential to increase patient throughput and reduce the waiting list for our department.

A report on the early experience using VMAT is presented here in a retrospective study that aims to compare the standard treatment technique, IMRT, to the innovative technique, VMAT, for the treatment of early stage prostate cancer. The two treatment techniques were compared by examining the quality of the dose distribution produced, as well as the impact each technique has on departmental planning and treatment resources.

As discussed in the overview of this thesis (chapter 1.8), an assumption made for each of the planning studies presented within the thesis is that the time needed to produce a treatment plan is constant irrespective of planner experience. That is, the time recorded to produce a treatment plan does not decrease as an individual planner gains
additional experience with VMAT. This assumption was not true in this study. It was observed that the time needed to generate the VMAT plans was reduced in cases 11-20 compared to cases 10-20. The observable reduction in time needed to produce a treatment plan for cases 10-20 was most likely attributed to the planner (the candidate) becoming more familiar with the VMAT planning process. After noting this within the results, the VMAT planning timing was repeated for cases 10-11 in an attempt to establish an accurate record that was not effected by the planner gaining experience with VMAT planning.

3.3 Statement of Contribution of Others:

The PhD candidate, Craig Elith, performed all planning and mock treatments in this study. Craig was also responsible for gathering and storing the data recorded. Fred Cao, a medical radiation physicist at the BCCA’s FVC had previous experience with VMAT and was a valuable resource to Craig. It was in part due to Fred’s input that Craig trialled using VMAT plans with two arcs to achieve the planning guidelines when these could not be met using a VMAT plan with one arc. Helen Warren-Forward assisted with the statistical analysis.

Preparation of the draft manuscript was done by Craig and significant feedback was provided by Craig’s PhD supervisors at the University of Newcastle, Shane Dempsey, Naomi Findlay and Helen Warren-Forward. Craig was ultimately responsible for preparation of the final manuscript and journal submission. Any edits required by the journal were made by Craig.

Importantly, Craig and Helen collaborated to secure ethics approval for this project.
3.3.1 Co-author Statements:

I attest that Research Higher Degree candidate, Craig Elith, made significant contribution to the paper/publication entitled *A Retrospective Planning Analysis Comparing Volumetric Modulated Arc Therapy (VMAT) to Intensity Modulated Radiation Therapy (IMRT) for Radiotherapy Treatment of Prostate Cancer*. Independently, Craig performed all VMAT and IMRT planning and mock treatments on a linear accelerator. Craig gathered all the data presented including plan quality assessment and resource utilisation. Craig was also responsible for the preparation of the manuscript and submission to the journal.

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A Retrospective Planning Analysis Comparing Volumetric-Modulated Arc Therapy (VMAT) to Intensity-Modulated Radiation Therapy (IMRT) for Radiotherapy Treatment of Prostate Cancer

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ABSTRACT

Purpose: This study aims to compare intensity-modulated radiation therapy (IMRT) to volumetric-modulated arc therapy (VMAT) for the treatment of prostate cancer. Particular focus was placed on the impact IMRT and VMAT have on departmental planning and treatment resources.

Materials and Methods: Twenty prostate cancer cases were retrospectively planned to compare 5-field IMRT to VMAT using a single arc (VMAT-1A) and 2 arcs (VMAT-2A). The impact on departmental resources was assessed by comparing the time needed to generate the dose distributions and to deliver the treatment plan. A comparison of plan quality was also performed by comparing homogeneity, conformity, the number of monitor units (MUs), and dose to the organs at risk.

Results: IMRT and VMAT-2A were able to produce adequate plans for all cases. Using VMAT-1A, planning guidelines were achieved in 8 of the 20 cases. IMRT provided an improved dose distribution and the best homogeneity to the planning target volume. Also, the IMRT plans were generated significantly faster than both VMAT techniques. VMAT planning provided significantly improved conformity and used significantly fewer monitor units than IMRT. VMAT-1A treatments were significantly faster than both IMRT and VMAT-2A. VMAT plans delivered lower dose to the bladder and heads of femur, and an increased dose to the rectum in the low dose region.

Conclusion: IMRT may have an advantage over VMAT for the treatment of prostate cancers. This is primarily due to the uncertainty of achieving planning guidelines using VMAT and the extended time needed to generate the VMAT plans.

RÉSUMÉ

But: Cette étude vise à comparer la radiothérapie conformationnelle avec modulation d’intensité de dose (RCMI) et l’irradiation avec modulation d’intensité volumétrique par archithérapie (VMAT) pour le traitement du cancer de la prostate. Un accent particulier a été mis sur les effets de la RCMI et de la VMAT sur les ressources de planification et de traitement du service.

Matériel et méthodes: Vingt dossiers de cancer de la prostate ont fait l’objet d’une planification rétrospective afin de comparer la RCMI à cinq champs à la VMAT utilisant un seul arc (VMAT-1A) et deux arcs (VMAT-2A). L’incidence sur les ressources du service a été évaluée en comparant le temps requis pour produire la distribution de dose et exécuter le plan de traitement. Une comparaison de la qualité des plans a aussi été effectuée en rapprochant l’homogénéité, la conformité, le nombre d’unités de surveillance et la dose aux organes à risque.

Résultats: La RCMI et la VMAT-2A ont donné lieu à des plans adéquats pour tous les cas. Avec la VMAT-1A, des directives de planification ont été produites pour 8 des 20 cas. La RCMI a fourni une distribution de dose améliorée et la meilleure homogénéité du volume cible de planification. Par ailleurs, la RCMI a permis de générer des plans beaucoup plus rapidement que les deux techniques VMAT. La planification VMAT a permis d’améliorer la conformité de façon marquée et a utilisé beaucoup moins d’unités de surveillance que la RCMI. Les traitements VMAT-1A ont été significativement plus rapides que les traitements RCMI et VMAT-2A. Les plans VMAT permettent une dose réduite à la vessie et aux têtes de fémurs, et une dose augmentée au rectum dans la région de faible dose.

Conclusion: La RCMI pourrait avoir un avantage sur la VMAT pour le traitement du cancer de la prostate, en raison...
Introduction

Intensity-modulated radiation therapy (IMRT) was introduced in the early 1990s and represented a major shift in modern radiotherapy over the pre-existing techniques of 2-dimensional radiation therapy and 3-dimensional conformal radiation therapy [1]. IMRT has enabled the delivery of a highly conformal dose distribution to the target while limiting dose to surrounding tissues and organs [2–4]. The advantages of IMRT come at a cost of increased treatment times and monitor units (MUs), resulting in a greater integral body dose from leakage and scatter radiation, increasing the risk of developing a secondary malignancy [5, 6].

On a linear accelerator, IMRT is conventionally delivered at fixed gantry angles using either the step-and-shoot or sliding window technique [7]. In 2008, Otto reported a novel form of IMRT called volumetric-modulated arc therapy (VMAT) [8]. In VMAT, treatment is delivered using a cone beam that rotates around the patient. The cone beam is modulated by the intertwining of dynamic multileaf collimators (MLCs), variable dose rates, and gantry speeds to generate IMRT quality dose distributions in a single optimized arc around the patient [9].

Since 2008, VMAT has rapidly attained widespread use. Published literature has reported the use of VMAT to treat various anatomical sites, most commonly; prostate, head and neck cancers, intracranial tumors, anal canal, breast cancers, and stereotactic body radiation therapy of the lung and abdomen. The majority of publications agree that VMAT reduces both treatment time and monitor units significantly when compared to conventional IMRT techniques [10]. This allows for quicker treatment times which improves patient comfort and allows for more time to be dedicated to patient care and support.

In mid-2010, the Fraser Valley Centre (FVC) of the British Columbia Cancer Agency, Canada, upgraded its infrastructure to be able to deliver VMAT treatments using Varian Medical Systems RapidArc™. To progress the development of VMAT treatments at FVC, the current study was undertaken retrospectively compare single-arc and dual-arc VMAT plans to the FVC standard fixed field IMRT for the treatment of localized prostate cancers. The comparison of IMRT and VMAT focuses on their impact within the planning and treatment resources in our department, but also examines the quality of the treatment plans produced using these techniques.

Prostate cancer was specifically selected for our department’s initial foray into VMAT planning for two reasons. First, the prostate is a relatively simple anatomical site on which to perform radiotherapy planning. It was therefore considered that generating a dose distribution for prostate treatments could provide a less complex experience when using VMAT for the first time. Second, and more importantly, treatment of early stage prostate cancers accounts for a high volume of work at our centre (approximately 10% of workload in 2010). If VMAT was demonstrated in this study to reduce treatment times as reported previously, VMAT treatment of prostate cancers could have the greatest potential to increase patient throughput and reduce the waitlist for our department.

Materials and Methods

Approval for this study was provided by the University of Newcastle, Australia, Human Research Ethics Committee (approval number: H-2011-0073) and the British Columbia Cancer Agency Research Ethics Board (approval number: H11-00108).

Cases and Plans

This study used deidentified computed tomography datasets from 20 patients that had been treated between July 2009 and September 2010 at FVC with IMRT to the prostate only (Table 1).

The original IMRT treatment plans were not used in this study. Instead, the IMRT plan was redone to establish consistency for comparison to VMAT planning. Two VMAT plans were generated for each dataset; a VMAT single-arc plan and a VMAT distribution using two arcs. All planning was done by the same radiation therapist using Varian Medical Systems Eclipse planning software version 8.6 (v8.6). Each plan was prescribed 7400 cGy in 37 fractions and intended to meet the FVC prostate IMRT planning guidelines outlined in Table 2.

CT Simulation

The original CT datasets were obtained on a Phillips Brilliance Big Bore scanner using 2-mm slices with the patient in a supine position. Patients were instructed to have a full bladder at time of simulation and treatment; however, bowel preparation to ensure an empty bowel was not performed.

Contouring

All original contours from the actual treatment plans were transferred onto the deidentified datasets.

A radiation oncologist contoured the prostate, bladder, and rectum from the sigmoid colon to the anus. A planning target volume (PTV) was generated by expanding the prostate contour with a 10-mm margin in all directions. If the dataset included prostate fiducial markers, the PTV was created using a 6-mm margin to the prostate posteriorly to spare additional rectal tissue from receiving radiation dose.
Optimization structures were created for the PTV, rectum, and bladder. A PTV$_{opti}$ was created by copying the PTV and extending the contour superiority and inferiorly by one slice. The size of the PTV$_{opti}$ on the new superior and inferior slices was reduced by half. The creation of the PTV$_{opti}$ was done to allow the superior and inferior ends of the PTV to receive adequate dose coverage via primary and scatter dose. Rectum$_{opti}$ and bladder$_{opti}$ structures were created by subtracting the rectum and bladder structures from the PTV$_{opti}$ plus a 3-mm margin.

In addition to the contours transferred from the original planning data, the heads of femur were also contoured. The dose to the heads of femur are not routinely considered for IMRT planning at FVC but were considered in this study. The heads of femur were contoured superiority from the caudal ischial tuberosity.

A couch structure was added to the plans so that beam attenuation from the treatment couch was considered. The couch structure was added differently for IMRT and VMAT planning due to different calculation algorithms being used for IMRT and VMAT (see the following section). For IMRT planning, the couch was contoured and combined with the body contour. For VMAT planning, a couch structure was added using the predefined couch structures available within the Varian Eclipse software.

**IMRT**

At our centre a 5-field sliding window IMRT technique is standardly used to treat the prostate. A template is used to expedite the planning process. The template defines the gantry angles of the five treatment fields as well as the optimization parameters. Each treatment beam uses 6-MV photons with the gantry angles fixed at 0°, 75°, 135°, 225°, and 285°. Dosimetric calculations were performed using the pencil beam convolution, with heterogeneity correction and a 5-mm calculation grid.

**VMAT**

VMAT plans were produced using Varian Medical Systems RapidArc software (v8.6). RapidArc is based on Otto’s original VMAT optimization platform [8, 10–12].

In this study both single-arc and 2-arc VMAT plans were developed. Similarly to IMRT, plan templates defining beam parameters and the initial optimization objectives were created to expedite the planning process. The single arc technique (VMAT-1A) used one complete counterclockwise rotation to deliver radiation treatment. The gantry start angle was 179.9° and the stop angle was 180.1°. The collimator was set at 45° to minimize MLC tongue-and-groove effect [13].

The 2-arc plan (VMAT-2A) combined both a complete counterclockwise rotation and a full clockwise (CW) gantry rotation to deliver radiation treatment. The gantry start angle was 179.9° and the stop angle was 180.1°. The collimator was set at 45° to minimize MLC tongue-and-groove effect [13].
rotation for treatment. The parameters for the first arc were identical to the VMAT-1A technique. The second arc had the gantry rotating in the opposite direction to minimize setup time. The gantry start angle was 180.1° and a stop angle of 179.9°. For the second arc, the collimator rotation was set to 135° to increase modulation. Routinely at our centre, dose calculations are performed using the pencil beam convolution as described for IMRT. However, VMAT calculations necessitate using the anisotropic analytical algorithm. In this study, VMAT calculations used the anisotropic analytical algorithm with heterogeneity correction on and a 2.5-mm calculation grid.

**Analysis**

**Plan Quality**

Plan quality was assessed by examining the ability of each planning technique to achieve the dosimetric guidelines. This qualitative assessment was aided by comparing the dose volume histogram (DVH) for the IMRT, VMAT-1A, and VMAT-2A plans.

Plan quality was quantitatively assessed by calculating the homogeneity index (HI) and conformity number (CN) for each plan. The HI is defined as

$$HI = \frac{D_{95\%} - D_{98\%}}{D_{Medin}}$$

Where $D_{n}$ is the dose covering $n$ of the target volume.

A HI value closer to zero indicates more homogeneous dose coverage within the PTV.

Dose conformity evaluates the dose fit of the PTV relative to the volume covered by the prescription dose [14]. Ideally the prescribed dose should fit tightly to the target volume, therefore reducing the side effects occurred by treating surrounding tissues and organs. The CN simultaneously takes into account irradiation of the target volume and irradiation of healthy tissues [15]. The CN is defined as

$$CN = \frac{V_{PTV \text{pres}}}{TV} \times \frac{V_{PTV \text{pres}}}{V_{PTV \text{pres}}}$$

Where $V_{PTV \text{pres}}$ is the total volume receiving the prescription, $TV$ is the target volume and $V_{PTV \text{pres}}$ is the target volume covered by the prescription [16].

A CN value closer to one indicates that the dose distribution fits more tightly to the target volume preserving healthy tissue.

**Dose to Organs at Risk (OAR)**

The dose to the OAR was compared by determining the percentage volume (V) of an organ receiving n dose ($V_{n}$).

To get a complete understanding of how IMRT and VMAT planning impacts on dose delivered across the rectum and bladder, the $V_{15}$, $V_{20}$, $V_{30}$ (rectum only), $V_{40}$, $V_{50}$, $V_{60}$, $V_{70}$ (bladder only), $V_{75}$, and $V_{80}$ (bladder only) were recorded. For each of the left and right heads on femur, the $V_{30}$ and $V_{40}$ were measured.

**Planning Time**

The time taken to perform the dosimetric calculations for each plan was recorded. For the purposes of this study, planning time does not include the time needed to perform contouring as this is considered neutral for both IMRT and VMAT planning. Instead, time measurement includes a sum of the time to place fields, plan optimization, dose calculation, and the period of evaluation of the final dose distribution to assess if the planning guidelines were achieved.

**Treatment Time**

The time taken to treat the IMRT, VMAT-1A, and VMAT-2A plans was measured and recorded. This was done by running the treatment plan for all three techniques in standby mode on a Varian Trilogy linear accelerator. Time measurement was started at the initial beam-on and was ended when the final monitor unit was delivered. The treatment time does include the time taken to move parameters such as gantry and collimator angles during treatment and between fields. The measured treatment time does not include patient setup time or the time that may be needed to verify treatment position.

**Number of MUs**

The total number of MUs needed to deliver each treatment plan was summed and recorded.

**Statistical Analysis**

A sample size of 20 cases was calculated using already published data to give a power of at least 0.8 at the 95% level. Statistical analysis was conducted using Graphpad InStat version 3 for windows (www.graphpad.com). The data were analyzed first to test for normality, and if it passed it was analyzed for statistical difference with the parametric paired t-test and repeated measures analysis of variance (ANOVA). If the data were not normal, then statistical difference was analyzed using Wilcoxon matched-pairs and the Friedman test (nonparametric repeated measures ANOVA). A paired test was chosen as the same datasets were used for each treatment option. To be statistically different, the values needed to be significant at the 95% level.

**Results**

An example dose distribution produced using IMRT, VMAT-1A, and VMAT-2A for a single dataset is displayed in Figure 1. The planning guidelines were able to be achieved for all 20 datasets for both the IMRT and VMAT-2A techniques. For the VMAT-1A technique, the planning guidelines were achieved for only eight datasets. The 12 VMAT-1A cases that did not meet guidelines failed because of the dose range across the PTV being beyond the minimum 90% and maximum 107% constraints.

When the PTV DVH is compared for a single dataset, the trend is for the IMRT plan to have the steepest dose gradient.
Figure 1. Example of dose distribution achieved using (A) intensity-modulated radiation therapy, (B) single-arc volumetric-modulated arc therapy (VMAT), and (C) double-arc VMAT beam arrangement for a single dataset. A 107%–30% isodose range is displayed.

Figure 2. The planning target volume (PTV) dose volume histograms for intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy using a single arc (VMAT-1A), and using a VMAT double arc (VMAT-2A) beam arrangement for a single computed tomography dataset.

Discussion
For each of the 20 datasets, both the IMRT and VMAT-2A techniques were able to produce plans that meet the defined guidelines. When using the VMAT-1A technique, the same planning guidelines were able to be achieved for only eight of the 20 datasets.

The IMRT technique demonstrated a better coverage and a more homogeneous dose across the PTV compared to both better than VMAT-2A, which in turn is significantly better than the VMAT-1A plans.

CN values indicate the conformity of the VMAT-1A plans is best, being significantly better than both the VMAT-2A and IMRT plans. The VMAT-2A plans demonstrate significantly improved CN compared to the IMRT plans.

IMRT plans were generated in a median time of 10.10 minutes. VMAT-1A plans took significantly longer time to generate (30.57 minutes), whereas VMAT-2A plans took significantly longer time still (45.85 minutes).

The times presented here to produce an IMRT, VMAT-1A, or VMAT-2A plan represents the time needed to generate a dose distribution with only one optimization and a single calculation. It does not include the time required to run multiple optimizations and calculations in order to meet the FVC guidelines. If the planning guidelines were not achieved after the first optimization and calculation, further attempts were made to meet these guidelines. However, the additional planning time required beyond the first optimization and calculation was not recorded.

The planning guidelines were met at the first attempt in all cases using IMRT. Using VMAT-1A, 18 cases required more than one attempt to achieve the planning guidelines and still the guidelines were not achieved in all cases. For the VMAT-2A technique, eight of the 20 datasets required more than one attempt to achieve the planning criteria.

VMAT-1A treatments were delivered significantly faster than both IMRT and VMAT-2A. Median values report VMAT-1A could be delivered in 1.3 minutes. IMRT and VMAT-2A treatments required 3.2 minutes and 3.3 minutes, respectively. There was no significant difference in the time needed to treat using IMRT or VMAT-2A.

The VMAT-1A technique required the lowest median number of MUs (512) to deliver a single 200-cGy treatment. The VMAT-2A method required the next lowest median number of MUs (566). There was not a statistically significant difference between the number of MUs used in both VMAT planning techniques. IMRT required significantly more MUs (614, median) than both VMAT-1A and VMAT-2A to deliver a single fraction.

The dose delivered to the OAR from each planning technique is reported in Table 4. IMRT delivers significantly less dose to the rectum than both VMAT methods at V20 and V30. VMAT delivers a significantly lower dose than IMRT to the bladder and heads of femur in the V60–V70 and V30–V40 ranges, respectively.

As with the dose uniformity observed in the DVHs, the median HI is best for IMRT planning which is significantly across the PTV, followed by the VMAT-2A technique, then for the VMAT-1A plan (Figure 2). This trend is observed in all dataset DVHs and indicates that dose uniformity across the PTV is best for the IMRT plan, followed by the VMAT-2A and, finally, the VMAT-1A plan.

The results for HI, CN, planning time, treatment time, and number of MUs are presented Table 3.
VMAT methods. Similarly, VMAT-2A plans had a significantly improved HI than VMAT-1A. The poor homogeneity observed for the VMAT-1A plans contributes to this method failing to achieve the FVC planning guidelines in 12 of the datasets.

Other prostate planning studies have reported lower HI in VMAT plans when compared to IMRT [10, 17, 18]. Unlike this study, in the previous publications, all VMAT plans were able to produce plans adequate for treatment. This is likely due to the planning guidelines for the PTV and OAR reported in the other studies differing to those adhered to here.

In this study, IMRT plans were produced significantly faster than both VMAT techniques. On average, IMRT plans were generated three times faster when compared to VMAT-1A plans and five times faster than VMAT-2A plans. Similar trends have been previously reported [5, 14, 19, 20]. In reality, the results presented here are flattering to VMAT techniques as they assume the planning guidelines are met at the first attempt. This was indeed the case for the IMRT plans generated with a clinically proven template. However, all but two of the VMAT-1A plans required several attempts and still did not guarantee the planning guidelines were achieved. There was no indication as to which datasets the VMAT-1A technique would successfully achieve the planning guidelines versus those that would fail. The VMAT-2A technique proved more successful with only eight of the 20 datasets requiring more than one attempt to achieve the planning criteria.

It is important to recognize the impact increased planning time may potentially have on a radiotherapy department.

### Table 3
Summary data representing the planning time, treatment time, monitor units required, homogeneity index and conformity number for the IMRT, VMAT-1A and VMAT-2A plans

<table>
<thead>
<tr>
<th></th>
<th>IMRT (N = 20)</th>
<th>VMAT-1A (N = 8)</th>
<th>VMAT-2A (N = 20)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>95% Confidence Interval</td>
<td>Median</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Planning Time (min)</td>
<td>10.1</td>
<td>9.23 – 10.71</td>
<td>30.57</td>
<td>28.82 – 32.05</td>
</tr>
<tr>
<td>Treatment Time (min)</td>
<td>3.23</td>
<td>3.16 – 3.32</td>
<td>1.34</td>
<td>1.33 – 1.35</td>
</tr>
<tr>
<td>Monitor Units</td>
<td>613.5</td>
<td>590.11 – 647.1</td>
<td>511.5</td>
<td>485.5 – 575.0</td>
</tr>
<tr>
<td>Homogeneity Index</td>
<td>0.0375</td>
<td>0.032 – 0.049</td>
<td>0.0655</td>
<td>0.058 – 0.071</td>
</tr>
<tr>
<td>Conformity Number</td>
<td>0.793</td>
<td>0.779 – 0.802</td>
<td>0.826</td>
<td>0.811 – 0.848</td>
</tr>
</tbody>
</table>

*Italic values indicate a significant difference was NOT observed.

### Table 4
The dose to the rectum, bladder and heads of femur represented as the percentage volume (V) of the organ receiving n dose (Vn)

<table>
<thead>
<tr>
<th></th>
<th>IMRT (N = 20)</th>
<th>VMAT-1A (N = 8)</th>
<th>VMAT-2A (N = 20)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>95% Confidence Interval</td>
<td>Median</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Rectum</td>
<td>V10</td>
<td>78.2</td>
<td>71.7 – 83.8</td>
<td>83.4</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>69.7</td>
<td>63.9 – 77.0</td>
<td>80.0</td>
</tr>
<tr>
<td></td>
<td>V50</td>
<td>60.5</td>
<td>54.0 – 66.5</td>
<td>71.0</td>
</tr>
<tr>
<td></td>
<td>V90</td>
<td>47.2</td>
<td>40.1 – 51.3</td>
<td>58.8</td>
</tr>
<tr>
<td></td>
<td>V95</td>
<td>31.3</td>
<td>27.3 – 36.8</td>
<td>36.0</td>
</tr>
<tr>
<td></td>
<td>V100</td>
<td>22.2</td>
<td>18.7 – 27.3</td>
<td>22.7</td>
</tr>
<tr>
<td>Bladder</td>
<td>V10</td>
<td>47.2</td>
<td>41.4 – 65.3</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>43.6</td>
<td>38.1 – 61.6</td>
<td>36.7</td>
</tr>
<tr>
<td></td>
<td>V50</td>
<td>24.2</td>
<td>22.2 – 39.7</td>
<td>23.9</td>
</tr>
<tr>
<td></td>
<td>V90</td>
<td>19.3</td>
<td>17.9 – 32.7</td>
<td>18.1</td>
</tr>
<tr>
<td></td>
<td>V95</td>
<td>15.3</td>
<td>14.3 – 26.5</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>V100</td>
<td>13.2</td>
<td>12.4 – 23.1</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>V105</td>
<td>10.5</td>
<td>10.0 – 18.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>V90</td>
<td>2.7</td>
<td>1.9 – 5.1</td>
<td>3.3</td>
</tr>
<tr>
<td>LT Femur</td>
<td>V10</td>
<td>25.1</td>
<td>20.5 – 32.5</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>6.9</td>
<td>4.4 – 11.2</td>
<td>0.1</td>
</tr>
<tr>
<td>RT Femur</td>
<td>V10</td>
<td>30.2</td>
<td>23.7 – 36.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>10.2</td>
<td>7.6 – 16.9</td>
<td>0</td>
</tr>
</tbody>
</table>

*Italic values indicate a significant difference was observed.
Presumably, when using VMAT, it is preferable to treat with one arc to take advantage of the reported reduction in MUs and shortened treatment time [10]. However, from the results presented, it is unlikely that the VMAT planning guidelines will be met on the first attempt, if at all, when planning with a single arc. The introduction of a second arc may be needed to successfully achieve the planning guidelines, but with a significant increase in planning time. Such uncertainty and exaggerated planning time for VMAT planning observed here may have significant impact on a radiotherapy departments planning resources, potentially reducing patient throughput and increasing waitlists. IMRT planning at FVC minimizes the uncertainty of achieving planning guidelines and reduces planning time significantly giving this technique a distinct advantage when comparing overall planning time.

The VMAT treatment planning systems are still in the early stages of development. The results presented here are obtained using Varian Medical Systems RapidArc v8.6, which uses aperture-based optimization. More recent versions of RapidArc use an optimizer that is both aperture- and fluence-based. Anecdotally, the primary author’s early experience with this new optimization process in RapidArc version 10.0 (v10.0) is that the overall planning time for VMAT is reduced compared to v8.6. Further improvements in optimization, dose calculation, and computer processor speed will continue to reduce overall planning time [14, 19].

The discussion so far highlights an important consideration for VMAT planning. The quality of the plans produced using VMAT can depend greatly on the experience of the planner. It is critical that planners understand the optimization process in order to achieve the desired dose distribution in a timely manner [10]. Although this article shares our department’s first experience with VMAT, inexperience is not likely accountable for the inability of the VMAT-1A technique to achieve departmental planning guidelines and the extended planning times using VMAT. One of the authors of this article has had previous experiences with VMAT planning [21]. Still the planning times using VMAT could not be shortened more than reported here and the planning guidelines were not always achieved with VMAT-1A.

In this study, VMAT did demonstrate some advantages over IMRT. The VMAT-1A plans were treated three times faster than IMRT. The observed reduction in treatment time using the VMAT-1A technique has the potential to increase the patient throughput of a radiation therapy department [5, 22]. Alternatively, the time saved by reducing the beam-on time could be used to implement online imaging without increasing a patient’s total time in the treatment room [8, 22, 23]. Additionally, a shorter delivery time indicates improved patient comfort and a reduced probability of treatment errors caused by patient motion during a treatment [17, 18, 24]. Both improved target localization provided by online imaging and reduced patient motion during treatment has the potential to allow the size of the PTV to be reduced. A smaller PTV could mean less healthy tissue is irradiated ultimately reducing radiation-associated morbidities.

A shorter treatment time may also prove to be biologically advantageous. Evidence has shown that the radiation survival is not only a function of the total dose delivered but also depends on the duration that the radiation is delivered [25, 26]. There is a potential tumour cell killing benefit to deliver radiation doses in a shorter time [19].

Importantly, the time taken to deliver the VMAT-2A and IMRT treatments did not differ significantly. Therefore, the time advantage VMAT offers for the treatment of prostate cancers is reduced when using more than one arc.

The results of this study upheld previous reports where VMAT treatments required significantly fewer MUs than IMRT [5, 8, 17–19, 22, 27]. As previously discussed, because VMAT uses fewer MUs to deliver a dose, the chances of secondary malignancies might be reduced. This is particularly relevant for patients with prostate cancer as they have a significant chance of long-term survival [27].

Dose conformity has been demonstrated to be better for VMAT plans compared to IMRT. The improved conformity is inherent to arc delivery that delivers dose from 360°. As with any reduction in MUs, the improved conformity could reduce the risk of secondary cancers developing in the high-dose region when compared to IMRT [28]. Improved conformity also increases the opportunity of dose escalation that, in prostate treatments, has been demonstrated to improve local control [22]. Despite VMAT demonstrating improved conformity, dose escalation using VMAT may still be limited by the planning hotspots that have been reported to be greater for VMAT plans than for IMRT [10, 17].

It has been reported that VMAT plans become less conformal in the low-dose range [14, 17, 18, 22]. This can be attributed to the dose being delivered from all directions. For IMRT plans, radiation dose is only deposited along the path of the fixed gantry angles. As a result, the volume of tissues receiving a low dose in VMAT is increased compared to IMRT. Therefore, the theoretical risk of secondary malignancies is not eliminated with VMAT [5]. For many sites, this may not be a concern. However, it may be problematic for some sites such as pediatric cancers [18].

VMAT plans were demonstrated to deliver lower dose to the bladder and heads of femur, and an increased dose to the rectum in the low-dose region when compared to IMRT. The results in the literature are conflicting regarding outcome for the dose delivered to the OAR. For example, it has been reported that sparing of the rectum, bladder, and femoral heads can be improved when using VMAT compared to IMRT [5, 10, 13, 17, 18, 28]. In contrast, to these reports, but in support of the present findings, others have reported that dose to the rectum is higher when using VMAT compared to IMRT [14, 20, 29]. The inconsistency across the studies is likely the result of the individual study characteristics. For example, variables such as PTV definition, OAR dose constraints, optimization values, and the number of treatment fields in IMRT or rotation arcs used in VMAT, could create inconsistencies between studies.
Conclusion

VMAT has been demonstrated to reduce the MUs and time required to treat prostate cancer compared to conventional IMRT. Despite these findings, our department is unlikely to adopt VMAT to treat the prostate primarily because of the uncertainty of achieving planning guidelines and increased planning time. This is not to rule out adopting VMAT for the treatment of prostate cancer in the future if improvements are made to plan optimization, dose calculation, and computer processor speed. The current version of VMAT may well yet prove to have an advantage for other sites being treated using IMRT at FVC such as head and neck cancers, and stereotactic body radiation therapy techniques.

References

Chapter Four
Study Two

This paper contains the published paper

Elith CA, Dempsey SE, Warren-Forward H.
4.1 A Retrospective Planning Analysis Comparing Intensity Modulated Radiation Therapy (IMRT) to Volumetric Modulated Arc Therapy (VMAT) Using Two Optimisation Algorithms for the Treatment of Early Stage Prostate Cancer

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4.2 Preface:

In chapter 3 VMAT was demonstrated to reduce the monitor units and time required to treat prostate cancer compared to conventional IMRT. Despite these findings, the FVC was unlikely to adopt VMAT for the treatment of prostate cancer primarily due to the uncertainty of achieving planning guidelines and increased planning time.

In October 2011, FVC upgraded to version 10.0 (v10.0) of the Varian’s \textit{RapidArc} (VMAT) system. Varian promoted the new version to be capable of producing VMAT plans of improved quality and in less time compared to the previous version. According to Varian, these improvements could be attributed to an upgrade in the progressive resolution optimiser algorithm (PRO) used in v10.0.

In this chapter, the methodology presented in chapter 3 is repeated using v10.0 of Varian’s \textit{RapidArc} software to assess if the VMAT planning time is reduced and the resulting plan quality is improved so that our centre may reconsider implementing VMAT for the treatment of early stage prostate cancer to take advantage of the reduced treatments times offered using VMAT.

4.3 Statement of Contribution of Others:

The PhD candidate, Craig Elith, performed all planning and mock treatments in this study. Craig was also responsible for gathering and storing the data recorded. Helen Warren-Forward assisted with statistical analysis.
Preparation of the draft manuscript was done by Craig and significant feedback was provided by Craig’s PhD supervisors at the University of Newcastle, Shane Dempsey and Helen Warren-Forward. Craig was ultimately responsible for preparation of the final manuscript and journal submission. Any edits required by the journal were made by Craig.

Importantly, Craig and Helen collaborated to secure ethics approval for this project.

### 4.3.1 Co-author Statements:

I attest that Research Higher Degree candidate, Craig Elith, made significant contribution to the paper/publication entitled *A Retrospective Planning Analysis Comparing Intensity Modulated Radiation Therapy (IMRT) to Volumetric Modulated Arc Therapy (VMAT) Using Two Optimisation Algorithms for the Treatment of Early Stage Prostate Cancer*.

Independently, Craig performed all VMAT and IMRT planning and mock treatments on a linear accelerator. Craig gathered all the data presented including plan quality assessment and resource utilisation. Craig was also responsible for the preparation of the manuscript and submission to the journal.
A retrospective planning analysis comparing intensity modulated radiation therapy (IMRT) to volumetric modulated arc therapy (VMAT) using two optimization algorithms for the treatment of early-stage prostate cancer

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Abstract

Introduction: The primary aim of this study is to compare intensity modulated radiation therapy (IMRT) to volumetric modulated arc therapy (VMAT) for the radical treatment of prostate cancer using version 10.0 (v10.0) of Varian Medical Systems, RapidArc radiation oncology system. Particular focus was placed on plan quality and the implications on departmental resources. The secondary objective was to compare the results in v10.0 to the preceding version 8.6 (v8.6). Methods: Twenty prostate cancer cases were retrospectively planned using v10.0 of Varian’s Eclipse and RapidArc software. Three planning techniques were performed: a 5-field IMRT, VMAT using one arc (VMAT-1A), and VMAT with two arcs (VMAT-2A). Plan quality was assessed by examining homogeneity, conformity, the number of monitor units (MUs) utilized, and dose to the organs at risk (OAR). Resource implications were assessed by examining planning and treatment times. The results obtained using v10.0 were also compared to those previously reported by our group for v8.6. Results: In v10.0, each technique was able to produce a dose distribution that achieved the departmental planning guidelines. The IMRT plans were produced faster than VMAT plans and displayed improved homogeneity. The VMAT plans provided better conformity to the target volume, improved dose to the OAR, and required fewer MUs. Treatments using VMAT-1A were significantly faster than both IMRT and VMAT-2A. Comparison between versions 8.6 and 10.0 revealed that in the newer version, VMAT planning was significantly faster and the quality of the VMAT dose distributions produced were of a better quality. Conclusion: VMAT (v10.0) using one or two arcs provides an acceptable alternative to IMRT for the treatment of prostate cancer. VMAT-1A has the greatest impact on reducing treatment time.

Introduction

It is well established that high-dose radical radiation therapy for localized prostate cancer improves disease control.1–4 Introduced in the early 1990s, three-dimensional conformal radiation therapy (3DCRT) allowed higher doses to be delivered to the prostate and/or planning target volume (PTV), and acceptable dose to be delivered to surrounding healthy tissues compared to previous methods.5 However, since the mid-2000s, intensity modulated radiation therapy (IMRT) has become the standard technique to deliver external beam radiation therapy treatment to the prostate, due to its increased ability to deliver higher dose treatment to the PTV while reducing dose to the surrounding critical organs and healthy tissues.6,7 Standard IMRT approaches achieve this through the use of multiple fixed gantry radiation fields which each deliver irregular intensity patterns.
The improved dose distribution achieved using standard IMRT comes with a cost of longer treatment times due to increased set-up and verification methods and increased monitor units (MUs). The longer treatment time using IMRT can lead to increased patient discomfort, reduced machine throughput, and an increased chance of geographical target miss due to patient movement. Increasing the number of MUs results in a greater integral body dose from leakage and scatter radiation, increasing the risk of developing a secondary malignancy. In 2008, Otto reported a novel form of IMRT called volumetric modulated arc therapy (VMAT). In VMAT, treatment is delivered using a cone beam that rotates around the patient. The cone beam is modulated by the intertwining of dynamic multileaf collimators (MLCs), variable dose rates, and gantry speeds to generate IMRT quality dose distributions in a single optimized arc around the patient. There is a growing body of literature supporting that VMAT is capable of delivering treatment to the prostate with a similar or better dose distribution compared to fixed-field IMRT, yet requires significantly fewer MUs and reduced treatment time than IMRT. In 2010, the Fraser Valley Centre (FVC) of the British Columbia Cancer Agency (BCCA) considered implementing VMAT utilizing Varian Medical System’s (Palo Alto, CA) RapidArc. To assess the degree to which the VMAT technology at FVC could provide for efficient and effective planning outcomes, the authors of this study undertook research which compared a 5-field sliding window IMRT technique (the standard technique at FVC for prostate treatment) to VMAT using either one or two treatment arcs. This research was done using version 8.6 (v8.6) of the RapidArc (VMAT) planning software, which was at this time the clinical planning system in use at FVC. Particular emphasis was placed on the utilization of planning and treatment resources. From this research it was concluded that VMAT demonstrated the ability to have increased treatment efficiency, as well as requiring fewer MUs to deliver a single treatment fraction. However, v8.6 was unable to achieve departmental planning guidelines for all of the plans tested when using a single arc. Also, extended time was needed to generate the VMAT plans compared to standard IMRT plans. The FVC therefore continued to use IMRT for the radical treatment of early prostate cancer in v8.6 of the planning software.

In October 2011, FVC upgraded to version 10.0 (v10.0) of the Varian’s RapidArc (VMAT) system. The most significant difference between v8.6 and v10.0 of the RapidArc (VMAT) planning software is in the progressive resolution optimizer algorithm (PRO). v8.6 uses PRO8.6.15, whereas v10.0 uses PRO10.0.28. It is beyond the scope of this article to detail the differences between the PRO algorithm utilized in v8.6 and v10.0, which has been reported elsewhere. For the purposes of this article, it suffices to say that in v10.0, the PRO algorithm has been modified and it is suggested that the newer version is able to generate plans of improved quality in less time than the version of PRO utilized in v8.6.

In the research presented within this study, IMRT and VMAT will be compared for the treatment of early-stage prostate cancer using v10.0 of the RapidArc (VMAT) software. Emphasis will be placed on the utilization of planning and treatment resources, while also examining the quality of the treatment plans being produced. Comparisons will also be made between the outcomes obtained previously in v8.6 and the upgraded v10.0 to assess if sufficient improvements have been made in the VMAT process to reconsider utilizing this technique to routinely treat prostate cancer at our department.

### Materials and Methods

Approval for this study was provided by the University of Newcastle, Australia, Human Research Ethics Committee (approval number: H-2011-0073), and the British Columbia Cancer Agency, Canada, Research Ethics Board (approval number: H11-00108).

Full details of the materials and methods used in this study have been reported previously in a study describing our experiences using v8.6 of Varian Medical System’s RapidArc (VMAT) software. The previously described methods have been reproduced here to detail our experience using v10.0 of the software.

### Cases and plans

The study used deidentified CT data sets from 20 patients who had been previously treated at FVC with IMRT to the prostate only. Dose distributions were generated retrospectively for each data set using three techniques: a 5-field sliding window IMRT, VMAT using one full gantry rotation (VMAT-1A), and VMAT with two complete arcs in opposite directions (VMAT-2A) (Fig. 1). All planning was done by the same radiation therapist using v10.0 of Varian Medical System’s Eclipse planning software (which includes RapidArc). All planning was done on the same computer which uses an XP (SP3) operating system, 16 processors (2.3 GHz each), and 24 GB of RAM. Each plan was prescribed 7400 cGy in 37 fractions and intended to meet the FVC prostate IMRT planning guidelines outlined in Table 1.
Table 1. The Fraser Valley Centre-specific planning objectives for both the intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) treatments of the prostate.

<table>
<thead>
<tr>
<th>Volume/organ at risk (OAR)</th>
<th>Dose constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning target volume (PTV)</td>
<td>99% of the volume to get ≥95% of the prescription</td>
</tr>
<tr>
<td></td>
<td>Minimum dose &gt;90% of the prescription</td>
</tr>
<tr>
<td></td>
<td>Mean dose &gt;99% of the prescription</td>
</tr>
<tr>
<td></td>
<td>Maximum dose &lt;107% of the prescription</td>
</tr>
<tr>
<td></td>
<td>The maximum dose must be within the PTV</td>
</tr>
<tr>
<td>Rectum</td>
<td>&lt;65% of the volume to receive 50 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;55% of the volume to receive 60 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;25% of the volume to receive 70 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;15% of the volume to receive 75 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;5% of the volume to receive 78 Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>&lt;50% of the volume to receive 65 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;35% of the volume to receive 70 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;25% of the volume to receive 75 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;15% of the volume to receive 80 Gy</td>
</tr>
</tbody>
</table>

Gy, dose in gray.

however, bowel preparation to ensure an empty bowel was not performed.

Contouring

All original contours from the actual treatment plans were transferred onto the deidentified data sets.

A radiation oncologist contoured the prostate, bladder, and rectum from the sigmoid colon to the anus. A PTV was generated by expanding the prostate contour with a 10-mm margin in all directions. If the data set included prostate fiducial markers, the PTV was created using a 6-mm margin to the prostate posteriorly to spare additional rectal tissue from receiving radiation dose.

Optimization structures were created for the PTV, rectum, and bladder. A PTV\textsubscript{opti} was created by copying the PTV and extending the contour superiorly and inferiorly by one slice. The size of the PTV\textsubscript{opti} on the new superior and inferior slices was reduced by half. The creation of the PTV\textsubscript{opti} was done to allow the superior and inferior ends of the PTV to receive adequate dose coverage via primary and scatter dose. Rectum\textsubscript{opti} and Bladder\textsubscript{opti} structures were created by subtracting the rectum and bladder structures from the PTV\textsubscript{opti} plus a 3-mm margin.

In addition to the contours transferred from the original planning data, the heads of femur were also contoured. The dose to the heads of femur is not routinely considered for IMRT planning at FVC, but was...
considered in this study. The heads of femur were contoured superiorly from the caudal ischial tuberosity.

A couch structure was added to the plans so that beam attenuation from the treatment couch was considered. The couch structure was added using the predefined couch structures available within the Varian’s Eclipse software.

**IMRT**

At our centre, a 5-field sliding window IMRT technique is standardly used to treat the prostate. A template is used to expedite the planning process. The template defines the gantry angles of the 5 treatment fields as well as the optimization parameters. Each treatment beam uses 6-MV photons with the gantry angles fixed at 0°, 75°, 135°, 225°, and 285° (Fig. 1A). Dosimetric calculations were performed using the anisotropic analytical algorithm (AAA) with heterogeneity correction on and a 2.5-mm calculation grid.

**VMAT**

In this study, both a single-arc and two-arc VMAT plan were developed. Similar to IMRT, plan templates defining beam parameters and the initial optimization objectives were created to expedite the planning process. Importantly, the initial optimization objectives used for VMAT planning were different to those set for IMRT. The same optimization template was utilized for both VMAT techniques; however, these objectives were adjusted during optimization to achieve the best plan.

The single-arc technique (VMAT-1A) utilized one complete counterclockwise (CCW) rotation to deliver radiation treatment (Fig. 1B). The gantry start angle was 179° and the stop angle was 181°. The collimator was set at 45° to minimize MLC tongue and groove effect.

The two-arc plan (VMAT-2A) combined both a complete CCW rotation and a full clockwise (CW) gantry rotation for treatment (Fig. 1C). The parameters for the first arc were identical to the VMAT-1A technique. The second arc had the gantry rotating in the opposite direction to minimize set-up time. The gantry start angle was 181° and the stop angle was 179°. For the two-arc plan, the collimator rotation was set to 135° to increase modulation. VMAT calculations utilized AAA with heterogeneity correction on and a 2.5-mm calculation grid.

**Analysis**

**Plan quality**

A dose distribution was considered acceptable for treatment if able to meet the FVC prostate IMRT planning guidelines (Table 1).

The plan quality was quantitatively assessed by calculating the homogeneity index (HI) and conformity number (CN) for each plan. The HI is defined as

\[ HI = \frac{D_\text{50} - D_{\text{98}}}{D_{\text{median}}} \]

where \( D_\text{50} \) is the dose covering 50% of the target volume.

A HI value closer to zero indicates more homogeneous dose coverage within the PTV.

Dose conformity evaluates the dose fit of the PTV relative to the volume covered by the prescription dose. Ideally the prescribed dose should fit tightly to the target volume, therefore reducing the side effects occurred by treating surrounding tissues and organs. The CN simultaneously takes into account irradiation of the target volume and irradiation of healthy tissues.

\[ CN = \frac{V_{\text{TPres}}}{TV} \times \frac{V_{\text{TPres}}}{V_{\text{Pres}}} \]

where \( V_{\text{TPres}} \) is the total volume receiving the prescription, \( TV \) is the target volume, and \( V_{\text{TPres}} \) is the target volume covered by the prescription.

A CN value closer to 1 indicates that the dose distribution fits more tightly to the target volume preserving healthy tissue.

**Dose to organs at risk**

The dose to organs at risk (OAR) was compared by determining the percentage volume (\( V \)) of an organ receiving \( n \) dose (\( V_n \)). To get a complete understanding of how IMRT and VMAT planning impacts on dose delivered across the rectum and bladder, the \( V_5 \), \( V_{15} \), \( V_{20} \), \( V_{30} \), \( V_{40} \), \( V_{50} \), \( V_{60} \), \( V_{65} \), and \( V_{70} \) were recorded. For each of the left and right heads on femur, the \( V_{30} \) and \( V_{40} \) were measured.

**Planning time**

The time taken to generate a dose distribution for each technique was recorded. For the purposes of this study, planning time does not include the time needed to perform contouring as this is considered neutral for both IMRT and VMAT planning. Instead, time measurement includes a sum of the time to place fields, plan optimization, dose calculation, and the period of evaluation of the final dose distribution to assess if the planning guidelines were achieved.

**Treatment time**

The time taken to treat the IMRT, VMAT-1A, and VMAT-2A plans was measured and recorded. This was
done by running the treatment plan for all three techniques in stand-by mode on a Varian Trilogy linear accelerator. Time measurement was started at the initial beam-on and was ended when the final MU was delivered. The treatment time does include the time taken to move parameters such as gantry and collimator angles during treatment and between fields. The measured treatment time does not include patient set-up time or the time that may be needed to verify treatment position.

**Number of MUs**

The total number of MUs needed to deliver each treatment plan was summed and recorded.

**Comparing v8.6 to v10.0**

The results of the planning of the 20 cases using v10.0 of the planning software were compared to the previously reported results using v8.6.24

**Statistical analysis**

A sample size of 20 cases was calculated to give a power of at least 0.8 at the 95% level. Statistical analysis was conducted using Graphpad InStat version 3 for windows (www.graphpad.com). The data were analysed first to test for normality, and if it passed it was analysed for statistical difference with the parametric paired t-test and repeated measures analysis of variance (RM ANOVA). If the data were not normal, then statistical difference was analysed using Wilcoxon matched-pairs and the Friedman repeated measures analysis of variance (RM ANOVA). A paired test was chosen as the same data sets were used for each treatment option. To be statistically different, the values were needed to be significant at the 95% level (i.e., \( P < 0.05 \)).

<table>
<thead>
<tr>
<th>Median (95% confidence interval)</th>
<th>IMRT</th>
<th>VMAT-1A</th>
<th>VMAT-2A</th>
<th>RM ANOVA</th>
<th>IMRT versus VMAT-1A</th>
<th>IMRT versus VMAT-2A</th>
<th>VMAT-1A versus VMAT-2A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning time (min)</td>
<td>9.75 (9.14–10.12)</td>
<td>18.4 (17.95–19.47)</td>
<td>18.42 (17.52–19.49)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.35*</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>3.14 (3.11–3.27)</td>
<td>1.3 (1.29–1.31)</td>
<td>3.18 (3.16–3.19)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.64*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monitor units</td>
<td>594.0 (578.3–638.8)</td>
<td>446.5 (436.5–461.9)</td>
<td>450.5 (442.0–464.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.27*</td>
</tr>
<tr>
<td>Homogeneity index</td>
<td>0.0385 (0.036–0.042)</td>
<td>0.065 (0.062–0.066)</td>
<td>0.061 (0.059–0.063)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>Conformity number</td>
<td>0.748 (0.73–0.76)</td>
<td>0.843 (0.84–0.845)</td>
<td>0.851 (0.84–0.85)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
</tbody>
</table>

**Results**

Using v10.0, a dose distribution that met the planning guidelines was able to be produced for each of the IMRT, VMAT-1A, and VMAT-2A techniques at the first attempt. The overall quality of the plans produced was similar; however, statistically significant differences were noted among the three techniques.

The results for HI, CN, planning time, treatment time, and number of MUs using v10.0 of the planning software are presented in Table 2.

Conformity of the dose to the PTV (CN) is significantly better for both VMAT plans than IMRT. The median CN for VMAT-2A is better than that for VMAT-1A, although there is no statistically significant difference between the two VMAT techniques.

The dose uniformity (HI) across the PTV is significantly better for the IMRT dose distributions compared to both VMAT techniques. The median HI for VMAT-2A is better than that for VMAT-1A, although not statistically significant.

IMRT plans were produced in a median time of 9.7 min. This was significantly faster than the VMAT-1A and VMAT-2A techniques, which required twice as long to generate (18.4 and 18.4 min, respectively).

VMAT-1A treatments were performed in 1.3 min. This was less than half the time needed for both VMAT-2A and IMRT treatments which were similar in treatment time (3.2 and 3.1 min, respectively).

Both VMAT techniques required a similar number of MUs to deliver a single fraction of treatment. VMAT-1A required a median of 446.5 MUs, whereas VMAT-2A used 450.5 MUs. IMRT required significantly more MUs (594) to deliver a single treatment.

A comparison of HI, CN, planning time, treatment time, and number of MUs between v8.6 and v10.0 is presented in Table 3. In the comparison between v8.6 and
v10.0 there are two outstanding items. First, when planning VMAT-1A in v8.6, the planning guidelines were only achieved in 8 of the 20 data sets, whereas in v10.0, the VMAT-1A technique was able to successfully meet the same planning guidelines for each of the same 20 data sets. Second, the time needed to generate VMAT-1A and VMAT-2A plans is significantly reduced in v10.0.

The doses delivered to the OARs using v10.0 are presented in Table 4. VMAT is demonstrated to deliver lower dose than IMRT to the bladder and heads of femur. Likewise, the dose delivered to the rectum in the V60–V70 range is improved using VMAT. In the V30–V50 range, IMRT delivers a lower dose to the rectal tissue.

Discussion

In the first part of this study, which sought to evaluate the differences between IMRT and VMAT techniques using v10.0 software, each technique was able to generate a dose distribution that was adequate for treatment. The overall quality of the plans produced were similar; however, statistically significant differences were noted among the three techniques.

The dose uniformity across the PTV reported by the HI is significantly better for IMRT than both VMAT techniques. Others have reported a similar trend for homogeneity. The lower homogeneity is reported to be inherent to the optimization algorithm used for VMAT planning.

Volumetric modulated arc therapy planning was demonstrated to produce dose distributions that had a better conformity to the PTV than IMRT. This outcome supports the findings from previous published research. The improved conformity observed using VMAT is a consequence of arc delivery that delivers dose from 360°. The improvement in dose conformity observed using VMAT may increase the potential of dose escalation without increasing treatment-related morbidities associated with radiation exposure to surrounding tissues. Dose escalation has been demonstrated to improve local control of prostate cancer. Despite demonstrating improved conformity to the PTV, dose escalation using VMAT may still be limited by planning hotspots that have been reported to be greater for VMAT than IMRT.

There is a growing body of evidence supporting that VMAT treatment of prostate cancer is significantly faster and requires fewer MUs compared to IMRT. As expected, our results demonstrate that the treatment time using the VMAT-1A technique was significantly faster than using IMRT. The reduced treatment time of VMAT-1A means there is less patient discomfort during treatment and a reduced risk of patient movement. The reduced treatment time may also prove to be biologically advantageous. Evidence has shown that the radiation survival is not only a function of the total dose delivered but also depends on the duration that the radiation is delivered. There is a potential tumour cell killing benefit to deliver radiation doses in a shorter time.

The reduced treatment time using VMAT-1A also holds enormous resource potential. The faster treatments could allow more patients to receive treatments daily and therefore reduce waitlists. Alternatively, the extra time available on a treatment unit can be utilized to implement advanced image-guided radiation therapy (IGRT) protocols or implement advanced treatment techniques for other treatment sites that require longer treatment times, without increasing waitlists.

It is important to note that there was no significant difference in the treatment times needed for the IMRT and VMAT-2A techniques. This result demonstrates that the treatment time advantage VMAT offers is reduced when using more than one arc for treatment.

Also as expected, it was demonstrated in this study that the VMAT plans required fewer MUs to deliver a fraction of treatment. The decrease in MUs required for VMAT

Table 3. Comparison of version 8.6 (v8.6) to version 10.0 (v10.0) of the Varian Medical System’s RapidArc.

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>VMAT-1A</th>
<th>VMAT-2A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>v8.6 median (N = 20)</td>
<td>v10.0 median (N = 20)</td>
<td>P-value</td>
</tr>
<tr>
<td>Planning time (min)</td>
<td>9.86</td>
<td>9.75</td>
<td>0.357</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>3.18</td>
<td>3.14</td>
<td>0.001</td>
</tr>
<tr>
<td>Monitor units</td>
<td>600.5</td>
<td>594.0</td>
<td>0.016</td>
</tr>
<tr>
<td>Homogeneity index</td>
<td>0.0365</td>
<td>0.0385</td>
<td>0.247</td>
</tr>
<tr>
<td>Conformity number</td>
<td>0.791</td>
<td>0.748</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Compared endpoints include median planning time, treatment time, monitor units required, homogeneity index, and conformity number for IMRT, VMAT-1A, and VMAT-2A plans. IMRT, 5-field sliding window intensity modulated radiation therapy; VMAT-1A, volumetric modulated arc therapy using one full arc; VMAT-2A, volumetric modulated arc therapy using two full arcs. Illustrates where a significant difference was NOT observed.

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may be explained in that the IMRT technique selects these structures.6,8,20 Secondary malignancy induction is a more important consideration as ongoing technical improvements in cancer diagnosis and treatment are improving the prognosis for patients being treated with radiation.21

The median dose to the bladder was lowered with VMAT for all measured volumes. Similarly, the dose delivered to the rectum in the V60–V70 range is improved using VMAT. These results are in compliance with VMAT demonstrating improved conformity to the PTV than IMRT. In the V30–V40 range, IMRT delivers a lower dose to the rectal tissue. The observed doses to the rectum may be explained in that the IMRT technique selects angles that avoid the rectum, whereas the VMAT techniques may distribute lower dose through the rectum to achieve conformal coverage of the PTV in the high-dose region. This phenomenon is not observed in the bladder as it mostly sits superior to the PTV.6

It was demonstrated here that the median dose to the heads of femur was lower using VMAT compared to IMRT. It is important to note that in this study constraints were not applied to the heads of femur during optimization for either the VMAT or IMRT plans. If constraints were applied, it would be reasonable to expect that the dose delivered to the heads of femur would be further reduced. Others have reported that when constraints are applied to the heads of femur during optimization, VMAT delivers a lower dose than IMRT to these structures.6,8,20

In the second part of this research, which compared IMRT and VMAT plans developed with v8.6 to v10.0 software, the outcomes demonstrate that the transition to

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>VMAT-1A</th>
<th>VMAT-2A</th>
<th>P-values (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (%)</td>
<td>95% confidence interval</td>
<td>Median (%)</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Rectum V5</td>
<td>94.2</td>
<td>86.1–95.1</td>
<td>93.4</td>
<td>86.3–95.2</td>
</tr>
<tr>
<td>V10</td>
<td>77.7</td>
<td>71.5–83.6</td>
<td>78.4</td>
<td>70.7–82.7</td>
</tr>
<tr>
<td>V20</td>
<td>69.1</td>
<td>62.8–75.9</td>
<td>75.1</td>
<td>67.8–79.6</td>
</tr>
<tr>
<td>V50</td>
<td>60.3</td>
<td>54.1–66.7</td>
<td>65.5</td>
<td>58.9–68.2</td>
</tr>
<tr>
<td>V70</td>
<td>48.6</td>
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<td>48.8</td>
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</tr>
<tr>
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<td>27.2–36.4</td>
<td>31.6</td>
<td>29.2–37.1</td>
</tr>
<tr>
<td>V500</td>
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<td>19.2–27.6</td>
<td>21</td>
<td>18.6–26.4</td>
</tr>
<tr>
<td>V700</td>
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</tr>
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<td>11.9</td>
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</tr>
<tr>
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<tr>
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<td>22.1–39.7</td>
<td>22.5</td>
<td>22.6–41.2</td>
</tr>
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<td>V90</td>
<td>19.2</td>
<td>18.1–32.9</td>
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<tr>
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<tr>
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<td>10.8–20.4</td>
<td>9.1</td>
<td>9.3–18.5</td>
</tr>
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<td>3.5</td>
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<td>2.1–5.2</td>
</tr>
<tr>
<td>Left femur V5</td>
<td>25.8</td>
<td>21.0–33.1</td>
<td>1.5</td>
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</tr>
<tr>
<td>V10</td>
<td>7.3</td>
<td>4.9–12.0</td>
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<td>0–0.9</td>
</tr>
<tr>
<td>V20</td>
<td>11.5</td>
<td>8.2–17.2</td>
<td>0</td>
<td>0–1.3</td>
</tr>
<tr>
<td>Right femur V5</td>
<td>29.1</td>
<td>23.9–36.8</td>
<td>2.5</td>
<td>1.3–10.9</td>
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<tr>
<td>V10</td>
<td>11.5</td>
<td>8.2–17.2</td>
<td>0</td>
<td>0–1.3</td>
</tr>
</tbody>
</table>

IMRT, 5-field sliding window intensity modulated radiation therapy; VMAT-1A, volumetric modulated arc therapy using one full arc; VMAT-2A, volumetric modulated arc therapy using two full arcs; Vn. The percentage volume (V) of an organ receiving n dose.

* illustrates where a significant difference was observed.
more advanced planning and treatment methods need to be implemented in line with the integration of the appropriate software.

In v10.0, plans suitable for treatment were produced for each of the 20 data sets using VMAT-1A. Importantly, these dose distributions achieved the planning guidelines at the first attempt. In contrast, using v8.6, VMAT-1A was capable of producing plans that achieved the planning guidelines for only eight of the 20 data sets. Notably, the guidelines were achieved at the first attempt for only two of the eight cases.24

In addition, VMAT plans were able to be generated using v10.0 in a fraction of the time required in v8.6. In the latest version of the software, IMRT plans were generated in a median time of 9.75 min, whereas both VMAT techniques required approximately 9 min longer to be produced. Statistically, the additional 9 min needed to generate a VMAT plan is significant; however, it may be argued that this time is clinically insignificant within the planning module. The additional minutes needed to produce a VMAT plan instead of an IMRT distribution is only a small fraction of the overall planning time when you also consider contouring times and quality assurance checks.

The improvements observed in v10.0 have significant resource implications in the utilization of VMAT clinically. Previously it was concluded that our department would not implement VMAT (v8.6) for the treatment of prostate cancer due to the inability to achieve the departmental planning guidelines and significantly prolonged planning time. In v10.0, the uncertainty of achieving the planning guidelines with VMAT is eliminated. Also the additional time needed to produce the VMAT plans has been reduced significantly and may now be considered of no consequence clinically.

**Conclusion**

It has been demonstrated that using v10.0 of Varian Medical System’s Eclipse and RapidArc (VMAT) software, a dose distribution that meets our departmental planning guidelines can be generated using IMRT, VMAT-1A, and VMAT-2A. The overall quality of the plans produced was similar; however, statistically significant differences were noted among the three techniques. Importantly, treatment times are reduced when using VMAT-1A, and the number of MUs required to deliver a fraction of treatment is lower for VMAT than IMRT.

Based on these findings our department is considering implementing VMAT for the radical treatment of prostate cancer to take advantage of the reduced treatment time and the reduced number of MUs. Future directions will include considering the resource implications of using VMAT-1A versus VMAT-2A or perhaps utilizing partial arcs to get the best mix of plan quality and utilization of departmental resources.

**Conflict of Interest**

None declared.

**References**


Chapter Five
Study Three

This chapter contains the published paper

Elith CA, Dempsey SE, Warren-Forward H.
5.1 Comparing Four Volumetric Modulated Arc Therapy Beam Arrangements for the Treatment of Early-Stage Prostate Cancer

Primary Author: Craig Elith a, b

Co-Authors: Shane E Dempsey b and Helen Warren-Forward b

a British Columbia Cancer Agency, Fraser Valley Centre, BC, Canada
b School of Health Sciences, University of Newcastle, Australia.

Journal: Journal of Medical Radiation Sciences, 2014; 61:91-101

5.2 Preface:

In chapter 4 it was concluded that v10.0 of Varian’s RapidArc (VMAT) system offers an acceptable alternative to IMRT for the treatment of early stage prostate cancer. Importantly, VMAT offers the advantage of reduced treatment time and a reduced number of MUs.

The research presented in chapter 5 explores which VMAT beam arrangement is best suited for implementation at FVC. The studies presented so far compare two VMAT beam arrangements, VMAT using one arc (VMAT-1A) and VMAT with two arcs (VMAT-2A). In this chapter these techniques are again compared in conjunction with another two VMAT beam arrangements, VMAT using a partial arc (VMAT-PA) and a technique that combines one arc plus a partial arc (VMAT-1A+PA).

5.3 Statement of Contribution of Others:

The PhD candidate, Craig Elith, performed all planning and mock treatments in this study. Craig was also responsible for gathering and storing the data recorded. Helen Warren-Forward assisted with the statistical analysis.

Preparation of the draft manuscript was done by Craig and significant feedback was provided by Craig’s PhD supervisors at the University of Newcastle, Shane Dempsey and Helen Warren-Forward. Craig was ultimately responsible for preparation of the final manuscript and journal submission. Any edits required by the journal were made by Craig.

Importantly, Craig and Helen collaborated to secure ethics approval for this project.
5.3.1 Co-author Statements:

I attest that Research Higher Degree candidate, Craig Elith, made significant contribution to the paper/publication entitled *Comparing Four Volumetric Modulated Arc Therapy Beam Arrangements for the Treatment of Early-Stage Prostate Cancer.*

Independently, Craig performed all VMAT planning and mock treatments on a linear accelerator. Craig gathered all the data presented including plan quality assessment and resource utilisation. Craig was also responsible for the preparation of the manuscript and submission to the journal. Any edits required by the journal were made by Craig.

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Shane Dempsey  
Date:  

(Signature of Co-Author)  
Helen Warren-Forward  
Date:  

(Signature of Candidate)  
Craig Elith  
Date: July 2 2014  

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(Full Name of ADRT)  
Date:
Comparing four volumetric modulated arc therapy beam arrangements for the treatment of early-stage prostate cancer

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Keywords
Prostate, radiation therapy, RapidArc, VMAT

Abstract

Introduction: This study compared four different volumetric modulated arc therapy (VMAT) beam arrangements for the treatment of early-stage prostate cancer examining plan quality and the impact on a radiotherapy department’s resources. Methods: Twenty prostate cases were retrospectively planned using four VMAT beam arrangements (1) a partial arc (PA), (2) one arc (1A), (3) one arc plus a partial arc (1A + PA) and (4) two arcs (2A). The quality of the dose distributions generated were compared by examining the overall plan quality, the homogeneity and conformity to the planning target volume (PTV), the number of monitor units and the dose delivered to the organs at risk. Departmental resources were considered by recording the planning time and beam delivery time. Results: Each technique produced a plan of similar quality that was considered adequate for treatment; though some differences were noted. The 1A, 1A + PA and 2A plans demonstrated a better conformity to the PTV which correlated to improved sparing of the rectum in the 60–70 Gy range for the 1A + PA and 2A techniques. The time needed to generate the plans was different for each technique ranging from 13.1 min for 1A + PA to 17.8 min for 1A. The PA beam delivery time was fastest with a mean time of 0.9 min. Beam-on times then increased with an increase in the number of arcs up to an average of 2.2 min for the 2A technique. Conclusion: Which VMAT technique is best suited for clinical implementation for the treatment of prostate cancer may be dictated by the individual patient and the availability of departmental resources.

Introduction

Perhaps understatedly, volumetric modulated arc therapy (VMAT) was first introduced in 2008 as a novel radiotherapy technique where treatment is delivered efficiently and accurately using a modulated arc.1 More specifically, VMAT treatment is delivered using a cone beam that rotates around the patient. The cone beam is modulated by the intertwining of dynamic multi-leaf collimators (MLCs), variable dose rates, and gantry speeds to generate high-quality dose distributions in a single optimised arc around the patient.2

Since being introduced, it is now well established that VMAT is capable of producing a dosimetric plan of similar or improved quality compared to intensity modulated radiation therapy (IMRT) for the treatment of early-stage prostate cancer.3 A previous study by our group supported this by demonstrating that when using either 5-field IMRT or VMAT with one and two arcs, a dose distribution that meets departmental planning guidelines was successfully produced for 20 prostate cancer cases. The overall quality of the IMRT and VMAT plans produced were similar. Importantly, beam delivery times were reduced when using VMAT with one arc and
the number of monitor units (MUs) required to deliver a fraction of treatment was lower for both VMAT techniques compared to IMRT.\(^4\)

On the basis of these findings the Fraser Valley Centre (FVC) of the British Columbia Cancer Agency (BCCA) is considering implementing VMAT for the radical treatment of prostate cancer to take advantage of the reduced treatment time to increase patient throughput in the department.

A decision has to be made on which VMAT beam arrangement is best suited for clinical implementation. In previous publications from the current authors, IMRT was compared to VMAT with either one or two arcs.\(^3,5\) Similar studies have been performed by others that also examine the use of one and/or two treatment arcs.\(^3,6-17\) Other authors have reported using partial arcs (PA) or a mix of full and PAs to treat the prostate.\(^6,15,18,19\) While some of these studies may have considered up to two different VMAT beam arrangements, to the best of our knowledge there is no study that compares a variety of VMAT techniques.

This study compared four different VMAT beam arrangements to aid in the decision as to which technique to implement clinically for the treatment of early-stage prostate cancer. The factors effecting the decision as to which technique to implement will be considered including plan quality and the impact on departmental planning and treatment resources.

**Methods**

Approval for this study was provided by the University of Newcastle, Australia, Human Research Ethics Committee (approval number: H-2011-0073) and the British Columbia Cancer Agency, Canada, Research Ethics Board (approval number: H11-00108).

**Cases and plans**

The study used de-identified CT data sets from 20 patients that had been previously treated at the FVC of the BCCA with IMRT to the prostate only. The presentation history of the 20 cases used has been described previously.\(^5\)

Dose distributions were generated retrospectively for each data set using four VMAT beam arrangements (detailed below). All planning was done by the same radiation therapist using v10.0 (PRO10.0.28) of Varian Medical Systems Eclipse planning software (which includes RapidArc). The planning was done on the same computer which uses an XP (SP3) operating system, 16 processors (2.3 GHz each) and 24 GB of RAM. Each plan was prescribed 74 Gy in 37 fractions and intended to

### Table 1. The Fraser Valley Centre specific planning objectives for intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) treatments of the prostate.

<table>
<thead>
<tr>
<th>Volume/organ at risk (OAR)</th>
<th>Dose constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning target volume (PTV)</td>
<td>99% of the volume to get ≥ 95% of the prescription</td>
</tr>
<tr>
<td></td>
<td>Minimum dose &gt; 90% of the prescription</td>
</tr>
<tr>
<td></td>
<td>Mean dose &gt; 99% of the prescription</td>
</tr>
<tr>
<td></td>
<td>Maximum dose &lt; 107% of the prescription</td>
</tr>
<tr>
<td></td>
<td>The maximum dose must be within the PTV</td>
</tr>
<tr>
<td>Rectum</td>
<td>&lt;65% of the volume to receive 50 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;55% of the volume to receive 60 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;25% of the volume to receive 70 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;16% of the volume to receive 75 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;5% of the volume to receive 78 Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>&lt;50% of the volume to receive 65 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;35% of the volume to receive 70 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;25% of the volume to receive 75 Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;15% of the volume to receive 80 Gy</td>
</tr>
</tbody>
</table>

Gy, dose in gray. meet the FVC prostate IMRT planning guidelines outlined in Table 1.

**CT simulation**

The original CT data sets were obtained on a Phillips Brilliance Big Bore scanner using 2 mm slices with the patient in a supine position. Patients were instructed to have a full bladder at time of simulation and treatment, however, bowel preparation to ensure an empty bowel was not performed.

**Contouring**

All original contours from the actual treatment plans were transferred onto the de-identified data sets.

A radiation oncologist contoured the prostate, bladder and rectum distally from the rectosigmoid flexure to the anus. A planning target volume (PTV) was generated by expanding the prostate contour with a 10 mm margin in all directions. If the data set included prostate fiducial markers, the PTV was created using a 6 mm margin to the prostate posteriorly to spare additional rectal tissue from receiving radiation dose.

Optimisation structures were created for the PTV, rectum and bladder. A PTV\(_{\text{opti}}\) was created by copying the PTV and extending the contour superiorly and inferiorly by one slice. The size of the PTV\(_{\text{opti}}\) on the new superior and inferior slices was reduced by half. The creation of the PTV\(_{\text{opti}}\) was done to allow the superior and inferior ends of the PTV to receive adequate dose.
coverage via primary and scatter dose. Rectum\textsubscript{opti} and Bladder\textsubscript{opti} structures were created by subtracting the rectum and bladder structures from the PTV\textsubscript{opti} plus a 3-mm margin.

In addition to the contours transferred from the original planning data, the heads of femur were also contoured. The dose to the heads of femur are not routinely considered for IMRT planning at FVC but were considered in this study. The heads of femur were contoured superiorly from the caudal ishial tuberosity.

A couch structure was added to the plans so that beam attenuation from the treatment couch was considered. The couch structure was added using the pre-defined couch structures available within the Varian Eclipse software.

**VMAT planning**

In this study, dose distributions were generated retrospectively for each data set using four VMAT beam arrangements: (1) PA, (2) one arc, (3) one arc plus a partial arc and (4) two arcs (Fig. 1).

1. The PA method utilised an arc that started with the gantry at 135° and rotated in a counter clockwise (CCW) direction stopping at 225°, for a total 270° degree arc (Fig. 1A). The arc deliberately avoided treating through the rectum from the posterior direction. The collimator was set at 45° to minimise MLC tongue and groove effect.\(^{20}\)

2. The one arc (1A) technique utilised one complete CCW rotation to deliver radiation treatment (Fig. 1B). The gantry start angle was 179° and the stop angle was 181°. As for PA, the collimator was set to 45°.

3. The third technique combined one full arc plus a partial arc (1A + PA) (Fig. 1C). The PA was delivered as described above. The additional one arc was delivered with the gantry moving in the opposite clockwise (CW) direction from 181° to 179°. For this additional arc the collimator was flipped to 135° to increase modulation.

4. The two-arc plan (2A) combined both a complete CCW rotation and a full CW gantry rotation for treatment (Fig. 1D). The parameters for the first arc were identical to the 1A technique. The second arc had the gantry rotating in the opposite direction to minimise set-up time. The gantry start angle was 181° and a stop angle of 179°. For the second arc, the collimator was set to 135° to increase modulation.

Planning templates defining the beam parameters and the initial optimisation objectives were created to expedite the planning process. Importantly, the initial optimisation objectives used for VMAT planning were the same for each of the four beam arrangements, however, these objectives were adjusted during optimisation to achieve the best plan. VMAT calculations utilised the anisotropic analytical algorithm (AAA) with heterogeneity correction on and a 2.5 mm calculation grid.

Figure 1. An example case displaying the planning target volume (in red) and the beam arrangement for the (A) partial arc (PA), (B) one arc (1A), (C) one arc plus a partial arc (1A + PA) and (d) two-arc (2A) volumetric modulated arc therapy (VMAT) techniques.
Analysis

Plan quality
A dose distribution was considered acceptable for treatment if able to meet the FVC prostate planning guidelines outlined in Table 1.

The plan quality was quantitatively assessed by calculating the homogeneity index (HI) and conformity number (CN) for each plan. The HI is defined as:

$$ HI = \frac{D_{2\%}}{D_{98\%}} $$

where $D_n$ is the dose covering $n$ of the target volume.

A HI value closer to zero indicates more homogeneous dose coverage within the PTV.

Dose conformity evaluates the dose fit of the PTV relative to the volume covered by the prescription dose. Ideally the prescribed dose should fit tightly to the PTV, therefore reducing the side effects incurred by treating surrounding tissues and organs. The CN simultaneously takes into account irradiation of the PTV and irradiation of healthy tissues. The CN is defined as:

$$ CN = \frac{V_{TPres}}{PTV} \times \frac{V_{TPres}}{V_{Pres}} $$

where $V_{Pres}$ is the total volume receiving the prescription, PTV is the planning target volume and $V_{TPres}$ is the target volume covered by the prescription.

A CN value closer to 1, indicates that the dose distribution fits more tightly to the PTV preserving healthy tissue.

Dose to organs at risk
The dose to the organs at risk (OAR) was compared by determining the percentage volume ($V$) of an organ receiving $n$ dose ($V_n$). To get a complete understanding of how each VMAT beam arrangement impacts on dose delivered across the rectum and bladder, the $V_2$, $V_{15}$, $V_{25}$, $V_{30}$, $V_{40}$, $V_{50}$, $V_{60}$, $V_{65}$, and $V_{70}$ were recorded. For each of the left and right heads on femur, the $V_{20}$, $V_{30}$ and $V_{40}$ were measured.

Planning time
The time taken to generate a dose distribution for each technique was recorded in minutes (min). For the purposes of this study, planning time does not include the time needed to perform contouring as this is considered neutral for each of the VMAT techniques. Instead, time measurement includes a sum of the time to place fields, plan optimisation, dose calculation and the period of evaluation of the final dose distribution to assess if the planning guidelines were achieved.

Beam delivery time
The time taken to deliver the treatment fields for the PA, 1A, 1A + PA and 2A plans was measured and recorded. This was done by running all four treatment plans for each of the 20 cases in standby mode on a Varian TrueBeam linear accelerator (linac). Time measurement was started at the initial beam-on and was ended when the final MU was delivered. The treatment time does include the time taken to move parameters such as gantry and collimator angles during treatment and between fields. However, the automation feature of the TrueBeam machine was used to minimise the delay due to collimator and gantry movement between treatment arcs. The measured treatment time does not include patient set up time or the time that may be needed to verify treatment position.

Number of MUs
The total number of MUs needed to deliver each treatment plan was summed and recorded.

Statistical analysis
A sample size of 20 cases was calculated to give a power of at least 0.8 at the 95% level. Statistical analysis was conducted using Graphpad InStat version 3 for windows (www.graphpad.com). The data were analysed first to test for normality, and if it passed it was analysed for statistical difference with the repeated measures analysis of variance (RM ANOVA). A RM ANOVA test was chosen as the same data sets were used for each treatment option. To be statistically different the values needed to be significant at the 95% level (i.e. $P < 0.05$).

Results
Each VMAT beam arrangement trialed, PA, 1A, 1A + PA and 2A, was able to produce an acceptable plan meeting the department guidelines for all 20 cases. An example of one case showing the dose volume histogram (DVH) for the PTV, rectum, bladder and heads of femur, for each of the four techniques is presented in Figure 2.

The results for the planning time, beam delivery time, number of MUs, HI and CN are presented in Table 2. Overall the plan quality of each technique was similar with some observable differences. The measured homogeneity was similar for the 1A, 1A + PA and 2A
techniques. These were significantly better than that observed for the PA arrangement (Table 2).

The conformity to the PTV as reported by the CN is similar for the 1A, 1A + PA and 2A techniques. These techniques demonstrate improved conformity compared to the PA technique, with the 1A + PA and 2A techniques being significantly better than the PA beam arrangement (Table 2).

The mean number of MUs required to deliver the 1A and 2A treatments are similar (460 and 470). Significantly more MUs are required to deliver PA (496) and 1A + PA (489) plans (Table 2).

The time required to generate a dose distribution for each beam arrangement is presented in Table 2. It was hypothesised that the PA dose distributions would be produced in the fastest time and that 2A plans would require the most time to generate. Unexpectedly, the 1A + PA plans were produced the fastest taking an average time of 13.1 min. The 1A plans took the longest mean time to generate (17.8 min). The PA and 2A plans required a mean time of 13.4 and 14.4 min respectively. Figure 3 drills down the overall planning time presented in Table 2, into the portion of time needed for plan optimisation and the time for plan calculation. The average time used for optimisation is lowest for the PA plans and increases as the number of treatments arcs (gantry rotation) increases. As such the 2A plans needed the most time to optimise. The 1A + PA and 2A plans require less time to calculate compared to the PA and 1A technique.

The mean beam delivery time recorded on the TrueBeam unit increases as the number of treatment arcs (gantry rotation) is increased (Table 2). Beam delivery time was fastest using the PA technique, requiring 0.9 min. The 1A technique was the next fastest requiring 1.0 min followed by the 1A + PA technique which required an average time of 1.9 min. The 2A arrangement took the longest with a mean time of 2.2 min.

The dose delivered to the rectum is presented in Table 3 and an example DVH from an actual case is presented in Figure 2B. From this data there is a trend for the PA technique to provide a greater sparing of tissue in the \( V_{15-30} \) range. In the \( V_{60-70} \) range the 1A + PA and 2A techniques provide the best sparing of rectal tissue.

As can be seen in Figure 2C, the dose delivered to the bladder is very similar for each of the four VMAT beam arrangements. The statistical differences between the techniques and the dose they deliver to the bladder is assessed in Table 4. In the \( V_{40-70} \) range the 1A + PA and 2A techniques provide the best sparing of rectal tissue.

As can be seen in Figure 2C, the dose delivered to the bladder is very similar for each of the four VMAT beam arrangements. The statistical differences between the techniques and the dose they deliver to the bladder is assessed in Table 4. In the \( V_{40-70} \) range the 1A + PA technique delivers more dose to the bladder compared to the 1A + PA technique.

The dose delivered to the heads of femur is presented in Figure 2D and Table 5. At all levels measured, the PA technique delivers a higher dose to the heads of femur.
Planning The next fastest were the PA plans followed by the 2A different VMAT beam arrangements for the treatment of examined were: (1) a partial arc (PA), (2) one arc (1A), different for each beam arrangement. The 1A (2A). Each technique was able to produce an acceptable early-stage prostate cancer. The four beam arrangements radiation therapy department’s resources for four This study examined plan quality and the impact on a

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>1A</th>
<th>1A + PA</th>
<th>2A</th>
<th>PA vs.</th>
<th>PA vs.</th>
<th>PA vs.</th>
<th>1A vs.</th>
<th>1A vs.</th>
<th>1A + PA vs. 2A</th>
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</thead>
<tbody>
<tr>
<td>Planning time (min)</td>
<td>13.4</td>
<td>17.8</td>
<td>13.1</td>
<td>14.4</td>
<td>***</td>
<td>ns</td>
<td>***</td>
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<tr>
<td>Beam delivery time (min)</td>
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<td>1.9</td>
<td>2.2</td>
<td>ns</td>
<td>***</td>
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<td>(2.1–2.2)</td>
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<td>485</td>
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<tr>
<td></td>
<td>(479.9–513.9)</td>
<td>(446.9–474.1)</td>
<td>(472–506.4)</td>
<td>(452.9–486.2)</td>
<td>(452.9–486.2)</td>
<td>(452.9–486.2)</td>
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<tr>
<td>Homogeneity index</td>
<td>0.073</td>
<td>0.068</td>
<td>0.069</td>
<td>0.066</td>
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<td></td>
<td>(0.070–0.074)</td>
<td>(0.066–0.071)</td>
<td>(0.066–0.072)</td>
<td>(0.064–0.068)</td>
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<tr>
<td>Conformity number</td>
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<td>0.853</td>
<td>0.857</td>
<td>0.854</td>
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<td>(0.84–0.86)</td>
<td>(0.85–0.86)</td>
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ns, not significant (P > 0.05).
*P < 0.05; **P < 0.01; ***P < 0.001.

Discussion

This study examined plan quality and the impact on a radiation therapy department’s resources for four different VMAT beam arrangements for the treatment of early-stage prostate cancer. The four beam arrangements examined were: (1) a partial arc (PA), (2) one arc (1A), (3) one arc plus a partial arc (1A + PA) and (4) two arcs (2A). Each technique was able to produce an acceptable plan as defined by the departmental planning guidelines.

The time required to generate a dose distribution was different for each beam arrangement. The 1A + PA plans were produced the fastest in a mean time of 13.1 min. The next fastest were the PA plans followed by the 2A technique requiring an average time of 13.4 and 14.4 min. The 1A plans took the longest mean time to generate (17.8 min).

The results obtained for the time required to generate a treatment plan were unexpected by the authors who hypothesised that the planning time would correlate with the number of control points being used to generate each plan. In Varian Medical Systems VMAT planning software, a control point is used approximately every 2° of gantry rotation during the optimisation and calculation processes. In this study the PA, 1A, 1A + PA and 2A plans used 113, 178, 291 and 356 control points. The authors, therefore, hypothesised the planning time from fastest to slowest would be PA, 1A, 1A + PA, then 2A. The hypothesised trend was observed when comparing the time needed for plan optimisation, however, this trend is not observed in the measured calculation time (Fig. 3). Instead, the calculation time of the two techniques with the greatest number of control points, 1A + PA and 2A, is the fastest. This observation can be explained by the way the FVC’s network for VMAT calculations is configured. The dosimetry department is set up so that when a VMAT plan utilises one arc or less, the calculation is performed by the local Eclipse workstation but is also farmed out to other available Eclipse workstations thus reducing the time needed for calculation. Presumably, if the calculation network is reconfigured so that all VMAT calculations are farmed out to other available Eclipse workstations, the plans with the least number of control points would be calculated in the fastest time. This is an important

Figure 3. The average optimisation, calculation and total planning time (in minutes) required for the: partial arc (PA), one arc (1A), one arc plus a partial arc (1A + PA) and two-arc (2A) volumetric modulated arc therapy (VMAT) techniques.
Table 3. The mean dose to the rectum delivered by the partial arc (PA), one arc (1A), one arc plus partial arc (1A + PA) and two-arc (2A) plans

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>1A</th>
<th>1A + PA</th>
<th>2A</th>
</tr>
</thead>
<tbody>
<tr>
<td>V&lt;sub&gt;5&lt;/sub&gt;</td>
<td>89.4 (84.8–94.2)</td>
<td>89.9 (85.3–94.5)</td>
<td>89.9 (85.2–94.6)</td>
<td>90.0 (92.8–94.7)</td>
</tr>
<tr>
<td>V&lt;sub&gt;15&lt;/sub&gt;</td>
<td>74.1 (63.0–80.8)</td>
<td>75.8 (69.6–82.0)</td>
<td>75.7 (69.6–81.7)</td>
<td>75.6 (69.5–81.7)</td>
</tr>
<tr>
<td>V&lt;sub&gt;20&lt;/sub&gt;</td>
<td>68.3 (61.6–75.1)</td>
<td>72.4 (66.3–78.5)</td>
<td>71.6 (65.8–77.5)</td>
<td>72.3 (66.3–78.3)</td>
</tr>
<tr>
<td>V&lt;sub&gt;30&lt;/sub&gt;</td>
<td>54.0 (47.0–61.0)</td>
<td>61.9 (56.3–67.4)</td>
<td>57.3 (51.3–63.0)</td>
<td>60.7 (55.7–65.7)</td>
</tr>
<tr>
<td>V&lt;sub&gt;40&lt;/sub&gt;</td>
<td>41.4 (35.1–47.8)</td>
<td>46.4 (41.4–51.6)</td>
<td>41.0 (35.4–46.7)</td>
<td>44.0 (39.2–49.0)</td>
</tr>
<tr>
<td>V&lt;sub&gt;50&lt;/sub&gt;</td>
<td>29.9 (24.6–35.1)</td>
<td>31.0 (26.8–35.4)</td>
<td>28.5 (23.6–33.5)</td>
<td>29.6 (25.1–34.2)</td>
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</tbody>
</table>

Table 4. The mean dose to the bladder delivered by the partial arc (PA), one arc (1A), one arc plus partial arc (1A + PA) and two-arc (2A) plans

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>1A</th>
<th>1A + PA</th>
<th>2A</th>
</tr>
</thead>
<tbody>
<tr>
<td>V&lt;sub&gt;5&lt;/sub&gt;</td>
<td>66.4 (56.0–76.7)</td>
<td>68.4 (58.3–78.6)</td>
<td>68.0 (57.8–78.2)</td>
<td>68.7 (58.6–78.2)</td>
</tr>
<tr>
<td>V&lt;sub&gt;15&lt;/sub&gt;</td>
<td>48.1 (36.6–60.0)</td>
<td>49.8 (37.8–61.8)</td>
<td>49.3 (37.5–61.1)</td>
<td>50.0 (38.6–62.0)</td>
</tr>
<tr>
<td>V&lt;sub&gt;20&lt;/sub&gt;</td>
<td>44.3 (32.9–55.9)</td>
<td>45.8 (34.1–57.5)</td>
<td>45.2 (33.8–56.6)</td>
<td>45.9 (34.1–57.7)</td>
</tr>
<tr>
<td>V&lt;sub&gt;30&lt;/sub&gt;</td>
<td>35.9 (26.5–46.2)</td>
<td>37.4 (26.7–48.2)</td>
<td>36.4 (26.2–46.6)</td>
<td>37.0 (26.4–47.7)</td>
</tr>
<tr>
<td>V&lt;sub&gt;40&lt;/sub&gt;</td>
<td>28.3 (19.5–37.0)</td>
<td>29.3 (20.2–38.4)</td>
<td>27.9 (19.5–36.3)</td>
<td>28.6 (19.8–37.3)</td>
</tr>
<tr>
<td>V&lt;sub&gt;50&lt;/sub&gt;</td>
<td>22.0 (14.8–29.2)</td>
<td>22.7 (15.3–30.1)</td>
<td>21.5 (14.6–28.4)</td>
<td>22.0 (14.9–29.1)</td>
</tr>
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</table>

Table 5. The mean dose to the heads of femur delivered by the partial arc (PA), one arc (1A), one arc plus partial arc (1A + PA) and two-arc (2A) plans

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>1A</th>
<th>1A + PA</th>
<th>2A</th>
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<tr>
<td>LT Femur</td>
<td>V&lt;sub&gt;20&lt;/sub&gt;</td>
<td>50.6 (42.9–58.4)</td>
<td>30.1 (22.8–37.4)</td>
<td>46.8 (36.6–56.9)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;15&lt;/sub&gt;</td>
<td>18.2 (12.5–23.9)</td>
<td>5.8 (2.2–9.4)</td>
<td>9.3 (4.6–14.0)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;10&lt;/sub&gt;</td>
<td>2.6 (1.0–4.2)</td>
<td>0.3 (-0.1 to 0.8)</td>
<td>0.4 (-0.3 to 0.1)</td>
</tr>
</tbody>
</table>

| RT Femur | V<sub>20</sub> | 56.2 (48.6–63.8)    | 41.2 (29.9–52.5)     | 39.0 (30.8–47.3)    |
|          | V<sub>15</sub> | 15.7 (9.6–21.3)     | 7.8 (2.7–12.7)       | 5.9 (3.1–8.8)       |
|          | V<sub>10</sub> | 2.3 (0.6–4.0)       | 0.4 (0.05 to 0.9)    | 0.4 (-0.04 to 0.8)  |
consideration for any radiation therapy department considering implementing VMAT.

Although it was demonstrated that there were some statistical differences in the mean time needed to generate a plan for each of the four VMAT styles, in reality there was less than 5 min difference between the fastest and slowest technique. Importantly, the planning time reported in this study includes the time to place fields, plan optimisation, dose calculation and the time needed to review the plan. It could be argued the observed difference in planning time of 5 min is insignificant from a resource management perspective, especially if you were also to consider the additional time required for contouring and quality assurance checks.

Overall, the quality of the plans produced were similar for each technique, however, there were some noted difference between the beam arrangements.

The homogeneity across the PTV as determined by the HI was similar for the 1A, 1A + PA and 2A techniques. The HI for these techniques was significantly better than that observed for the PA arrangement. This observation is in agreement with previous findings from this group and the reports of others who have demonstrated that the homogeneity across the PTV is improved as more gantry angles or arcs are used for treatment. Although statistical differences in the HI have been determined here, the actual values are similar and, therefore, the clinical significance of such small differences remains unclear.

The 1A and 2A techniques require the fewest number of MUs to deliver a single fraction of treatment. Significantly, more MUs are required to deliver the PA and 1A + PA plans. The significance of the number of MUs used in a treatment becomes important when considering the theoretical risk of inducing secondary malignancies as a consequence of radiation treatment. A greater number of MUs may result in an increase in the whole body dose due to an increase in scatter and leakage radiation. In turn, the increased whole body dose theoretically increases the risk of developing secondary malignancies. Secondary malignancy induction is an important consideration for prostate cancers patients who have a significant chance of long term survival. On the basis of the results presented in this study, patients being treated with one or two arcs may hypothetically have a reduced risk of generating a treatment-related secondary malignancy than patients treated using either PA or 1A + PA which require a greater number of MUs.

Any improvement in dose conformity observed using VMAT may increase the potential of dose escalation without increasing treatment-related morbidities associated with radiation exposure to surrounding tissues. Importantly, dose escalation has been demonstrated to improve local control of prostate cancer. The conformity to the PTV as reported by the CN is similar for the 1A, 1A + PA and 2A techniques. These are shown to be improved compared to the PA technique. The improved conformity observed using VMAT techniques with relatively more arcs is a consequence of a treatment that delivers dose from more gantry angles. In this study, a significant improvement in CN was not observed as the number of arcs used for treatment is increased above one arc. The PTV used here contains the prostate only and is relatively spherical, without irregularities in shape. For this PTV it has been demonstrated here that an increase in the number of arcs/gantry angle used beyond one arc does not improve the conformity of the plan. It may be reasonable to expect that a more irregularly shaped PTV, such as those including the seminal vesicles, may become more conformal as a greater number of arcs/gantry angle are used for treatment. Sale and Moloney compared VMAT treatments using one or two arcs to irregularly shaped PTVs for post-prostatectomy patients or a prostate PTV that includes the seminal vesicles. They report that the conformity is improved for these more complex PTVs using two arcs compared to the single-arc technique. Conformity to the PTV can in-part explains the dose levels being delivered to the rectum in this study. It has been demonstrated that when using the PA technique, a greater volume of rectal tissue receives 60–70 Gy compared to the 1A + PA and 2A techniques. This may be attributed to the 1A + PA and 2A techniques generating a more conformal dose to the PTV therefore sparing more of the rectal tissue. Increased sparing of rectal tissues in this dose range is critical as it has been reported that parts of the rectum receiving ≥260 Gy are more likely to experience acute and late side effects including moderate diarrhoea, excessive rectal mucus, rectal bleeding and obstruction. Therefore VMAT treatments with the 1A + PA and 2A techniques may reduce the occurrence of these acute and late toxicities. In the 15–30 Gy range, the PA technique actually spares more of the rectum than the other beam arrangements. This can be attributed to the geometry of the PA beam arrangement which avoids delivering dose to the PTV through the rectum. The PA technique delivers more dose to the heads of femur at all levels measured. This is also due to the geometry of the PA beam arrangement. As the PA avoids the rectum it is forced to push more dose from other angles including those which treat through the heads of femur, delivering a greater dose to these OAR. An option not investigated here that could be used to reduce the dose delivered to the heads of femur would be to consider using avoidance sectors. Another option to reduce the dose to the heads of femur would be
to consider using couch rotations to create non-coplanar plans. If a non-coplanar technique is used, this would likely increase the time needed to deliver a treatment as additional time would be needed to enter the room to change the couch angle.

The mean beam delivery time on the TrueBeam unit was different for each technique. Beam delivery time was fastest using the PA technique requiring 0.9 min, while the 2A technique needed the most time (2.1 min). The beam delivery time correlated with the total gantry movement in each technique. As the amount of gantry movement increased, so did the beam delivery time. The PA technique utilised the smallest total gantry rotation while the 2A techniques had the greatest total gantry rotation.

The significance of faster beam delivery is that there is less chance of intrafraction movement. Positioning studies have reported that reducing treatment time has the potential to increase prostate treatment accuracy. That is, the longer a treatment lasts the higher the risk is of patient movement and anatomical deviation. As discussed earlier, a more irregularly shaped treatment target may benefit from using multiple arcs to achieve the best dose distribution, however, this comes with the cost of an increased beam delivery time.

It is important to remember that the reported beam delivery time represents only a fraction of the time the patient is actually on the treatment couch. An overall treatment appointment also includes the time needed for patient positioning, portal imaging and general patient care. None the less, any reduction in the beam delivery time will increase patient comfort and reduce the chance of intrafraction movement. If the time needed for the overall treatment appointment can be reduced, it may be possible to increase patient throughput and reduce the wait list of radiation therapy department. Alternatively, the newly available time could be used to implement advanced image guidance radiation therapy (IGRT) techniques such as cone beam CT, without increasing the overall treatment appointment time.

The purpose of this study was to compare four different VMAT beam arrangements to aid our radiation therapy department in deciding which VMAT beam arrangement to implement clinically for the treatments of early-stage prostate cancer. As demonstrated here each technique has its own pros and cons. Quan et al. consider dual arcs superior to single arc in terms of a compromise between plan quality and delivery efficiency. Their group prefer the dual arc VMAT plans which provide improved rectal and bladder sparing which they consider outweighs the cost of increased treatment time compared to the single-arc technique. Sale and Maloney elect to use the one arc technique for more spherical PTV structures (prostate only) and choose the two-arc technique when planning irregular PTV structures such as post-prostatectomy cases and where the seminal vesicles are included in the PTV. The preferred technique at the BCCA is the 1A technique which is considered to provide an adequate dose distribution while still reducing the treatment time considerably compared to IMRT.

**Conclusion**

This study examines the plan quality of four different VMAT beam arrangements for the treatment of prostate cancer and their potential impact on a radiation therapy department’s resources. Although statistical differences were noted, the four techniques considered: PA, 1A, 1A + PA and 2A, produced a dose distribution of similar quality that achieved the departmental planning guidelines. The conformity to the PTV was best for the 1A, 1A + PA and 2A techniques which translated to improved rectal sparing in the 1A + PA and 2A plans in the 60–70 Gy range. The improved conformity and reduced rectal dose observed using the 1A + PA and 2A techniques may allow for dose escalation without increasing rectal toxicity. However, the 1A + PA and 2A plans did have the longest beam delivery times, reducing patient comfort and increasing the chance of intrafraction movement. The PA and 1A + PA techniques also required the highest number of MUs to deliver a treatment fraction, increasing the theoretical risk of generating a radiation-induced secondary malignancy.

Ultimately, which VMAT technique is best suited for clinical implementation for the treatment of early-stage prostate cancer may be dictated by the individual patient and the availability of resources in each radiotherapy department.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


Chapter Six
Study Four

This chapter contains the published paper

Elith CA, Dempsey SE, Warren-Forward H.
6.1 The Quality Assurance of Volumetric Modulated Arc Therapy (VMAT) Plans for Early Stage Prostate Cancer: A Technical Note

Primary Author: Craig Elith

Co-Authors: Shane E Dempsey, Fred Cao, Afrooz Farshadi and Helen Warren-Forward

a British Columbia Cancer Agency, Fraser Valley Centre, BC, Canada
b School of Health Sciences, University of Newcastle, Australia.

Journal: Journal of Medical Radiation Sciences, first published online: 29 Oct 2014

6.2 Preface:

The preceding chapters present a series of retrospective studies that have validated VMAT as an acceptable alternative to IMRT for the treatment of early stage prostate cancers. The research presented in this chapter considers the quality assurance (QA) of VMAT treatment plans. The increased complexity of VMAT planning and treatment dictates that patient specific QA is required to ensure accurate dose delivery. FVC purchased ArcCHECK (Sun Nuclear Corp, Melbourne, FL) specifically for the purpose of performing patient specific plan QA for VMAT dose distributions. ArcCHECK is a phantom based QA tool that requires time on a linear accelerator to perform the physical measurement of dose delivered. If VMAT QA using ArcCHECK is performed during clinical hours it reduces the availability of the treatment unit for patient care, however, if the QA is not performed during the hours of clinical operation, the after-hours workload is increased for the department’s medical physicists.

An alternative to phantom based QA tools such as ArcCHECK is treatment plan QA software that can act as an independent plan evaluation and dosimetry check. Plan QA software eliminates the need to perform dose measurements on a linear accelerator and can greatly reduce the time needed to perform the QA for complex plans. At FVC the QA software IMSure (Standard Imaging, Middleton, WI) is used to perform plan QA for prostate IMRT cases. A study is presented in this chapter that compares the QA software IMSure with the standard phantom-based tool ArcCHECK for the QA of VMAT treatment plans for early stage prostate cancer. If IMSure proves to be as reliable as ArcCHECK for performing QA on prostate VMAT plans, utilising the IMSure software
may eliminate the need to perform dose based measurements on a linear accelerator and may reduce the time needed for a medical Physicist to perform patient specific QA.

6.3 Statement of Contribution of Others:

The PhD candidate, Craig Elith, was responsible for preparing all VMAT treatment plans used in this study. All quality assurance checks using both IMSure and ArcCHECK were performed by Afrooz Frashadi (Medical Physicist Student) under the supervision of Dr Fred Cao (Senior Medical Physicists). Craig was then responsible for gathering and storing the data recorded. Helen Warren-Forward assisted with statistical analysis.

Preparation of the draft manuscript was done by Craig and significant feedback was provided by Craig’s PhD supervisors at the University of Newcastle, Shane Dempsey and Helen Warren-Forward. Craig was ultimately responsible for preparation of the final manuscript and journal submission.
6.3.1 Co-author Statements:

I attest that Research Higher Degree candidate, Craig Elith, made significant contribution to the manuscript *The Quality Assurance of Volumetric Modulated Arc Therapy (VMAT) Plans for Early Stage Prostate Cancer: A Technical Note.*

Independently, Craig performed all VMAT planning and preparations necessary for physics staff to perform quality assurance. Craig was responsible for collating and storing all data recorded. Craig was also responsible for the preparation of the manuscript and submission to the journal.

Craig and Helen collaborated to secure ethics approval for this project.

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(Signature of Co-Author)  
Shane Dempsey  
Date:  

(Signature of Co-Author)  
Fred Cao  
Date: July 2 2014

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(Signature of Co-Author)  
Afrooz Frashadi  
Date: May 7 2014  

(Signature of Co-Author)  
Helen Warren-Forward  
Date:

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(Signature of Candidate)  
Craig Elith  
Date: July 2 2014  

(Signature of Assistant Dean Research Training (ADRT))  
(Full Name of ADRT)  
Date:
The quality assurance of volumetric modulated arc therapy (VMAT) plans for early stage prostate cancer: a technical note

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Keywords
ArcCHECK, IMSure, quality assurance, VMAT

Abstract
As radiation therapy transitions from intensity modulated radiation therapy (IMRT) to volumetric modulated arc therapy (VMAT) it is important to consider the quality assurance (QA) of VMAT plans in light of what has previously been learned and developed in IMRT QA. This technical note assesses if IMRT based plan QA software, which has reduced the need in IMRT for phantom dose measurements on the linear accelerator, can be incorporated into VMAT QA processes. Twenty prostate cases were retrospectively planned using VMAT with one arc to deliver a prescription of 74 Gy in 37 fractions. A plan QA was performed using both IMSure (version 3.3), a software-based IMRT QA program, and ArcCHECK (version 6.2.3.5713), a phantom-based VMAT QA tool. Outcomes assessed included the time needed to perform the QA of both the IMSure and ArcCHECK QA methods, and agreement between planned dose and QA measured dose. On average per case, the ArcCHECK technique needed 31.5 min to perform the VMAT plan QA, while IMSure required 3.5 min to perform the same QA. All 20 cases passed dosimetric QA using ArcCHECK. However, using IMSure, three cases failed dosimetric QA using the departments existing IMRT QA criteria. This research has demonstrated that the IMRT QA software IMSure may be incorporated into the QA of VMAT plans, however the criteria to assess the dosimetry of the VMAT plans may need to be different to that for IMRT cases. The implication of this research for radiation therapists is to be critically aware of the differences between the plan QA requirements and methods for IMRT and those required for VMAT.

Introduction
In terms of dosimetry, intensity modulated radiation therapy (IMRT) treatments utilising a linear accelerator (linac) with dynamic multi-leaf collimators (MLCs) are extremely complex and require patient-specific quality assurance (QA) be performed to ensure the dose predicted to be delivered by the treatment planning system (TPS) is the actual dose being delivered to the patient at the treatment unit. Typically, IMRT patient-specific QA is performed on a linac using a phantom and distribution. This method of plan IMRT QA requires time on a linac to perform the physical measurement of dose delivered and increases the after hours workload for medical physicists. It can also be difficult to adequately replicate patient geometries and heterogeneities using phantom-based QA methods.

Treatment plan QA software is now available which can act as an independent plan evaluation and dosimetry check removing the need to perform a dose measurement on a linac and greatly reducing the time needed to perform the QA for...
IMRT plans. IMSure (Standard Imaging, Middleton, WI) is one example of treatment plan QA software available commercially. Patient-specific fluence maps generated from the TPS can be imported into IMSure, which uses a patented “3-Source Model” algorithm developed at Stanford University that considers dose from primary and scattered photon sources, to produce dose calculations and monitor units (MUs) calculations allowing for patient-specific QA plan comparison to be completed.3–5

Previous research at the Fraser Valley Centre (FVC) of the British Columbia Cancer Agency (BCCA) demonstrated that for a five-field IMRT treatment of prostate cancer, the IMSure software point dose calculations showed agreement with the Eclipse (Varian Medical Systems, Palo Alto, CA) TPS to within 1%.6 This research established that the IMSure software can be a reliable tool for prostate IMRT QA. As such, IMSure is routinely used to QA the plans for five-field IMRT treatments of prostate cancers at FVC.

FVC has recently upgraded its linacs to be capable of delivering volumetric modulated arc therapy (VMAT) treatment using Varian Medical Systems, RapidArc. VMAT treatments further increase treatment and dosimetric complexity by utilising dynamic MLCs in combination with variable dose rates and variable gantry speeds to generate IMRT quality dose distributions in a single optimised arc around the patient.7 Research by the authors has demonstrated that VMAT is a realistic option for early stage prostate cases at FVC, however, prior to implementation the centre needs to establish a system of QA for its VMAT plans.8–10 The increased complexity of VMAT planning and treatment dictates that patient-specific QA is required to ensure accurate dose delivery. FVC purchased ArcCHECK (Sun Nuclear Corp., Melbourne, FL) specifically for the purpose of performing patient-specific plan QA for VMAT dose distributions. ArcCHECK uses a cylindrical diode array that ensures an orthogonal beam-to-diode configuration for all angles (Fig. 1).11 For a coplanar treatment delivery, the ArcCHECK system accumulates and records the dose in two areas of the dose distribution, one for the diodes close to the beam source and the other for the diodes measuring the beam exiting the phantom. Therefore, the ArcCHECK measured peripheral dose is the sum of the entrance and exits doses which is then compared to the dose calculated by the TPS.12

ArcCHECK QA of VMAT plans, much like the earlier phantom based methods of IMRT QA, requires physical measurements be performed on a linac. This can be time consuming for the physicist performing the measurement, and if not performed after clinical hours may utilise time on a linac that could otherwise be used for patient treatment. If a treatment plan QA software, such as IMSure, could be used instead, less time and departmental resource would be needed to QA a VMAT plan.

The study presented here assesses if the plan IMRT QA software IMSure, which has largely replaced phantom-based QA at FVC, can be used for the QA of VMAT plans for the treatment of early stage prostate cancer. IMSure will be benchmarked against ArcCHECK which is the current accepted standard of performing QA for VMAT plans at FVC. The QA tools have been compared in terms of the time required to perform patient-specific VMAT QA, and plan quality and/or dose delivered.

**Methods**

Approval for this study was provided by the University of Newcastle, Australia, Human Research Ethics Committee (approval number: H-2011-0073) and the British Columbia Cancer Agency, Canada, Research Ethics Board (approval number: H11-00108).

The study used de-identified CT data sets from 20 patients that had been previously treated at FVC with IMRT to the prostate only. The original CT data sets were obtained on a Philips Brilliance Big Bore scanner using 2 mm slices with the patient in a supine position. All planning was done using v10.0 (PRO10.0.28) of Varian Medical Systems Eclipse planning software (which includes RapidArc). A VMAT plan was retrospectively produced for each data set that delivered a prescribed dose of 7400 cGy in 37 fractions to a planning target volume (PTV) that include the...
prostate plus a margin of 10 mm in all directions (6 mm posteriorly if fiducial markers were implanted). The VMAT plan utilised a single counterclockwise arc from 179° to 181°. The collimator was set to 45° in all cases. VMAT calculations utilised the anisotropic analytical algorithm (AAA) with heterogeneity correction on and a 2.5 mm calculation grid. Of note, cases 1–10 were planned for treatment on a Varian TrueBeam linac and cases 11–20 were planned for treatment on a Varian Trilogy linac. Both the Trilogy and TrueBeam units are equipped with a Millennium MLC incorporating 120 leaves.

**ArcCHECK QA**

ArcCHECK is the current standard of VMAT planning QA at FVC. Plan QA using ArcCHECK was performed in this study to set a standard for IMSure QA to be compared against. The ArcCHECK measurement was performed by running the VMAT treatment on a linac with the ArcCHECK QA tool in place. The measured data were then transferred to the SNC Patient software (version 6.2.3.5713, Sun Nuclear Corp.) which analyses the measured data against the treatment plan imported from the TPS. The differences between the two dose distributions are evaluated using the gamma method that takes into account two parameters for every point analysed in the distribution; a dose value difference and a distance to agreement. The passing gamma criteria of 3%/3 mm of 90% was used.13 In this study, plan QA using ArcCHECK was performed for all 20 cases on the Trilogy linac and all 20 cases on the TrueBeam unit. Measured results were recorded as pass or fail. The time needed to perform the QA for 20 cases was also measured and recorded (10 cases on the Trilogy linac and 10 cases on the TrueBeam unit). The time measured included; preparation time in Eclipse TPS, the time to set up the ArcCHECK phantom, the QA plan delivery time and the post delivery analysis.

**IMSure QA**

Version 3.3 (v3.3) of IMSure was used in this study. To perform plan QA using IMSure, the Eclipse developed plan was exported to the IMSure software and an analysis performed. The IMSure QA software calculated the number of MUs required for treatment delivery and then compared this value to the MUs estimated by the TPS and provides a difference in the MUs as a percentage value. An in-house threshold of less than 3% difference in MUs as determined by IMSure and the TPS is used at FVC to assess if a prostate IMRT plan passes QA. The same 3% threshold was used as the pass/fail criteria for the VMAT plans assessed in this study. IMSure QA was performed for all 20 cases and recorded as pass or fail. The time needed to perform the QA for each of the 20 cases was measured and recorded. The time measured included the time needed to run a QA in the IMSure program as well as the time required to prepare the treatment plan for QA in the TPS (including; the time to open each case in Eclipse, copy the treatment plan and export the copied plan into IMSure).

**IMSure versus ArcCHECK**

The IMSure plan QA software and ArcCHECK QA tool were compared using ArcCHECK as the accepted standard of VMAT plan QA. The efficacy of the techniques was examined by comparing the QA pass/fail results. The time needed to perform IMSure and ArcCHECK QA was measured as described above and the average time required compared. Statistical analysis was not performed on the average time difference.

For IMSure QA, a plan is considered to pass QA if the number of MUs calculated in the TPS and the QA software differed by less than 3%. Using the ArcCHECK system, a plan was considered to pass QA if the gamma analysis of 3%/3 mm is greater than 90%.

**Results**

The average time per case needed to perform the IMSure and ArcCHECK QA is presented in Table 1. On average, the VMAT QA took 3.5 min using the IMSure plan QA software, and 31.5 min using the ArcCHECK system. A significant portion of the time needed to perform ArcCHECK QA was the time to set up the QA phantom which took 15 min per case.

The dosimetric QA results using ArcCHECK and IMSure are presented in Table 2. All 20 cases passed plan QA using ArcCHECK irrespective of whether the QA was planned and/or treated on a Varian Trilogy or TrueBeam linac. Of the 20 cases, 3 failed QA (cases 4, 16–17) using IMSure, that is, the difference in the number of MUs as determined by IMSure was greater than 3% of the TPS calculated MUs for these three cases. Two of the failed distributions (cases 16 and 17) were planned for the Trilogy unit, while the other (case 4) was planned for the TrueBeam linac.

**Discussion**

The average time needed to perform a plan QA using the IMSure software was substantially reduced compared to the ArcCHECK system. In this sense, IMSure holds an advantage over ArcCHECK for efficiency. This result was expected as it is appreciated that performing a physical
therapy (VMAT) treatments of early stage prostate cancer.

Table 2. Measured time to perform QA using ArcCHECK and IMSure (in minutes [min] and seconds [sec]).

<table>
<thead>
<tr>
<th>Case number</th>
<th>ArcCHECK</th>
<th>IMSure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparations in Eclipse</td>
<td>Set up of phantom</td>
<td>Planned dose delivery</td>
</tr>
<tr>
<td>1</td>
<td>9 min 20 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>2</td>
<td>7 min 55 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>3</td>
<td>9 min 41 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>4</td>
<td>7 min 51 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>5</td>
<td>8 min 45 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>6</td>
<td>8 min 27 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>7</td>
<td>8 min 28 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>8</td>
<td>8 min 33 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>9</td>
<td>8 min 43 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>10</td>
<td>8 min 56 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>11</td>
<td>6 min 41 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>12</td>
<td>7 min 25 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>13</td>
<td>8 min 22 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>14</td>
<td>9 min 20 sec</td>
<td>15 min</td>
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<td>15</td>
<td>8 min 27 sec</td>
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<td>16</td>
<td>7 min 51 sec</td>
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<td>17</td>
<td>8 min 27 sec</td>
<td>15 min</td>
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<tr>
<td>18</td>
<td>8 min 43 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>19</td>
<td>6 min 41 sec</td>
<td>15 min</td>
</tr>
<tr>
<td>20</td>
<td>7 min 25 sec</td>
<td>15 min</td>
</tr>
</tbody>
</table>

ArcCHECK Average: 31 min 31 sec (31.51 min)

(3.45 min)

Table 2. The pass/fail results for the ArcCHECK and IMSure methods for the quality assurance (QA) of volumetric modulated arc therapy (VMAT) treatments of early stage prostate cancer.

<table>
<thead>
<tr>
<th>ArcCHECK</th>
<th>IMSure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trilogy</td>
<td>TrueBeam</td>
</tr>
<tr>
<td>Case number</td>
<td>Gamma value</td>
</tr>
<tr>
<td>1</td>
<td>99.7</td>
</tr>
<tr>
<td>2</td>
<td>98.8</td>
</tr>
<tr>
<td>3</td>
<td>97.8</td>
</tr>
<tr>
<td>4</td>
<td>97.9</td>
</tr>
<tr>
<td>5</td>
<td>98.4</td>
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<td>6</td>
<td>98.4</td>
</tr>
<tr>
<td>7</td>
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<td>98.8</td>
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<td>9</td>
<td>99.0</td>
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<tr>
<td>10</td>
<td>99.0</td>
</tr>
<tr>
<td>11</td>
<td>97.7</td>
</tr>
<tr>
<td>12</td>
<td>99.1</td>
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<tr>
<td>13</td>
<td>98.2</td>
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<td>14</td>
<td>99.5</td>
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<td>15</td>
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<tr>
<td>17</td>
<td>97.6</td>
</tr>
<tr>
<td>18</td>
<td>98.9</td>
</tr>
<tr>
<td>19</td>
<td>97.7</td>
</tr>
</tbody>
</table>

Failed cases are presented in italics.
dose measurement on a linac using ArcCHECK requires time to set up the QA phantom and time to run the treatment beams. In this study, it was measured that 15 min was required to set up the ArcCHECK QA phantom. If the QA of multiple plans could be coordinated so that the QA phantom only needed to be set up one time for more than one case, the overall efficiency of QA using ArcCHECK would be improved.

All 20 cases in this study passed plan QA using the ArcCHECK system irrespective of whether the QA was planned and/or treated on a Varian Trilogy or TrueBeam linac. Three cases failed QA using IMSure, that is, the difference in the number of MUs as determined by IMSure was greater than 3% of the TPS calculated MUs for these 3 cases. As all cases passed QA using ArcCHECK, the departmental standard for VMAT QA, the three cases that failed QA using IMSure may be considered false fails. Initial interpretation of this result may be that the planning software IMSure is not consistently accurate for VMAT cases using the existing 3% action level and should not be used as a replacement for the phantom-based ArcCHECK.

The reason for the three false fail cases reported using IMSure is uncertain. As cases failed on both the Trilogy and TrueBeam machines it is unlikely the linac type was the cause of the reported false fail cases. It is possible the false fails could be attributed to the calculation algorithm being used by the TPS. A study by Yoo et al., reported using IMSure as an independent MU verification of breast cases calculated in the Eclipse TPS (version 8.6) using either AAA or the pencil beam convolution (PBC) algorithm. Their study demonstrated that IMSure had significantly higher agreement with the PBC algorithm than with AAA. They attributed this to the IMSure calculation including phantom scatter for the heterogeneity correction based on a simplified one-dimensional path length correction similar to how PBC handles the heterogeneity correction. Yoo et al., also used a 3% action level for their IMSure MU verification which was considered adequate when using PBC, but would result in a large number of false fail cases when using the AAA algorithm. They recommend using a 5% action level threshold when using the AAA algorithm.

The AAA algorithm was used in the current study. If the 5% action level recommended by Yoo et al., was applied to the IMSure QA in the current study, only one case would have been reported as a false fail. A reasonable approach to incorporating IMSure into routine QA of prostate VMAT plans at FVC would be to change the IMSure action level to 5%. If IMSure reports a difference in MUs of greater than 5% compared to the TPS, a measurement on a linac using ArcCHECK could be performed to confirm dose delivery. If this approach was used for the 20 cases in this study, 1 of the 20 cases (5%) would have required a physical measurement using ArcCHECK. The benefits of this approach would be twofold. Firstly, the efficiency of IMSure would reduce the workload for the medical physicists. Secondly, fewer QA measurements will need to be performed on a linac further reducing the workload for the medical physicists and potentially increasing the availability of the linac for patient treatment.

As elucidated by Yoo et al., as well as in this study, the action level set when using the plan QA software IMSure may be dependent on the calculation algorithm being utilised by the TPS. In the previous research at FVC which demonstrated agreement between IMSure and the Eclipse TPS point dose calculations to within 1% for a five-field IMRT treatment of prostate cancer, the PBC algorithm was used. The current research utilises the AAA algorithm and a 5% action level is recommended when using IMSure to QA VMAT plans for prostate cases. It is likely the 5% action level for IMSure will need to be reconsidered if using a calculation algorithm other than AAA. For example, most recently Varian Medical Systems has introduced the advanced dose calculation algorithm Acuros XB (AXB) into the Eclipse TPS. AXB is considered to be similar to classic Monte Carlo methods for accurate modelling of dose deposition in heterogeneous media. A validation study by Rana et al., demonstrated that AXB can perform dose computation comparable to AAA in single arc VMAT treatment of prostate cancer. Importantly, Rana et al., reported that utilising either AXB or AAA resulted in some dose-point differences throughout the plans which would translate to different MUs depending on which calculation algorithm was being used. Therefore, if IMSure was to be used to QA VMAT plans calculated in the TPS using the AXB algorithm, the 5% action level will need to be reconsidered.

An alternative approach to incorporate IMSure into the plan QA process was suggested by Fan (2009). Their recommendation is to use IMSure as an additional safeguard against any gross errors before a VMAT plan is approved for treatment. They recommend using a tolerance of ±10% for IMSure validation of VMAT plans to verify the MUs calculated in the TPS. Importantly, in this process the software validation is not meant to replace the measurement based QA using either film dosimetry or detector arrays such as ArcCHECK.

The current study was performed using v3.3 of IMSure. Of note, version 3.4 of IMSure is now commercially available which is promoted to have additional features increasing the accuracy of its
modelling to VMAT plans. It is reasonable to expect that in the future more treatment plan QA software products will become available which will continue to have increased accuracy potentially eliminating the need to perform dose measurement based QA on a linac.

**Conclusion**

This study aimed to investigate if the plan QA software IMSure could be used to perform the QA of VMAT treatments for early stage prostate cancer. It has been demonstrated here that IMRT plan QA process cannot just be adopted into a VMAT plan QA process, and that VMAT-specific QA criteria are recommended. Importantly, the action level criteria set will be influenced by factors including the calculation algorithm being used by the TPS. The implication of this research for radiation therapists is to be critically aware of the differences between the plan QA requirements and methods for IMRT and those required for VMAT.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**

Chapter Seven
Study Five

This chapter contains the submitted paper

Elith CA, Dempsey SE, Warren-Forward H.
A Comparison of the Acute Toxicities Using Moderate Hypo-Fractionated Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) for the Treatment of Early Stage Prostate Cancer. Journal of Radiotherapy in Practice, Submitted January 2015
7.1 A Comparison of the Acute Toxicities Using Moderate Hypofractionated Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) for the Treatment of Early Stage Prostate Cancer

Primary Author: Craig Elith a, b

Co-Authors: Shane E Dempsey b and Helen Warren-Forward b

a British Columbia Cancer Agency, Fraser Valley Centre, BC, Canada
b School of Health Sciences, University of Newcastle, Australia.

Journal: Radiotherapy and Oncology, Submitted July 2014

7.2 Preface:

Chapter 7 presents the final piece of research of this thesis that is designed to compare the acute toxicities recorded in patients during moderate hypo-fractionated radiation therapy treatment for early stage prostate cancer treated with either IMRT or VMAT.

At FVC early stage prostate cancers are routinely treated using a 5-field IMRT technique as described in chapters 3 and 4. The same patient group is treated with a one arc VMAT technique at the BC Cancer Agency’s Centre for the North (CN). Both centres prescribe 73.68Gy in 28 fractions. Acute toxicities are routinely reported at both centres using the standardised National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 to assess symptom toxicity. Toxicity assessment is performed on day 1 of treatment to establish a baseline, then once weekly thereafter. Having a standardised system to assess toxicity during treatment allows for the reported toxicities using either IMRT or VMAT to be compared. For this study, eight common symptoms were assessed; diarrhoea, proctitis, fatigue, pain, dermatitis, urinary frequency, urinary retention and urinary tract pain.

The study reported in this chapter is essential in that it is important to assess if the innovative VMAT technique causes additional harm to prostate cancer patients compared with the standard treatment technique, IMRT. It has been demonstrated in the
preceding chapters that both IMRT and VMAT are capable of producing dose distributions of similar quality for the treatment of early stage prostate cancer. Therefore, based on this evidence it is hypothesised that the acute toxicities reported during treatment will not be significantly different for the IMRT and VMAT treatment techniques.

7.3 Statement of Contribution of Others:

The PhD candidate, Craig Elith, was responsible for performing the chart review and extrapolating the reported acute toxicities. Once collected, Craig was responsible for storing the data recorded. Helen Warren-Forward assisted with the statistical analysis.

Preparation of the draft manuscript was done by Craig and significant feedback was provided by Craig’s PhD supervisors at the University of Newcastle, Shane Dempsey and Helen Warren-Forward. Craig was ultimately responsible for preparation of the final manuscript and journal submission.

This study required ethics to be reconsidered. Craig obtained new ethics approval from the BC Cancer Agency’s Research Ethics Board, while Craig and Helen collaborated to secure approval for an ethics variation from the University of Newcastle’s Human Research Ethics Committee.
7.3.1 Co-author Statements:

I attest that Research Higher Degree candidate, Craig Elith, made significant contribution to the manuscript *A Comparison of the Acute Toxicities Using Moderate Hypo-Fractionated Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) for the Treatment of Early Stage Prostate Cancer.*

Independently, Craig reviewed patient charts to ensure each case met the eligibility criteria before extrapolating the toxicity data. Craig was responsible for storing all data recorded. Craig was also responsible for the preparation of the manuscript and submission to the journal.

Craig and Helen collaborated to secure ethics approval for this project.

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(Signature of Co-Author)
Shane Dempsey
Date: 

(Signature of Co-Author)
Helen Warren-Forward
Date: 

(Signature of Candidate)
Craig Elith
Date: July 2 2014

(Signature of Assistant Dean Research Training (ADRT))
7.4 Submitted Paper

Abstract:

**Aim:** This study compared the acute toxicities recorded in patients during moderate hypo-fractionated radiation therapy treatment for early stage prostate cancer treated with either Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT).

**Method:** Acute toxicities are routinely reported at the clinical site for all early stage prostate patients using the National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 to assess symptom toxicity. Toxicity assessment is performed on day one of treatment to establish a baseline, then once weekly thereafter. The recorded toxicities of 40 cases treated with 5-field IMRT, and 32 matched cases treated using VMAT were compared. All cases were prescribed 73.68Gy in 28 fractions. For this study, eight symptoms were assessed; diarrhoea, proctitis, fatigue, pain, dermatitis, urinary frequency, urinary retention and urinary tract pain.

**Results:** In terms of the overall toxicity recorded, VMAT was shown to reduce the toxicities of dermatitis, fatigue, pain and urinary frequency (p<0.05). Using IMRT, grade 2 toxicities were reported for the following symptoms; proctitis, pain, urinary frequency, urinary retention and urinary tract pain. Using VMAT, grade 2 toxicities were reported only for urinary frequency and urinary retention.

**Conclusion:** Previous research has demonstrated the equivalence of plan quality between VMAT and IMRT, and the reduced treatment times associated with VMAT compared with IMRT; however, few people have assessed toxicity differences. The research reported here is one of the first publications to demonstrate that VMAT is associated with decreased toxicities compared with IMRT for the treatment of early stage prostate cancer.
Introduction:

Since the late 1990’s, Intensity Modulated Radiation Therapy (IMRT) has been established as the standard of care for delivering radiation therapy treatment for early stage prostate cancer. IMRT can provide a highly conformal shaped and high-dose treatment to the prostate and/or seminal vesicles, while reducing dose to the surrounding critical organs and healthy tissues.\(^1,2\)

In 2008, Otto reported a novel form of IMRT called Volumetric Modulated Arc Therapy (VMAT).\(^3\) In VMAT, treatment is delivered using a cone beam that rotates around the patient. The cone beam is modulated by the intertwining of dynamic MLCs, variable dose rates, and variable gantry speeds to generate IMRT quality dose distributions in a single optimised arc around the patient.\(^4\)

Based on previous retrospective planning analyses, it is now well established that for the treatment of early stage prostate cancer VMAT is capable of delivering a treatment plan of similar quality to IMRT, with the distinct advantage of faster treatment times that also require fewer monitor units to deliver.\(^2,5-13\) Some studies have reported that VMAT provides improved conformity to the target volume and increased sparing of nearby rectal tissue.\(^1,7,14-21\) These findings suggest VMAT provides a greater opportunity to use dose escalation or hypo-fractionation to improve disease control, without increasing treatment-related morbidities associated with radiation exposure to surrounding tissues.\(^22-25\) Not surprisingly, VMAT has rapidly attained widespread use around the world for the treatment of early stage prostate cancer.

While a large body of literature exists investigating the quality of plans produced using VMAT for the treatment of early stage prostate cancer, few articles are available examining the treatment related toxicities using VMAT. In 2010, Pesce et al., reported on early clinical experience using VMAT for radiation therapy treatments of prostate cancer. Their report included analysis of VMAT plan quality and a measure of acute toxicities as scored according to the Common Terminology Criteria for Adverse Events (CTCAE) scale (v3). In a group of 45 patients treated with one arc to a dose of either 76Gy or 78Gy in 2Gy fractions, no patients showed grade 2-3 rectal toxicity, 12 percent of patients experienced grade 2 dysuria and 44 percent of patients preserved complete or
Chapter 7: Study 5 - Paper 6

partial erectile function. Their study concluded VMAT was a safe, qualitative and advantageous treatment for prostate cancer. The same study also commented that the potential implementation of VMAT should be further investigated using more aggressive fractionation regimes with either hypo-fractionation or dose escalation. They also encouraged the investigation into including a simultaneous integrated boost (SIB) in prostate cancer treatments with VMAT.26

In 2012 Alongi et al., examined the acute toxicity profiles for patients treated with SIB in a hypo-fractionated regime. Their study population of 70 patients included low, intermediate and high risk cases. Their study concluded moderate hypo-fractionation with SIB using VMAT was shown to be safe with acceptable acute toxicity.27

Another study by Alongi et al., compared acute and late toxicities in postoperative prostate cancer patients treated with either Three-Dimension Conformal Radiation Therapy (3DCRT) or hypo-fractionated VMAT. In that study VMAT was demonstrated to reduce the incidence of acute genitourinary and grade 2 lower gastrointestinal toxicities compared to 3DCRT, demonstrating the feasibility of a hypo-fractionation regime with VMAT in the postoperative setting.28

The current study is intended to add to the limited body of literature examining VMAT toxicity by comparing the acute toxicities observed in patients during moderate hypo-fractionated radiation therapy treatment for early stage prostate cancer using either IMRT or VMAT.

Methods:

Ethics approval for this study was provided by the University of Newcastle, Australia, Human Research Ethics Committee (approval number: H-2011-0073), and the British Columbia Cancer Agency, Canada, Research Ethics Board (approval number: H13-02127).

A chart review was performed on a total of 72 patients that had received a moderate hypo-fractionated radiation therapy treatment of 73.68Gy in 28 fractions using either IMRT (n=40) or VMAT (n=32) for the treatment of early stage prostate cancer between November 2012 and April 2014. The 40 IMRT cases included in this study had received
treatment at the British Columbia Cancer Agency’s (BCCA) Fraser Valley Centre (FVC) where IMRT is the standard prostate treatment. The 32 VMAT cases included in this study received treatment at the BCCA’s Centre for the North (CN) where VMAT is the standard prostate treatment. An attempt was made to ensure that the two groups of patients were similar for a range of personal and cancer data, these included: age, stage, Prostate Specific Antigen (PSA) and Gleeson score.

**Inclusion Criteria:**

The cases included in the study were patients with stage I or II prostate cancer where the prostate was intact and treatment was to the prostate only with or without fiducial markers. Patients were excluded from the study if they had undergone prostatectomy or if the treatment area extended beyond the prostate (ie to include the seminal vesicles or regional nodes). The number of cases included in this study was limited by strict adherence to the inclusion criteria. No more than 40 IMRT cases could be included as prior to November 2012, FVC utilised a standard treatment fractionation of 74Gy in 37 fractions. Similarly, the CN first started treating patients with VMAT in November 2012 and eligible cases were further limited by the remote location of the CN where many possible inclusions for the study had elected to have surgery making them ineligible for this study.

**IMRT and VMAT Planning and Treatment:**

As per protocol at both centres, all patients were positioned supine and instructed to have a full bladder at the time of simulation and treatment, however no specific bowel preparation to ensure an empty bowel was performed. The planning CT data sets for the IMRT cases were obtained on a Phillips Brilliance Big Bore scanner using 2mm slices, and the VMAT planning scans were obtained using a GE Optima 580 CT scanner with 2.5mm slices. For both IMRT and VMAT the pelvis was scanned from the superior aspect of the sacroiliac joint to 4cm below the ischial tuberosities.

The clinical target volume (CTV) was defined as the entire prostate. At FVC the IMRT planning target volume (PTV) was generated by expanding the CTV with a 10mm margin in all directions. If the data set included prostate fiducial markers, the PTV was
created using a 6mm margin to the prostate posteriorly to spare additional rectal tissue from receiving radiation dose. At CN the VMAT PTV was generated by expanding the CTV posteriorly by 6mm and 10mm in all other directions. The organs at risk (OAR) including the bladder, rectum and the heads of femur were also contoured as described in Table 7-1.

All dosimetric calculations were performed using Varian Medical Systems, Eclipse 3D planning software (version 10.0). Each calculation utilised the anisotropic analytical algorithm (AAA) with heterogeneity correction on and a 2.5mm calculation grid.

A 5-field sliding window technique was used to treat the IMRT cases. Each treatment beam utilised 6MV photons with the gantry angles fixed at 0°, 75°, 135°, 225°, and 285°. VMAT treatments utilised a single clockwise arc having a start angle of 181° and a stop angle of 179°. The collimator was set to 45° to minimise the MLC tongue and groove effect. Each case was prescribed 73.68Gy in 28 fractions and planned to meet the dosimetric objectives described in Table 7-1.

IMRT treatments were performed using either a Varian TrueBeam or Varian IX linear accelerator. All VMAT treatments were delivered using a TrueBeam linear accelerator. Each linear accelerator was equipped with Millennium 120-MLC.

**Toxicity Assessment:**

Both the FVC and CN use the National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 to assess symptom toxicity. The level of toxicity (0-5) was assessed by a radiation therapist on the first day of treatment to establish a baseline and once weekly thereafter. The assessed level of toxicity is recorded shortly after assessment and entered into the patient’s electronic medical record (EMR). All radiation therapists receive the same training on how to use the CTCAE scale as part of their orientation to the department.

For this study, the outcomes for eight toxicity symptoms were collected and compared; diarrhoea, proctitis, fatigue, pain, dermatitis, urinary frequency, urinary retention and urinary tract pain. The CTCAE scale to grade these symptoms is presented in Table 7-2. The electronic medical records of the 40 IMRT and 32 VMAT cases used in this study
were reviewed to collect the toxicity grade recorded during treatment. The collected data was grouped into the following categories: baseline measurement, fractions (Fx) 6-10, Fx 11-15, Fx 16-20, Fx 21-25 and Fx 26-28. The data was accessed and collected between January and May 2014. The following assumptions were made when reviewing the data collected. If there was a symptom at baseline, and this continued throughout treatment then it was not added as a symptom during treatment. If the symptom was Grade 1 at baseline and increased to Grade 2 then it was counted as a Grade 1 during treatment. If there was a symptom at baseline, and disappeared during the first, second weeks etc, and then reappeared, it was counted as a symptom on reappearance.

**Statistical Analysis:**

The Odds Ratio (OR, a measure of the symptom occurring with IMRT compared with VMAT) was calculated for each data collection point and the whole course of treatment. An OR greater than 1.0 indicates the symptom is more likely to occur in IMRT where-as an OR value of less 1.0 demonstrates the symptoms is more likely using VMAT. The data was tested for significance at the 95 percent level using Fisher’s exact test. All analysis was conducted using GraphPad Instat. A P-value less than 0.05 means that the difference in symptoms between IMRT and VMAT area attributed to the treatment method.

**Results:**

Of the 40 IMRT cases assessed, one patient did not have any data recorded for fractions 26-28, leaving a total of 199 data entries for consideration. Similarly, of the 32 VMAT cases reviewed, one patient did not have any data recorded for fractions 26-28, leaving a total of 159 data entries for consideration.

The relative percentage frequency of each assessed symptom reported for the 40 cases treated with IMRT and the 32 cases treated using VMAT for the overall treatment course is presented in Figure 7-1. The same data broken down into weekly milestones throughout the treatment course is presented in Figure 7-2. The odds ratio (OR) and P-values are presented in Table 7-3.
Table 7-1: The critical structures and dose constraints applied during radiation therapy treatment planning.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Contouring</th>
<th>IMRT</th>
<th>VMAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Planning Target Volume (PTV)</strong></td>
<td>IMRT:</td>
<td>- 99% of the volume to get ≥ 95% of the prescription</td>
<td>- 99% of the volume to get ≥ 95% of the prescription</td>
</tr>
<tr>
<td></td>
<td>- 10 mm margin on the prostate (all directions)</td>
<td>- Minimum dose &gt; 90% of the prescription</td>
<td>- 95% of the volume to get ≥ 100% of the prescription</td>
</tr>
<tr>
<td></td>
<td>- 6mm posteriorly if fiducial markers inserted</td>
<td>- Mean dose &gt;99% of the prescription</td>
<td>- 99.5% of the volume to get ≥ 93% of the prescription</td>
</tr>
<tr>
<td></td>
<td>VMAT:</td>
<td>- Maximum dose &lt;107% of the prescription</td>
<td>- Mean dose &gt;99% of the prescription</td>
</tr>
<tr>
<td></td>
<td>- 6mm posteriorly and 10mm all other directions</td>
<td>- The maximum dose must be within the PTV</td>
<td>- Maximum dose &lt;107% of the prescription</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;65% of the volume to receive 50Gy</td>
<td>&lt;40% of the volume to receive 42Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;55% of the volume to receive 60Gy</td>
<td>&lt;25% of the volume to receive 55Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;25% of the volume to receive 70Gy</td>
<td>&lt;15% of the volume to receive 64Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;15% of the volume to receive 75Gy</td>
<td>&lt;10% of the volume to receive 68Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;5% of the volume to receive 78Gy</td>
<td></td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td>From the sigmoid colon to the anus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td>&lt;50% of the volume to receive 65Gy</td>
<td></td>
<td>&lt;50% of the volume to receive 47Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;35% of the volume to receive 70Gy</td>
<td></td>
<td>&lt;25% of the volume to receive 65Gy</td>
</tr>
<tr>
<td></td>
<td>&lt;25% of the volume to receive 75Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;15% of the volume to receive 80Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heads of Femur</strong></td>
<td>Superiorly from the caudal ishial tuberosity</td>
<td>None</td>
<td>&lt;10% of the volume to receive 45Gy</td>
</tr>
</tbody>
</table>
Table 7-2: The National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0, used to assess symptom toxicity in this study. 30

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>None</td>
<td>Increase of &gt; 4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4-8 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of ≥ 7 stools per day over baseline; incontinence; hospitalisation indicated, severe increase in ostomy output compared to baseline; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Proctitis</td>
<td>None</td>
<td>Rectal discomfort; intervention not indicated</td>
<td>Symptoms (eg, rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; faecal urgency or stool incontinence; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Fatigue</td>
<td>None</td>
<td>Fatigue relieved by rest</td>
<td>Fatigue not relieved by rest; limiting instrumental ADL</td>
<td>Fatigue not relieved by rest; limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td>Pain</td>
<td>None</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>None</td>
<td>Faint erythema or dry desquamation</td>
<td>Moderate to brisk erythema; patchy moist desquamation’ mostly confined to skin folds and creases; moderate oedema</td>
<td>Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion</td>
<td>Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated</td>
</tr>
<tr>
<td>Urinary</td>
<td>None</td>
<td>Present</td>
<td>Limiting instrumental ADL; medical management indicated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>None</td>
<td>Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual</td>
<td>Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated</td>
<td>Elective operative or radiological intervention indicated; substantial loss of affected kidney function or mass</td>
<td>Life-threatening consequences; organ failure; urgent operative intervention indicated</td>
</tr>
<tr>
<td>Retention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>None</td>
<td>Mild Pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td>Tract Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADL = Activities of Daily Living
The OR values demonstrate that over the full course of treatment, the symptoms dermatitis, fatigue, pain, proctitis, urinary frequency and urinary tract pain are reported more frequently with IMRT. These results are statistically significant for the symptoms dermatitis, fatigue, pain and urinary frequency. Diarrhoea and urinary retention are observed more frequently using VMAT, however a statistically significant increase is not observed compared with IMRT.

Similarly to the overall treatment course, significant differences were reported at the data collection points during treatment. The following symptoms were reported more often, with statistical significance, during treatment with IMRT; dermatitis (Fx 26-28), fatigue (Fx 6-10 and Fx 16-20), and urinary frequency (Fx 16-20, Fx 21-25 and Fx 26-28). Between fractions 6-10, diarrhoea is reported significantly more frequently in cases treated with VMAT. A statistically significant difference in the reported incidence of diarrhoea at all other stages of the treatment course was not observed between IMRT and VMAT.

The results presented so far consider the reported frequency of the symptoms only. They do not consider the grade of the symptom being experienced. The frequency at which grade 2 toxicities were observed is presented in Figure 7-3. Using IMRT, grade 2 toxicities were reported for the following symptoms: proctitis, pain, urinary frequency, urinary retention and urinary tract pain. Using VMAT, grade 2 toxicities were reported only for urinary frequency and urinary retention. Due to the small number of grade 2 toxicity reported, it was not possible to perform statistical analysis. Of note, grade 2 urinary frequency symptoms was reported in 13 percent of all measured data using compared to one percent using VMAT. This may be considered clinically significant.
Figure 7-1: The incidence (in percent) of all 8 treatment related symptoms recorded over the full treatment course during Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT).
Figure 7-2: The incidence (in percent) of all 8 treatment related symptoms recorded at weekly milestones during Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT).
### Table 7-3: The statistical comparison of all 8 treatment related symptoms recorded during Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) treatments. Recorded toxicities are presented as a percentage of cases where the symptom was observed and at which fraction (Fx) of treatment. The odds ratio (OR) of the symptom occurring with IMRT compared to VMAT, is also presented.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Fx 6-10</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Fx 11-15</th>
<th></th>
<th></th>
<th></th>
<th>Fx 16-20</th>
<th></th>
<th></th>
<th></th>
<th>Fx 21-25</th>
<th></th>
<th></th>
<th></th>
<th>Fx 26-28</th>
<th></th>
<th></th>
<th></th>
<th>All Treatment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis</td>
<td>IMRT</td>
<td>VMAT</td>
<td>OR</td>
<td>p-value</td>
<td>IMRT</td>
<td>VMAT</td>
<td>OR</td>
<td>p-value</td>
<td>IMRT</td>
<td>VMAT</td>
<td>OR</td>
<td>p-value</td>
<td>IMRT</td>
<td>VMAT</td>
<td>OR</td>
<td>p-value</td>
<td>IMRT</td>
<td>VMAT</td>
<td>OR</td>
<td>p-value</td>
<td>IMRT</td>
<td>VMAT</td>
<td>OR</td>
<td>p-value</td>
<td>IMRT</td>
<td>VMAT</td>
</tr>
<tr>
<td></td>
<td>n=40</td>
<td>n=32</td>
<td></td>
<td></td>
<td>n=40</td>
<td>n=32</td>
<td></td>
<td></td>
<td>n=40</td>
<td>n=32</td>
<td></td>
<td></td>
<td>n=39</td>
<td>n=31</td>
<td></td>
<td></td>
<td>n=199</td>
<td>n=159</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>5</td>
<td>0</td>
<td>4.2</td>
<td>ns</td>
<td>10</td>
<td>0</td>
<td>8.0</td>
<td>ns</td>
<td>13</td>
<td>0</td>
<td>10.1</td>
<td>ns</td>
<td>15</td>
<td>0</td>
<td>5.4</td>
<td>ns</td>
<td>18</td>
<td>0</td>
<td>14.5</td>
<td>*</td>
<td>12</td>
<td>1</td>
<td>21.7</td>
<td>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16</td>
<td>0</td>
<td>0.06</td>
<td>*</td>
<td>18</td>
<td>22</td>
<td>0.8</td>
<td>ns</td>
<td>20</td>
<td>16</td>
<td>1.3</td>
<td>ns</td>
<td>23</td>
<td>9</td>
<td>2.8</td>
<td>ns</td>
<td>15</td>
<td>19</td>
<td>0.8</td>
<td>ns</td>
<td>15</td>
<td>16</td>
<td>0.9</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
<td>14.6</td>
<td>*</td>
<td>50</td>
<td>25</td>
<td>3.0</td>
<td>ns</td>
<td>60</td>
<td>31</td>
<td>3.3</td>
<td>*</td>
<td>55</td>
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<td>38</td>
<td>1.7</td>
<td>ns</td>
<td>47</td>
<td>26</td>
<td>2.5</td>
<td>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>0</td>
<td>4.2</td>
<td>ns</td>
<td>3</td>
<td>0</td>
<td>2.4</td>
<td>ns</td>
<td>15</td>
<td>3</td>
<td>5.5</td>
<td>ns</td>
<td>10</td>
<td>9</td>
<td>1.1</td>
<td>ns</td>
<td>15</td>
<td>6</td>
<td>2.6</td>
<td>ns</td>
<td>10</td>
<td>4</td>
<td>2.7</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>ns</td>
<td>3</td>
<td>0</td>
<td>2.5</td>
<td>ns</td>
<td>10</td>
<td>13</td>
<td>0.8</td>
<td>ns</td>
<td>18</td>
<td>13</td>
<td>1.5</td>
<td>ns</td>
<td>18</td>
<td>9</td>
<td>2.0</td>
<td>ns</td>
<td>10</td>
<td>7</td>
<td>1.4</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>13</td>
<td>9</td>
<td>1.4</td>
<td>ns</td>
<td>30</td>
<td>16</td>
<td>2.3</td>
<td>ns</td>
<td>53</td>
<td>25</td>
<td>3.3</td>
<td>*</td>
<td>65</td>
<td>25</td>
<td>5.3</td>
<td>*</td>
<td>60</td>
<td>28</td>
<td>3.9</td>
<td>**</td>
<td>44</td>
<td>21</td>
<td>2.9</td>
<td>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>15</td>
<td>16</td>
<td>0.9</td>
<td>ns</td>
<td>23</td>
<td>19</td>
<td>1.3</td>
<td>ns</td>
<td>23</td>
<td>25</td>
<td>0.9</td>
<td>ns</td>
<td>20</td>
<td>31</td>
<td>0.5</td>
<td>ns</td>
<td>35</td>
<td>41</td>
<td>0.8</td>
<td>ns</td>
<td>23</td>
<td>27</td>
<td>0.8</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Pain</td>
<td>20</td>
<td>6</td>
<td>3.8</td>
<td>ns</td>
<td>23</td>
<td>22</td>
<td>1.04</td>
<td>ns</td>
<td>23</td>
<td>25</td>
<td>0.9</td>
<td>ns</td>
<td>20</td>
<td>25</td>
<td>0.8</td>
<td>ns</td>
<td>25</td>
<td>19</td>
<td>1.4</td>
<td>ns</td>
<td>22</td>
<td>19</td>
<td>1.2</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ns = Not Significant, * = <0.05, ** = <0.01, *** = <0.0001
Figure 7-3: The incidence of grade 2 toxicities recorded during a course of treatment using either Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT).
Discussion:

The study reported in this paper was designed to compare the acute toxicities observed in patients during moderate hypo-fractionated radiation therapy treatment for early stage prostate cancer using IMRT or VMAT. From the 72 cases reviewed it has been demonstrated that over the full course of treatment, the symptoms dermatitis, fatigue, pain and urinary frequency are significantly higher in the cases treated with IMRT compared with VMAT.

The higher levels of dermatitis observed using the IMRT technique may be attributed to the difference in beam arrangements utilised for IMRT and VMAT. The VMAT technique delivers dose to the PTV from a full 360 degrees around the patient, whereas the IMRT technique delivers dose from five set angles. The 5-field IMRT technique is therefore concentrating a higher intensity of dose via the five treatment angles increasing the chance of developing dermatitis compared to the rotational delivery of VMAT which creates a more even distribution and a less concentrated dose pattern to the patient's skin.

Importantly, others have reported using seven or nine field IMRT techniques to treat early prostate cancers.\textsuperscript{2,5,9,11,13,31} Increasing the number of IMRT treatment fields would be expected to deliver a more evenly distributed intensity of radiation to the skin tissue. It is therefore reasonable to expect the levels of dermatitis being experienced using seven or nine field IMRT would be less than that observed here using a 5-field technique. It remains unclear how the seven or nine field IMRT techniques would compare to VMAT.

In this study IMRT is reported to increase both grade 1 and 2 urinary frequency symptoms. Presumably, the increased incidence of urinary frequency observed using IMRT correlates to higher dose being delivered to the bladder. This can likely be attributed to the dose constraints that are applied to the bladder during optimisation being tighter for VMAT compared with IMRT.

Previous retrospective studies from the current authors and others have demonstrated that compared with IMRT, VMAT can reduce the dose delivered to the OAR including the rectum, bladder and heads of femur.\textsuperscript{1,14-21} These studies suggested that the reduction in dose delivered to the OAR using VMAT may translate into a reduction of toxicities associated with that organ. This phenomenon has been observed in this study.
in that a reduction in dose delivered to the base of the bladder using VMAT has translated into a reduction in reported urinary frequency.

The same phenomenon was not observed in this study when considering rectal tissue. The constraints applied to the rectum in this study are tighter for VMAT compared to IMRT, however this did not translate into a reduction in rectal toxicities within the VMAT cohort. In fact, as reported by the odds ratio, diarrhoea is reported more frequently in cases treated with VMAT compared with IMRT in fractions 6-10. The early onset of diarrhoea when using VMAT may possibly be attributed to the beam arrangements used in the IMRT and VMAT techniques. IMRT uses a beam arrangement that deliberately avoids delivering dose through the rectal tissue. VMAT uses a 360 degrees rotational arc and some dose is being delivered through the rectum which could cause an earlier onset of diarrhoea. By fractions 11-15 a similar percentage of cases are reporting diarrhoea for both the IMRT and VMAT group which is typically managed using an antidiarrheal medication.

It is difficult to find an explanation for the observed increase in pain reported in patients treated with IMRT. However, the increase in both urinary frequency and pain could in-part explain the increase in fatigue reported for the IMRT group. Increased urinary frequency may translate into an increase in nocturia and therefore a disrupted sleep pattern. Likewise an increase in pain may also contribute to disturbed sleep. A reduced or disrupted sleep pattern as a result of pain and or urinary frequency could lead to increased fatigue as observed within the IMRT patient population.

The greatest challenge to this study is that it relies on information gathered from two different radiation therapy departments. Several steps were taken to minimise the effect of using data from two departments on the validity of this study. Firstly, the inclusion criteria for the study was strictly adhered to ensuring similar patient populations are being compared. Secondly, the departments used in this study were deliberately selected to enable comparison of the same moderate hypo-fractionation treatment regime. However, it is recognised there are minor differences in the constraints applied to the organs at risk during IMRT and VMAT planning, the impact of which on observed toxicity has been discussed here. Thirdly, the BCCA uses standard training guidelines to introduce all radiation therapists to the CTCAE toxicity scale, however, it is possible some individual user variability may still exist.
Another limitation of the present study is that the study population is relatively small. A larger study population would allow a more accurate trend to be established for the frequency of morbidities as well as the grade of toxicities being reported. A larger study cohort would also allow for more meaningful statistical analysis to be performed. Likewise a longer follow-up would be recommended to examine the late toxicities and clinical outcome for these patients.

**Conclusion:**

This study was designed to compare the acute toxicities experienced by patients treated for early stage prostate cancer using IMRT or VMAT with moderate hypofractionation, and add to a growing body of evidence for the similarities and differences between IMRT and VMAT.

Herein it has been demonstrated that the symptoms dermatitis, fatigue, pain and urinary frequency are significantly higher in cases treated with IMRT compared with VMAT. This is one of the first publications to demonstrate that VMAT is associated with decreased toxicities compared to IMRT for the treatment of early stage prostate cancer.

Future long term studies with a larger study population are recommended to confirm these results for acute toxicities and to investigate late toxicities and clinical outcome for this group of patients. This can be done as the number of cases treated with VMAT continues to grow.

**References:**


Chapter Eight

Discussion and Clinical Significance
8.1 Discussion:

A series of studies are presented here that when combined describe the process of clinical implementation of the innovative radiation therapy treatment technique, Volumetric Modulated Arc Therapy (VMAT) for the treatment of early stage prostate cancer.

In 2008, Otto reported a novel form of radiation therapy treatment called Volumetric Modulated Arc Therapy (VMAT).1 In VMAT, treatment is delivered on a linear accelerator using a cone beam that rotates around the patient. The cone beam is modulated by the intertwining of dynamic multi-leaf collimators (MLCs), variable dose rates and variable gantry speeds to generate high quality dose distributions in a single optimized arc around the patient.2

In mid-2010, the Fraser Valley Centre (FVC) of the British Columbia Cancer Agency (BCCA), Canada, upgraded its infrastructure to be capable to delivering VMAT treatments using Varian Medical Systems RapidArc™. It was this upgrade and the desire to learn how to best use this new technology that proved to be the catalyst of this PhD research.

Before initiating any research activities, a literature review was performed to develop an understanding of the principles behind VMAT, how it compares to the existing standards of practice (including Intensity Modulated Radiation Therapy, IMRT) and how VMAT may be best utilised in a radiation therapy department. The resulting literature review is presented in chapter 2. This literature review was also published as a directed reading article in the Canadian Association of Medical Radiation Technologists (CAMRT's) Journal of Medical Imaging and Radiation Sciences, therefore highlighting the relevancy of VMAT to a wider audience in radiation therapy. To briefly summarise the literature review, the outstanding benefits of VMAT included this innovative technique was capable of generating high quality dose distributions that accurately delivered the prescribed radiation dose to the target volume while providing maximum sparing of the surrounding tissues and vital organs. Importantly, the treatment time was significantly reduced when using VMAT compared to other available IMRT treatment techniques. Since 2010, when this literature review was performed, VMAT has rapidly gained widespread use throughout the world, proving the validity of this PhD research.
Based on what was learned by performing the literature review, it was decided to explore the use of VMAT for the treatment of early stage prostate cancer. Prostate cancer was specifically selected for two reasons. Firstly, the prostate is a relatively simple anatomical site on which to perform radiotherapy planning. It was therefore considered an ideal treatment site on which to gain experience when utilising VMAT for the first time. Secondly, and more importantly, treatment of early stage prostate cancers accounted for a high volume of work at FVC (approximately 10 percent of workload in 2010). If VMAT was demonstrated to reduce treatment times as reported in the available literature, VMAT treatment of prostate cancers could have the greatest potential to increase patient throughput and reduce the waiting list for the department.

The first research study contributing to this thesis aimed to compare the existing standard treatment method, IMRT, with the innovative technique, VMAT, for the treatment of early stage prostate cancer. This study is presented in chapter 3 of this thesis. Specifically, twenty prostate cancer cases were retrospectively planned to compare 5-field IMRT with VMAT using a single arc (VMAT-1A) and two arcs (VMAT-2A). The impact on departmental resources was assessed by comparing the time needed to generate the dose distributions and to deliver the treatment plan. A comparison of plan quality was also performed by comparing homogeneity, conformity, the number of monitor units (MUs) and dose to the organs at risk (OAR).

As expected, this research supported the findings of others presented in the literature review in that treatment times were significantly reduced using the VMAT-1A technique and the number of monitor units required to deliver a fraction of treatment was reduced using VMAT-1A and VMAT-2A compared with IMRT.\(^1,3-8\) It was also demonstrated that both IMRT and VMAT-2A were able to produce adequate plans for all cases, however, IMRT provided an improved dose distribution and the best homogeneity to the planning target volume (PTV). The VMAT-1A technique was able to achieve the planning guidelines in only eight of the 20 cases. Upon further investigation it was reported that the VMAT-1A plans had poor homogeneity which contributed to this technique failing to achieve the planning guidelines for 12 of the 20 cases. Other prostate planning studies using an earlier version of Varian’s RapidArc system have reported lower homogeneity in VMAT plans when compared with IMRT.\(^4,5,9\) Unlike this study, in the other publications, all VMAT plans were able to produce plans adequate for treatment. This is likely due to the planning guidelines for the PTV and OAR reported in the other studies differing to those adhered to at FVC.
Importantly the IMRT plans were generated significantly faster than both VMAT techniques. Others had commented anecdotally that planning times using VMAT were longer than IMRT. However, the measurements in this study indicated IMRT has a significant advantage over VMAT when considering the time required to generate a treatment plan. The IMRT plans were produced three times faster when compared to VMAT-1A plans and five times faster than VMAT-2A plans. From these results it was concluded IMRT had an advantage over VMAT for the treatment of prostate cancers. This is primarily due to the uncertainty of achieving planning guidelines using VMAT and the extended time needed to generate the VMAT plans.

The study outlined above was performed using version 8.6 (v8.6) of Varian Medical Systems RapidArc. In October 2011, FVC upgraded to version 10.0 (v10.0) of the Varian’s RapidArc (VMAT) system. The most significant advancement made in v10.0 was that the progressive resolution optimiser (PRO) algorithm was modified and had been demonstrated to be capable of producing plans of improved quality and in less time than the version of PRO utilised in v8.6. The advancements reported in v10.0 warranted further investigation leading to the second study presented in this thesis. Therefore, the original retrospective planning study comparing IMRT and VMAT was repeated, this time using v10.0. Comparisons were made between the outcomes obtained with v10.0 and those previously reported using v8.6 to assess if sufficient improvements were made in the VMAT process to reconsider utilising this technique to routinely treat prostate cancer at FVC.

The data gathered when the original retrospective study was repeated using v10.0 is presented in chapter 4. In summary, using v10.0, VMAT-1A and VMAT-2A were able to produce a dose distribution that achieved the departmental planning guidelines in all 20 cases. The VMAT plans provided better conformity to the target volume, a lower median dose to the bladder and heads of femur, as well as improved dose to the rectum in the $v_{60} - v_{70}$ range. These findings are in agreement with others who reported VMAT was capable of producing radiation therapy treatment plans for prostate cancer that are of similar quality to IMRT plans. Once again the treatments using VMAT-1A were significantly faster than both IMRT and VMAT-2A and the number of MUs required were fewer using VMAT compared with IMRT.

In v10.0 the IMRT plans remained faster to produce than VMAT plans, however the difference between IMRT and VMAT planning time was now less than 10 minutes. Statistically, the additional time needed to generate a VMAT plan was significant,
however it may be argued that this time is clinically insignificant within the planning module. The additional minutes needed to produce a VMAT plan instead of an IMRT distribution is only a small fraction of the overall planning time when you also consider contouring times and quality assurance checks.

The improvements observed in v10.0 have significant resource implications in the utilisation of VMAT clinically. When using v8.6 it was concluded that our department would not implement VMAT for the treatment of prostate cancer due to the inability to achieve the departmental planning guidelines using VMAT-1A and significantly prolonged planning time of VMAT-2A. In v10.0, the uncertainty of achieving the planning guidelines with VMAT was eliminated. Also the additional time needed to produce the VMAT plans had been reduced substantially and may be considered of no consequence clinically. Based on these results, VMAT using v10.0 offered an acceptable replacement of IMRT for the radical treatment of prostate cancer as VMAT offers the advantage of reduced treatment time and a reduced number of MUs.

Having demonstrated VMAT as an acceptable alternative to IMRT treatment, the research then progressed to investigate the VMAT beam arrangement that would best suit the treatment of early stage prostate cancer. The two retrospective studies presented in chapters 3 and 4 investigated VMAT using either one or two arcs. Others had also reported using one and two arcs for the treatment of prostate cancer.3,5,7,9-11,17,18,20-23 There were other reports in the literature that had investigated the use of partial arcs or a mix of full and partial arcs for the treatment of prostate cancer.7,13,16,20 The next study performed as part of this thesis retrospectively compared four VMAT beam arrangements for the treat of early stage prostate cancer. These being; (i) a partial arc (PA), (ii) one arc (1A), (iii) one arc plus a partial arc (1A+PA) and (iv) two arcs (2A). This study is presented in chapter 5.

Each technique produced a plan of similar quality that was considered adequate for treatment, however some differences were noted. The conformity to the PTV was best for the 1A, 1A+PA and 2A techniques that translated to improved rectal sparing in the 1A+PA and 2A plans in the 60-70Gy range. The improved conformity and reduced rectal dose observed using the 1A+PA and 2A techniques may allow for dose escalation without increasing rectal toxicity. However, the 1A+PA and 2A plans did have the longest beam delivery times, reducing patient comfort and increasing the chance of intra-fraction movement. The PA and 1A+PA techniques also required the
highest number of MUs to deliver a treatment fraction, increasing the theoretical risk of generating a radiation induced secondary malignancy.

Ultimately, the VMAT technique that was best suited for clinical implementation for the treatment of early stage prostate cancer may be dictated by the individual patient and the availability of resources in each radiotherapy department. Quan et al consider dual arcs superior to single arc in terms of a compromise between plan quality and delivery efficiency. Their group prefer the dual arc VMAT dose distributions that provided improved rectal and bladder sparing that they consider outweighs the cost of increased treatment time compared to the single-arc technique. Sale and Maloney elected to use the one arc technique for more spherical PTV structures (prostate only) and choose the two-arc technique when planning irregular PTV structures, such as post-prostatectomy cases and where the seminal vesicles are included in the PTV. The preferred technique at FVC and other centres within the BCCA is the 1A technique that is considered to provide the best compromise between plan quality and treatment efficiency.

The next study, chapter 6, concentrated on performing quality assurance (QA) of VMAT plans. The increased complexity of VMAT planning and treatment dictates that patient specific QA is required to ensure accurate dose delivery. FVC purchased ArcCHECK (version 6.2.3.5713, Sun Nuclear Corp, Melbourne, FL) specifically for the purpose of performing patient specific plan QA for VMAT dose distributions. ArcCHECK has been clinically proved to be a highly accurate method to QA VMAT treatment plans. Some negative aspects of using ArcCHECK include that it is a phantom based tool that requires time on a linear accelerator to perform the physical measurement of dose delivered, time that if the QA is performed during clinical hours could be spent treating patients. If the QA is not performed during the hours of clinical operation, the after-hours workload is increased for the departmental medical physicists.

An alternative to phantom based QA techniques is treatment plan QA software that can act as an independent plan evaluation and dosimetry check. Plan QA software eliminates the need to perform dosimetry measurements on a linear accelerator and can greatly reduce the time needed to perform the QA for complex plans. As part of this thesis a study was performed to assess if the plan IMRT QA software IMSure version 3.3 (v3.3), which has largely replaced phantom based QA at FVC, can replace
ArcCHECK for the QA of VMAT plans for the treatment of early stage prostate cancer. It was demonstrated that the planning software IMSure (v3.3) was not consistently accurate for the VMAT cases. A reasonable approach to incorporating IMSure into routine QA of prostate VMAT plans at FVC would be to change the IMSure action level to 5 percent. If IMSure reports a difference in MUs of greater than 5 percent compared to the treatment planning system (TPS), a measurement on a linac using ArcCHECK could be performed to confirm dose delivery. This study highlighted that IMRT plan QA process cannot just be adopted into a VMAT plan QA process, and that VMAT specific QA criteria are recommended.

The final piece of research presented in chapter 7 of this thesis set out to compare the acute toxicities recorded in patients during moderate hypo-fractionated radiation therapy treatment for early stage prostate cancer treated with IMRT or VMAT. Early reports on clinical experience with VMAT have demonstrated VMAT to be a safe treatment option for prostate cancer with acceptable toxicity.25,26 Another publication by Alongi et al compared acute and late toxicities in postoperative prostate cancer patients treated with either Three-Dimension Conformal Radiation Therapy (3DCRT) or hypo-fractionated VMAT.27 In that study VMAT was demonstrated to reduce the incidence of acute genitourinary and grade 2 lower gastrointestinal toxicities compared to 3DCRT, demonstrating the feasibility of a hypo-fractionation regime with VMAT in the postoperative setting.27 The study presented in chapter 7 is the first reported investigation comparing the measured acute toxicities in patients being treated with either IMRT or VMAT for the treatment of early stage prostate cancer.

At the outset of this study it was hypothesised that the IMRT and VMAT techniques would produce similar toxicities during treatment, proving that VMAT is a safe alternative to IMRT for the treatment of early stage prostate cancer. This hypothesis was based on the preceding research that had demonstrated that, although some statistical differences were observed, the dose distributions produced using IMRT and VMAT were similar that the author hypothesised would result in a similar level of treatment related side effects. Importantly, the study demonstrated that over the full course of treatment, the symptoms dermatitis, fatigue, pain and urinary frequency were reported significantly more frequently in the cases treated with IMRT compared with VMAT. The significance of this result cannot be understated. This is arguably the first research in the world to demonstrate that VMAT is associated with decreased toxicities compared with IMRT for the treatment of early stage prostate cancer.
8.2 Clinical Significance of Research Outcomes:

The research presented within this thesis has provided several outcomes with clinical significance that are discussed in further detail below. Briefly, the clinically significant outcomes included:

1. VMAT reduces the acute treatment related toxicity symptoms dermatitis, fatigue, pain and urinary frequency.
2. VMAT reduces beam-on (treatment) times.
3. VMAT increases the opportunity to use dose escalation.
4. The opportunity to use hypo-fractionation is increased with VMAT.
5. The cost of radiation therapy can be reduced using VMAT.
6. VMAT reduces the risk of generating radiation induced secondary malignancies.
7. The plan verification software IMSure should not be used for the quality assurance of VMAT plans.

8.2.1 VMAT reduces acute treatment related toxicities:

In a world first, it has been demonstrated that VMAT is associated with a reduction in acute toxicities compared with IMRT for the treatment of early stage prostate cancer. Specifically the symptoms dermatitis, fatigue, pain and urinary frequency were reduced in cases treated with VMAT. Any reduction in these toxicities would be expected to contribute to an improved quality of life of patients being treated with VMAT.

8.2.2 VMAT reduces beam-on (treatment) times:

It has been evidenced that compared with IMRT, VMAT-1A reduces the beam-on time and therefore the overall treatment time for each fraction of treatment for early stage prostate cancer. The faster treatments reported with VMAT can have several clinical implications.

- Positioning studies have reported that reducing treatment time has the potential to increase prostate treatment accuracy.\textsuperscript{11} That is, the longer a treatment lasts the higher the risk is of patient movement and anatomical deviation.\textsuperscript{28,29} The reduced
treatment time of VMAT means there is less patient discomfort during treatment and a reduced risk of patient movement.

- The reduced treatment time may also prove to be biologically advantageous. Evidence has shown that the radiation survival is not only a function of the total dose delivered but also depends on the duration that the radiation is delivered, that is dose rate.\textsuperscript{30,31} There is a potential tumour cell killing benefit in delivering radiation doses at a higher dose rate.\textsuperscript{6}

- The faster treatments could allow more patients to receive treatments daily and therefore reduce waiting lists for radiation therapy treatment.

- The extra time made available on a treatment unit by the use of faster VMAT treatments could be utilised to implement advanced image-guided radiation therapy (IGRT) protocols, such as cone beam CT (CBCT), or implement advanced treatment techniques for other treatment sites that require longer treatment times, without increasing waiting lists.

### 8.2.3 VMAT increases the opportunity to use dose escalation:

It is the basic premise of radiobiology that higher radiation doses result in proportionately greater tumour cell killing. That is, the probability of tumour control is a function of the radiation dose delivered.\textsuperscript{32,33} In radiation therapy, delivering a dose of radiation higher than that considered standard is called dose escalation. In prostate cancer, dose escalation beyond the standard 70Gy has been demonstrated to improve tumour control, but is associated with increased side effects.\textsuperscript{34,35}

The current research has demonstrated that VMAT is capable of improving the conformity of the prescribed dose to the PTV. The improved conformity also translated to a reduction in the median dose delivered to the bladder and heads of femur at all levels measured as well as a decrease in the dose delivered to the rectum in the $v_{60} - v_{70}$ range. The improved conformity reported using VMAT increases the opportunity to use dose escalation to improve tumour control, without increasing the dose delivered to the OAR and the risk of increasing radiation induced toxicities. This claim is supported in a study by Ost \textit{et al} who reported VMAT allowed for dose escalation of an
intraprostatic lesion with better sparing of the rectum than static three, five and seven field IMRT set-ups.\textsuperscript{23}

It is important to mention the important role IGRT contributes to dose escalation. Advanced IGRT techniques such as CBCT or the use of fiducial markers can be used daily to accurately localise the prostate target prior to treatment permitting the accurate and safe delivery of higher doses per fraction.

\textbf{8.2.4 Opportunity to use hypo-fractionation is increased with VMAT:}

Hypo-fractionation in radiation therapy means to give fewer radiation therapy treatment fractions at higher dose levels per fraction. Conventional prostate radiation therapy is delivered in 1.8 - 2.0Gy fractions. However, hypo-fractionated treatment of prostate cancer has gain widespread use in the past few years. This is based on the assumption that prostate cancer cells have a higher sensitivity to fraction size due to a lower alpha/beta (\(\alpha/\beta\)) ratio, than late responding OAR such as the rectum and bladder.\textsuperscript{36-38} Based on this hypothesis, hypo-fractionation for prostate cancer has the potential to improve the therapeutic window with the advantage to reduce the total treatment time, while maintaining the same clinical outcomes of the conventional fractionation.\textsuperscript{26,39}

As discussed for dose escalation, the improved conformity and reduced dose to the OAR observed using VMAT compared with IMRT increases the opportunity to use hypo-fraction for the treatment of prostate cancer without increasing the radiation related toxicities.

Again, IGRT plays an important role in delivering hypo-fractionated treatments by accurately localising the prostate target prior to treatment allowing the safe delivery of a higher dose per fraction.

\textbf{8.2.5 The cost of radiation therapy treatment is reduced using VMAT:}

A report by Fogarty \textit{et al} compared VMAT to IMRT for the treatment of prostate cancer at an Australian radiation therapy department.\textsuperscript{40} Uniquely, their paper examined the average treatment staff cost per patient and they reported a savings of $174.25 (AUD) per patient using VMAT compared with IMRT.\textsuperscript{40} The reported cost savings using VMAT was attributed to VMAT treatment being delivered faster than IMRT. Similar time savings have been reported in this thesis and it would be reasonable to expect the cost
saving experienced at the Australian centre may also be experienced at FVC. As the cost savings reported by Fogarty et al are based on a full treatment courses ranging between 37-39 fractions, it would also be reasonable to expect that if a hypofractionation regime was utilised, the cost savings would be further increased.

Importantly, the cost savings reported by Fogarty et al are based on their findings that a significance difference in the planning time between IMRT and VMAT was not observed. In the research reported in this VMAT planning does take longer than IMRT. However, the difference reported in this thesis was not greater than 10 minutes, which is unlikely to have significant impact on staff costs.

The report by Fogarty et al also assumes the time to perform plan QA is the same for both IMRT and VMAT. In chapter 6 of this thesis it is reported that using VMAT at FVC requires the plan QA be performed using the ArcCHECK QA tool. In a comparison with the standard prostate IMRT QA tool IMSure, ArcCHECK was reported to take approximately 30 minutes longer to perform the QA. This translates to an additional 30 minutes of physics staff cost. Even with the additional physics staffing cost to perform QA, the VMAT technique still saves money compared with IMRT due to the reduction in treatment times over the full course of treatment.

### 8.2.6 VMAT reduces the chance of generating radiation induced secondary malignancies:

It has been demonstrated that VMAT treatments require fewer MUs to deliver a single fraction of treatment compared with IMRT. The reduction in MUs required for VMAT treatments reduces a patient’s exposure to scatter and leakage radiation, reducing the risk of developing secondary cancers. Secondary malignancy induction is an important consideration for cancers such as prostate cancer where due to ongoing technical improvements in cancer diagnosis and treatment, patients have a greater chance of long term survival.

### 8.2.7 The plan verification software IMSure should not be used for the Quality Assurance of VMAT plans:

The plan verification software IMSure v3.3 is the standard platform used to perform the QA of prostate IMRT plans at FVC. ArcCHECK (v6.2.3.5713) is a phantom based QA tool purchased for the specific purpose to perform plan verification QA of VMAT plans.
at FVC. *ArcCHECK* has the disadvantage requiring time on a linear accelerator to perform dose measurements, time that if performed during clinical hours could be better used for the treatment of patients. In study 4, chapter 6 it was investigated if *IMSure* could be utilised to perform the QA of prostate VMAT plans. It was demonstrated that *IMSure* is not as accurate as *ArcCHECK* for the QA of prostate VMAT plans and therefore the plan verification software *IMSure* should not be used for the Quality Assurance of VMAT plans.

It is recognised that plan verification software has an advantage over phantom based QA tools that require dose measurements to be performed on a linear accelerator. It is likely that as computer based dose modelling is continued to be improved a plan verification software will be available in the future that will replace the need to use a dose measurement based technique.

### 8.3 Future directions of prostate cancer treatment and the role of VMAT:

In the introduction of this thesis it was indicated that the screening of prostate specific antigen (PSA) plays a significant role in the early detection and diagnosis of prostate cancer. As of 2014, the continued role of a PSA screen in detecting prostate cancer is controversial.

The controversy stems from two major studies that have conflicting outcomes. The first study was a European Randomised study of Screening for Prostate Cancer (ERSPC) that compared a group of men invited for prostate-cancer screening based on PSA with a control group without any active intervention, with a median follow-up of nine years. This study concluded PSA-based screening has reduced the rate of death from prostate cancer by 20 percent but is also associated with a high risk of over diagnosis. The controversy arose when it was questioned if the benefit in reduced cancer mortality documented outweighs the harms of over detection, which include the complications associated with unnecessary biopsy or treatment for individuals and the additional strains put on the health care system to care for a large group of patients who do not require care in the first place. The controversy was further heightened by another large study, the US-based Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) screening trial, which found no difference in prostate-cancer mortality between
men randomised to screening and those in the control group at 11.5 years of follow-up.44

In November of 2014 the ministry of health in Canada announced a landmark decision to recommend against the use of PSA screening for the diagnosis of prostate cancer. In other countries PSA testing continues to play a significant role in the early detection of prostate cancer, but for how much longer remains uncertain.

If or when it is recommended that PSA screening for prostate cancer be discontinued, an alternative to physical examination currently being investigated is the use of magnetic resonance imaging (MRI).45 MRI is an advanced imaging modality that allows for improved imaging of soft tissue anatomy. An advantage of using MRI for the early detection and grading of prostate cancer is that the improved imaging of soft tissue may allow for the area of disease to be localised within the prostate. However, due to the current limited availability of MRI machines, utilising MRI to screen for prostate cancer may not be a realistic option, none the less it is being considered.

Another opportunity to benefit from the advanced imaging offered by MRI for the treatment of prostate cancer is being realised in the development of a radiation therapy simulator that combines CT and MRI imaging. The advanced imaging of soft tissue provided by MRI permits the area of disease to be localised in the prostate therefore allowing a concentrated treatment to the area of disease rather than treating the entire prostate gland. Such concentrated, individualised treatment is called focal therapy. As VMAT has been demonstrated here to be capable of delivering a highly conformal dose to the target volume, VMAT could be used to deliver focal therapy treatments or treatments with a simultaneous integrated boost to the area of disease within the prostate.

The future possibilities of prostate cancer care presented here including the cessation of PSA screening, utilisation of MRI for early detection and diseases staging, and the increased use of focal therapy may or may not eventuate. For now VMAT offers the best option to provide external beam radiation therapy treatment for early stage prostate cancers offering the opportunity to use dose escalation and hypo-fractionation without increasing the incidence of radiation related toxicities.
8.4 Conclusion:

This PhD thesis by publication presents a series of published studies that compared the existing standard of treatment, IMRT, with the innovative technique, VMAT, for the treatment of early stage prostate cancer. The outcomes of this research can be linked with the seven objectives described in the introduction of this thesis as follows.

**Objective 1:** To compare the quality of the dose distributions generated using IMRT or VMAT for the radiation therapy treatment of early stage prostate cancer.

**Conclusion 1:** VMAT is capable of providing a more conformal dose to the prostate target volume compared with IMRT, while providing improved sparing of the adjacent rectum, bladder and heads of femur. The improved dose distribution reported with VMAT increases the opportunity to use dose escalation or hypo-fractionation for the treatment of early stage prostate cancer without increasing associated toxicities.

**Objective 2:** To compare the time needed in radiation therapy treatment planning to generate an acceptable dose distribution for the treatment of early stage prostate cancer using IMRT or VMAT.

**Conclusion 2:** Using v10.0 of Varian’s RapidArc (VMAT) software, VMAT-1A and VMAT-2A plans required approximately nine minutes longer than IMRT plans to generate. This difference was reported as statistically significant, however it may be argued that the additional nine minutes is clinically insignificant within the planning module where the extra minutes needed to produce a VMAT plan is only a small fraction of the overall planning time considering the time to contour and perform QA checks.

**Objective 3:** To compare the time needed on a linear accelerator to deliver a single treatment fraction for prostate cancer using IMRT or VMAT.

**Conclusion 3:** VMAT treatments are faster than those with IMRT. The faster treatment times using VMAT can reduce the chance of intra-fraction variation and potentially increase patient throughput in a department.

**Objective 4:** To compare the number of MUs needed to deliver a single fraction of treatment for prostate cancer using IMRT or VMAT.
Conclusion 4: VMAT requires fewer MUs than IMRT to deliver each fraction of radiation therapy treatment therefore reducing the theoretical chance of generating a radiation induced secondary malignancy.

Objective 5: To develop the best VMAT technique for the treatment of early stage prostate cancer that makes the best use departmental resources at FVC.

Conclusion 5: In an analysis of four VMAT beam arrangements, these being; (i) a partial arc (PA), (ii) one arc (1A), (iii) one arc plus a partial arc (1A+PA) and (iv) two arcs (2A), it was determined that the 1A technique provided the best balance of plan quality and treatment efficiency for implementation at the BC Cancer Agency.

Objective 6: To compare the usability of IMSure (quality assurance software) with ArcCHECK, (a phantom based tool) for the quality assurance (QA) check of VMAT treatment plans.

Conclusion 6: It was demonstrated that the planning software IMSure (v3.3) was not consistently accurate for the VMAT cases and cannot be used as a replacement for the phantom based ArcCHECK (v6.2.3.5713)

Objective 7: To monitor the clinical implementation of VMAT for the treatment early stage prostate cancer to ensure VMAT causes no additional harm than IMRT by comparing the acute side effects.

Conclusion 7: VMAT is associated with a reduction in acute toxicities compared to IMRT for the treatment of early stage prostate cancer. Specifically the symptoms dermatitis, fatigue, pain and urinary frequency were reduced in cases treated with VMAT.

From the data presented in this PhD thesis it is concluded VMAT using v10.0 of Varian Medical System’s RapidArc offers an advantage over IMRT for the treatment of early stage prostate cancer. The benefits of VMAT include faster treatments that require fewer MUs to deliver. Most importantly, VMAT reduces the treatment related toxicities dermatitis, fatigue, pain and urinary frequency. A limitation of the current research is that the retrospective planning studies were performed on a relatively small number of cases (twenty). Similarly, the number of cases eligible for the toxicity comparison study was limited by the recent transition to the assessed moderate hypo-fractionated...
treatment regime and strict adherence to the inclusion criteria to exclude post-prostatectomy patients, which is the preference for patients in the remotely located Centre for the North (CN). Future long term studies with a larger study population are recommended to confirm the reported results for acute toxicities and to investigate late toxicities and clinical outcome for this group of patients. Future studies may also include investigating the benefits of using VMAT on post-prostatectomy patients that were excluded from the current studies. It is also recommended that VMAT be trialled on other treatment sites at FVC such as head and neck cancers or sites currently treated with stereotactic body radiation therapy (SBRT). Both head and neck, and SBRT treatments can be complicated and require long treatment times that may be reduced using VMAT therefore further improving treatment efficiency and potentially reducing the waiting list at FVC.
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