An evaluation of contouring and planning methods to expand the role of SBRT with CyberKnife in the treatment of localised prostate and renal cancers

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Author's declaration

I declare as sole author of this thesis that the work presented here represents my personal research conducted as a clinical research fellow at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust between 2016 and 2019. Tables and figures contained herein are my own work unless credited otherwise.

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Abstract

Technological advancement has led to the substantial evolution of stereotactic body radiotherapy (SBRT). The CyberKnife SBRT platform achieves a high degree of precision through robotic delivery of multiple non-coplanar beams, combined with intrafraction motion compensation to submillimetre accuracy[1]. This enables tumour dose escalation while limiting dose to normal tissues, although any benefit is largely dependent on the quality of contouring and planning processes. The newly developed multi-leaf collimator (MLC) improves CyberKnife delivery by reducing treatment time and has the potential to treat large, complex tumours more effectively[2].

A large body of data supports the use of SBRT in early prostate cancer and randomised trial data from the PACE-B trial demonstrates rates of acute toxicity to be equivalent to standard radiotherapy[3]. The evidence in high-risk prostate cancer is limited and is being addressed in the PACE-C trial. This thesis investigates methods of improving SBRT quality in early prostate cancer and evaluates its application in high-risk prostate cancer and primary renal cancer.

Pending long-term randomised trial data, I report 5-year outcomes from the first UK prostate Cyberknife cohort, involving 62 patients treated at a single centre. I then explore the impact of prostate volume and dosimetry on toxicity and consider potential preventative strategies. To ensure the quality of clinical outlining I evaluate interobserver variability within the PACE trial quality assurance programme, and develop a more consistent method for seminal vesicle (SV) delineation for use in PACE-C.

To expand the utility of SBRT to higher risk prostate cancer patients, I explore the feasibility of Cyberknife planning for larger target volumes with a greater proportion of SV and test the benefit of using MLC in this setting. I will begin to assess the wider applicability of MLC in urological malignancy by comparing with the Iris variable collimator in SBRT planning for primary renal cancer.

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Abbreviations

ADT:	Androgen deprivation therapy
AP:	Anteroposterior
bDFS:	biochemical Disease-free Survival
BED:	Biologically effective dose
bPFS:	biochemical Progression-free Survival
BR:	Biochemical Recurrence
bRFS:	biochemical Relapse-free Survival
CA:	Cryoablation
CBCT:	Cone beam computed tomography
CFMHRT:	Conventionally fractionated or moderately hypofractionated radiotherapy
CRT:	Conformal radiation therapy
CT:	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV:	Clinical Target Volume
DIL:	Dominant intraprostatic lesions
DVH:	Dose volume histograms
EBRT:	External beam radiotherapy
ECE:	Extracapsular extension
ECOG:	Eastern Cooperative Oncology Group
eGFR:	estimated Glomerular Filtration Rate
EORTC:	European Organisation for Research & Treatment of Cancer
FFBR:	Freedom from Biochemical Recurrence
G2:	Grade 2
G3:	Grade 3
GI:	Gastrointestinal
GU:	Genitourinary

Gy:	Gray
HDPTV:	High dose Planning Target Volume
HDR:	High Dose Rate
HDR-BT:	High dose rate brachytherapy
IGRT:	Image-guided radiotherapy
IMRT:	Intensity-modulated radiotherapy
IROCK:	International Radiosurgery Oncology Consortium for Kidney
KV:	Kilo voltage
LDPTV:	Low dose Planning Target Volume
LR:	Left-right
MLC:	Multileaf Collimator
mpMRI:	multiparametric MRI
MR:	Magnetic Resonance
MTD:	Maximum tolerated dose
MU:	Monitor Units
NCCN:	National comprehensive Cancer Network
OAR:	Organs at risk
PACE:	Prostate Advances in Comparative Evidence
PRV:	Planning Risk Volume
PSA:	Prostate Specific Antigen
pSV:	Proximal Seminal Vesicle
PTV:	Planning Target Volume
QOL:	Quality of Life
RFA:	Radiofrequency ablation
RMH:	Royal Marsden Hospital
RP:	Radical Prostatectomy
RTOG:	Radiation Therapy Oncology Group
SAD:	Source-axis distance
SBRT:	Stereotactic body radiotherapy

SD: Standard deviation

SI: Superior-inferior

SIB: Simultaneous integrated boost

SV: Seminal Vesicle

SVI: Seminal Vesicle Involvement

VMAT: Volumetric arc therapy

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It has been a challenging time for research due to the pandemic. I have therefore made the decision with my supervisor to prioritise completing the thesis but will submit my work for publication in due course.

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Chapter 1: Introduction

Sections of the following chapter have been published/ presented as:

- Summary of Ongoing Prospective Trials Using SBRT for Prostate Cancer[1]

  Morrison K, van As N.

  Book chapter in Stereotactic Radiosurgery for Prostate Cancer, Sep 2018

  Editor Zelefsky M,

  Pages 197-215

- Prostate Cancer

  Updated Prostate Cancer chapter for UK SABR Consortium guidelines 2019[2]

  Pages 75-92

- The PACE trial: International randomised study of laparoscopic prostatectomy vs. stereotactic body radiotherapy (SBRT) and standard radiotherapy vs. SBRT for early-stage organ-confined prostate cancer[3].

  Morrison K, Tree A, van As N, et al.

  Poster presentation, GU ASCO, Feb 2018

  Abstract in Journal of Clinical Oncology 2018; 36: TPS153.

1.1. Outline of thesis

This aim of this thesis is to evaluate the efficacy and tolerability of stereotactic body radiotherapy with CyberKnife in localised prostate cancer and to investigate contouring and planning techniques which may be applied to patients with higher risk disease and primary renal cancer.

Technological innovation has accelerated the development of stereotactic body radiotherapy (SBRT) within the United Kingdom (UK) over the past decade. A particular example is the CyberKnife robotic radiosurgery system which incorporates a linear accelerator on a robotic arm, delivering multiple beams to the target from a number of different coordinates around the patient[4,5]. The other unique feature of this system is its ability to robotically compensate for intrafraction motion with submillimetre accuracy. This creates a high dose within the target with a steep dose gradient and allows the use of small treatment margins thereby minimising dose to surrounding structures.

1.1.1. Five-year outcomes following Stereotactic Body Radiotherapy (SBRT) with CyberKnife in localised prostate cancer - UK experience

SBRT for low- and intermediate- risk prostate cancer had been shown to be safe and effective in a large number of studies mainly from the United States (US)[6-10]. However, there is a lack of long-term randomised trial data confirming SBRT to be, at least, as effective as conventional treatment with radiotherapy or surgery. This is being addressed by the PACE trial which has already published data demonstrating no

significant difference in acute toxicity between SBRT and conventional or moderately hypofractionated radiotherapy[11]. Pending the long-term results, data from single-centre prospective trials remains highly informative.

In my first data chapter (chapter 2) long-term efficacy and toxicity outcomes from a prospective study of the first UK cohort are evaluated in order to confirm results are consistent with worldwide data. Results from larger prospective trials and metanalyses, are used for comparison, and are discussed in the background section of chapter 1. Chapter 2 then focuses on an evaluation of factors, including volumetric and dosimetric CyberKnife plan data, which may contribute to toxicity. This concludes with a discussion regarding the implications of my findings with consideration of methods to minimise patients side effects following prostate SBRT.

1.1.2. Quality assurance in SBRT planning for localised prostate cancer using data from multiple centres within the PACE B trial.

The benefit of SBRT is particularly dependent on the accuracy of target volume and normal tissue outlining by the clinician, since high precision techniques and small margins leave less room for error. A robust quality assurance programme is therefore an important aspect of a large multicentre SBRT trial, such as PACE, to ensure the adequacy and consistent of clinical outlining amongst centres.

Interobserver variability is common problem in radiotherapy planning, and has been shown to be a significant issue in prostate radiotherapy[12,13]. At least the proximal seminal vesicles (pSV) are often included in the clinical target volume (CTV) for

prostate radiotherapy, but there is no clear consensus on either the extent that should be included, nor the method of delineation[14]. Irradiating the seminal vesicles can be associated with increased toxicity due to the close proximity to rectum and bladder[15,16]. Therefore, a more consistent pSV delineation method is needed, particularly for use in SBRT trials for high-risk patients such as PACE C.

Chapter 3 includes a retrospective evaluation of clinical contouring, completed by centres within the quality assurance benchmark exercise for the PACE B trial. Firstly, in order to identify the most common tissue sites for outlining deviations, data from the benchmark case feedback proformas for each centre are analysed with reference to PACE trial protocol. Secondly, the CTV contours from each centre are analysed to quantitively assess the degree of interobserver contouring variability for prostate and pSV delineation, respectively. Finally, a semi-automated method for pSV outlining is evaluated to confirm a reduction in interobserver variability, amongst experienced radiation oncologists at the British Urology Group (BUG) annual conference.

1.1.3. The feasibility of CyberKnife planning for SBRT in high-risk prostate cancer and a comparison of plans using the Iris variable collimator and Incise multileaf collimator

The evidence for SBRT in high-risk prostate cancer is more limited and many unanswered questions remain regarding the optimum treatment strategy, including the potential benefits of further dose escalation or pelvic irradiation. The risk of seminal vesicle (SV) involvement is greater in these patients, and therefore a greater proportion of SV (usually ≥2cm) is often included in the CTV which can lead to more

complex SBRT planning and an increased risk of toxicity. In chapter 4 I complete a planning study to evaluate the effect on dosimetry and plan delivery efficiency by increasing the extent of SV included within the CTV, thereby assessing the feasibility of CyberKnife planning for high-risk patients.

The Incise multi-leaf collimator (MLC) is a more recent development of the CyberKnife which enables the use of large, irregular shaped fields[17]. This can result in improved treatment delivery times compared to the Iris variable collimator, which is discussed in more detail in this chapter. I conduct a further planning study to compare the quality and efficiency of MLC and Iris plans in delivering SBRT to target volumes which include a large proportion of SV.

1.1.4. Comparison of the CyberKnife Incise multi-leaf collimator and Iris variable collimator in SBRT planning for primary renal cancer

Primary renal cancer is most common in the elderly population, often with associated comorbidities, and, therefore, some patients are not suitable for standard treatment with surgery[18,19]. Historically, renal cancer was perceived to be radioresistant however evidence suggests that this may be overcome with ablative doses of radiotherapy, as used in SBRT[20,21]. A number of, mainly retrospective, studies have demonstrated SBRT in primary renal cancer to be relatively well tolerated with favourable rates of local control compared to other nephron-sparing treatments[22-24]. However, renal tumours can be difficult to plan due to the location close to bowel and adjacent renal parenchyma.

In chapter 5 I evaluate the potential benefit of the MLC in this setting, comparing with Iris planning. In addition to a treatment time reduction, I assess for any improvement in target coverage or normal tissue sparing and aim to identify the subset of patients who may gain the most benefit from the use of MLC.

1.2. Background

1.2.1. Stereotactic body radiotherapy

The development of stereotactic body radiotherapy (SBRT) has significantly impacted the management of urological malignancies over the past decade. SBRT involves the delivery of high precision, ultra-fractionated radiotherapy, usually in five fractions or less. The aim of treatment is to improve the therapeutic outcome by enabling dose escalation to the tumour, while limiting dose to the surrounding normal tissues. Additionally, the reduction in the number of fractions and total treatment duration improves convenience for patients and may lead to resource benefits in terms of cost and departmental capacity.

The implementation of SBRT relies on the use of advanced radiotherapy techniques to deliver highly accurate treatment, with a steep dose gradient and smaller treatment margins. Treatment can be delivered using either a gantry-based technique, or dedicated SBRT platform, such as the CyberKnife® robotic radiosurgery system (Accuray inc., US). Given the high degree of accuracy, it is of fundamental importance that sophisticated planning systems are combined with effective patient immobilisation, precise target localisation and advanced image guidance techniques.

1.2.2. The CyberKnife robotic radiosurgery system

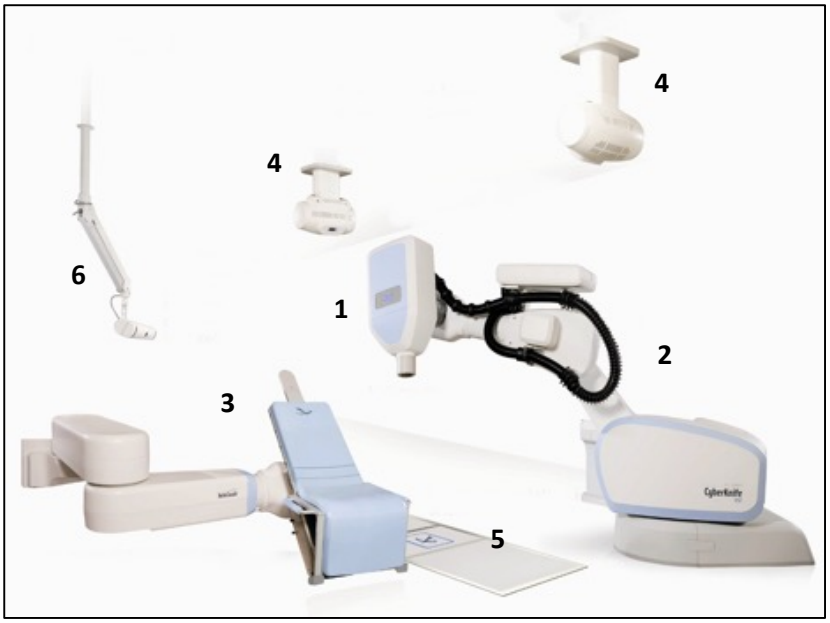
The CyberKnife (Figure 1.1) is composed of a linear accelerator attached to a treatment using a vast number of possible beam orientations without the need to

reposition the patient. Multiple non-coplanar and non-isocentric beams are directed at different points (Figure 1.2), usually within the target volume, creating a heterogenous high dose distribution with steep dose gradient, limiting dose to the surrounding normal structures[5].

Treatment involves the movement of the robot around the patient delivering multiple beams from a number of source co-ordinates, known as nodes. The nodes form the treatment path set which is selected for each patient at the start of the planning process, depending on the particular tumour site. The number of nodes in each path ranges between 23 and 133[5]. At each nodal position, the robot re-orientates itself to deliver each beam in the required direction. The robot motion time is, therefore, dependent on the number of nodes and beams included in the treatment plan, traveling between node positions taking longer than the reorientation between beams at each node position[25].

Inverse planning methods are used to create a treatment plan which comprises individual beam data including the relative weighting, field size, and monitor units of each beam, as well as the position and orientation of each beam in relation to the target volume. One of the features of the sequential optimisation process is the use of virtual shell structures created around the target, which limit the dose to a specified threshold (Figure 1.3). Once an acceptable quality of plan is achieved, in terms of target coverage and normal tissue sparing, beam, node and time reduction algorithms can be selected to optimise plan delivery efficiency. The final plan is often a satisfactory compromise between quality and efficiency of delivery.

Figure 1.1: The CyberKnife® robotic radiosurgery system



Photographic image of the CyberKnife robotic radiosurgical system. 1. Linear accelerator; 2. Robotic arm; 3. Robotic treatment couch (Robocouch®); 4. X-ray sources; 5. Image detectors; 6. Synchrony® respiratory tracking device.

Figure 1.2: Beams eye view (BEV) of CyberKnife prostate plan

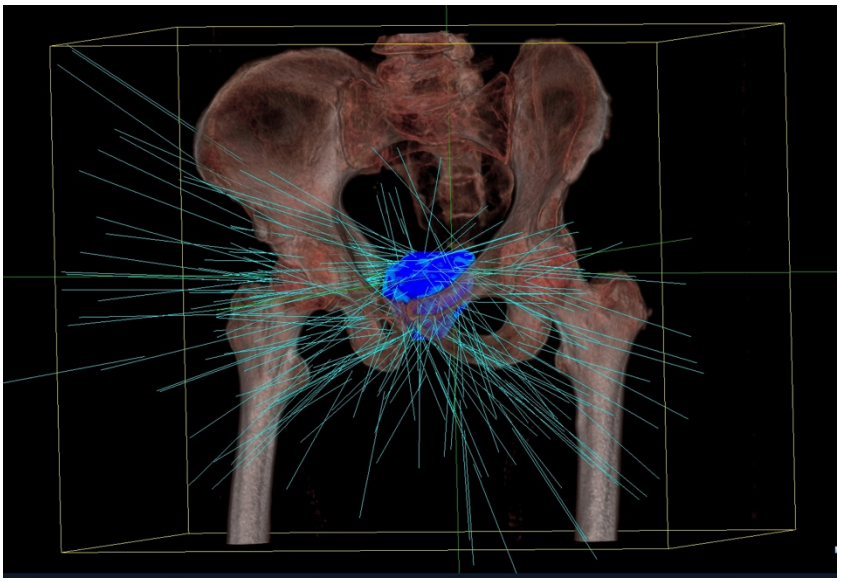
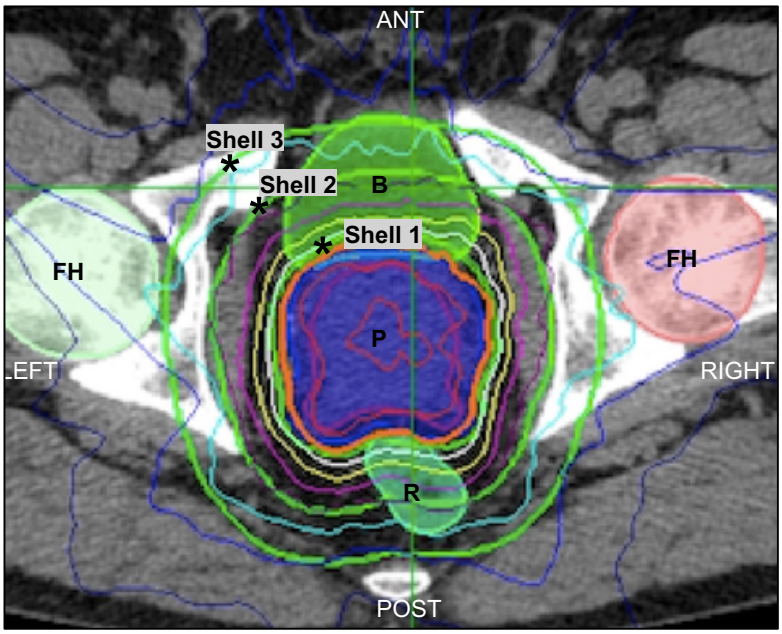


Image of a beams eye view (BEV) of a prostate CyberKnife plan demonstrating multiple non-coplanar beams directed towards a target volume (blue) in the pelvis.

Figure 1.3: CyberKnife plan demonstrating dose-limiting virtual shells



Axial slice of a Cyberknife prostate plan demonstrating the dose-limiting virtual shells in green, identified by the black stars. Ant, anterior; Post, posterior; P, prostate; R, rectum; FH, femoral heads. Clinical target volume (CTV) contour in red and planning target volume (PTV) in blue segment. Isodose lines are demonstrated surrounding the PTV: prescription isodose (orange); 100% isodose (red); 70% isodose (white); 60% isodose (yellow); 50% isodose (magenta); 40% isodose (purple); 30% isodose (cyan); 20% isodose (blue).

1.2.2.1. Collimators

Each beam size is defined by collimators, of which there are three available types (Figure 1.4). Fixed circular collimators, of varying sizes, are stored externally to the treatment head on the Xchange system table[5]. In order to change collimator size, the robot is required to change aperture after completing the delivery of all equally sized beams within a full path set, before repeating the treatment path to deliver beams of the specified collimator size. Treatment plans, including the use of fixed collimators, are, therefore, usually limited to 1-3 field sizes since the robotic aperture changes will significantly add to total treatment time.

1.2.2.2. Iris^{TM} variable aperture collimator

The Iris^{TM} variable aperture collimator (Iris) collimator (Figure 1.4) within the treatment head allows the delivery of multiple beams of varying field sizes within a single path set. Located within the CyberKnife treatment head, the aperture consists of 12 metal segments with the ability to produce, approximately circular, polygonal treatment beams, varying in field diameter from 5mm – 60mm[26]. The Iris negates the need for robotic change of aperture, enabling the use of up to 12 field sizes within a single journey of the robot through the full path set. Planning studies have confirmed improvements in plan quality with improved target volume coverage, conformality and monitor unit reduction, without an increase in treatment time[26].

1.2.2.3. Multileaf Collimation

The incorporation of multileaf collimation to the CyberKnife system in 2015 has provided the option of delivering treatment using a variety of irregularly shaped fields, allowing the use of fewer beams and lower total monitor units (MU) compared to treatment using fixed or Iris collimated fields. The Incise 2^{TM} multileaf collimator (MLC)(Figure 1.4) consists of 26 pairs of independently-controlled tungsten leaves, each leaf measuring 90mm in length, and 3.85mm in width at 800 mm source-axis distance (SAD)[17,27]. The robot moves through a treatment path set, stopping at each node to deliver a beam from static MLC apertures, but compared to fixed or Iris collimation, the density of nodes is reduced, with one beam delivered per nodal position. The MLC leaves move simultaneously to create different shapes, known as segments, allowing a maximum treatment field of 115 x110 mm. One or several segments can be used with each beam, which are automatically selected during the planning process. The design of the CyberKnife M6 allows MLC, Iris and fixed collimators to be automatically changed, as defined by each treatment plan, with the most appropriate aperture being selected at the start of the planning process.

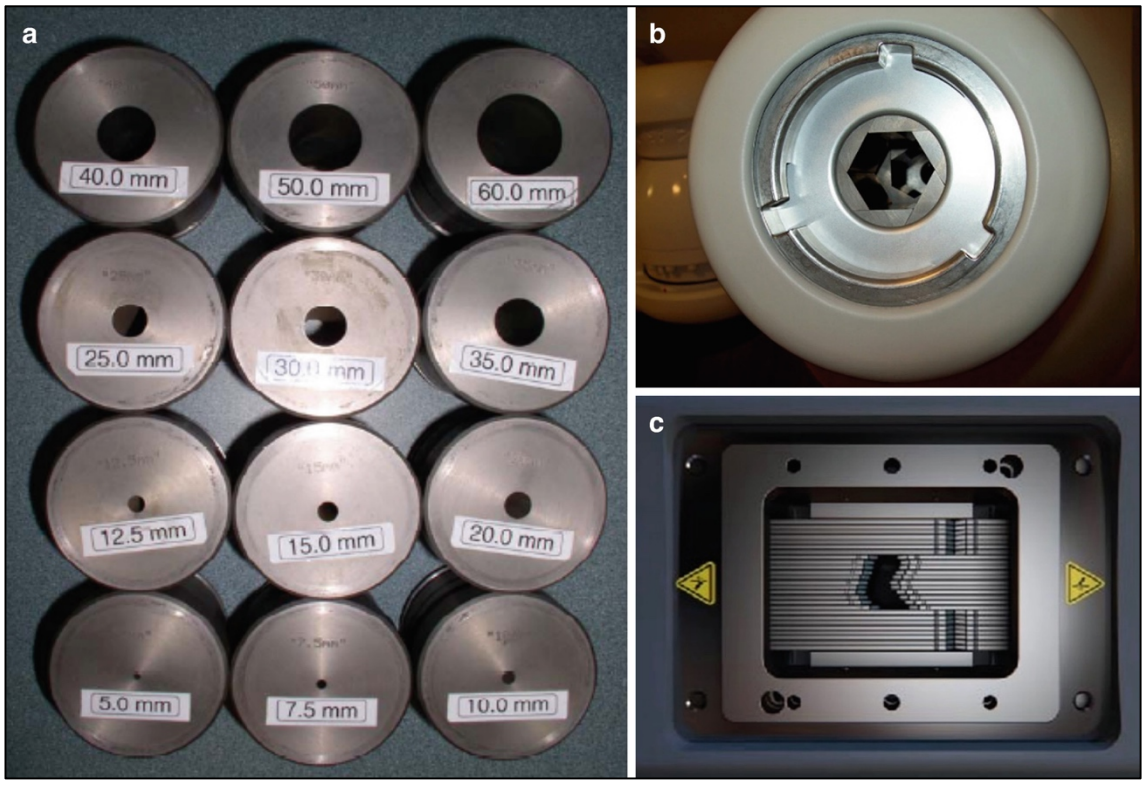
Planning studies have confirmed that MLC can produce plans which are equivalent in terms of conformality, but required fewer beams, potentially resulting in a reduction of treatment time and monitor units in comparison to the Iris[25,27-29]. This has been shown to be of particular benefit in treating large, irregular-shaped tumours. Van de Water et al demonstrated in 10 lung cancer cases that Iris plans were on average 40% longer than MLC plans for small targets (<80 cm^3) and that this difference increased with increasing target volume[25]. McGuiness et al demonstrated in 5 prostate and 5 brain

cases that MLC plans reduced the treatment time by 50% in all cases and the total MU was reduced by 40% in the prostate plans and 70% in the brain plans[28]. Kathriarachichi et al demonstrated in 10 prostate cancer cases that MLC plans were equivalent in terms of dosimetry and OAR sparing but produced 36% faster delivery time and 40% MU reduction[29].

1.2.2.4. Image Guidance

Precise image guidance is one of the key hallmarks of SBRT which on CyberKnife is achieved using KV imaging, acquired from a pair of orthogonal x-ray sources attached to the ceiling, projecting to x-ray detectors on the floor (Figure 1.1). Images are correlated with the target volume, commonly using surrogate fiducial makers to assess the degree of positional change[30]. Other available options which do not rely on the use of fiducials include skull tracking for brain tumours and Xsite® spine and lung tracking for appropriate treatment of tumours at these locations. In addition, the Synchrony® Respiratory Tracking System (Figure 1.1) is available for real-time tracking of tumours that move with respiration, avoiding the need for patient breath-holding[5]. A defining feature of the CyberKnife system is its ability to compensate for intrafraction motion. The patient treatment couch (RoboCouch, Accuray Inc) (Figure 1.1) has the ability to automatically adjust the patient into the required position within less than 1mm accuracy. The frequency of imaging and compensatory movement of the patient typically occurs every 30 – 60 seconds and is automatically adjusted, depending on the magnitude of motion detected[5].

Figure 1.4: Images of the three different CyberKnife collimators



Photographic images of the three types of CyberKnife collimators (a) fixed collimators ranging between 5.0 – 60.0 mm diameter; (b) Iris variable collimator; and (c) Incise multileaf collimator. Images by Moutsatsos et al[4].

1.2.2.5. Limitations and developments

In comparison to gantry-based SBRT, the CyberKnife is superior in terms of its ability to deliver non-coplanar beams and to compensate for intra-fraction motion with a very high degree of precision, although, currently, it remains unclear whether the choice of platform contributes to beneficial clinical outcomes. Gantry-based techniques utilise volumetric arc therapy (VMAT) which incorporates continuous rotation of the gantry through an arc, while dynamically delivering dose, modulated with the use of continuous MLC motion. This provides an advantage in terms of treatment delivery time, which is one of the main limitations of the CyberKnife. Even with the addition of MLC, the serial process of robotic motion between nodal positions, MLC leaf motion, beam-on time, intrafraction motion tracking and compensation, all account for the relatively long treatment time. Recently, work has been done to develop a dynamic arc for use with the CyberKnife system, in order to improve on this[31].

Another current advantage of gantry-based SBRT is the availability of soft-tissue imaging with cone-beam CT image guidance or the more recently developed MR-linac[32]. This avoids the need to rely on fiducial markers to track target volume position, which is vital for the treatment of extracranial soft tissue tumours (not amenable to spine- or lung-tracking) on CyberKnife. Finally, there is limited availability of CyberKnife platforms worldwide, including within the UK, and, therefore, the development of gantry-based techniques provides greater capacity for treating a larger population of patients with SBRT.

1.2.3. Prostate cancer

Prostate cancer is the most common cancer affecting men in the UK with approximately 48,500 new cases every year and over one third diagnosed in patients over 75 years of age[33]. The majority of patients present with localised prostate cancer which carries a good prognosis and can be effectively treated with radical prostatectomy (RP), external beam radiotherapy (EBRT) +/- androgen deprivation therapy (ADT), brachytherapy, or active surveillance in selected patients. The ProtecT trial, which randomised over 1,600 men between active monitoring, prostatectomy and EBRT, demonstrated that less than 2% of men died from prostate cancer with no significant difference between groups, although the mortality rate was higher in the active surveillance group, in addition to higher rates of disease progression and development of metastases[34,35].

The choice of treatment is determined by the patient risk-group as defined by the level of serum prostate specific antigen (PSA), clinical stage (T-stage), Gleason score and number of involved cores on biopsy[36]. The majority of patients present with low- or intermediate-risk disease, as defined the National Comprehensive Cancer Network (NCCN) risk group criteria (Table 1.1)[37]. As shown, intermediate-risk patients can be further categorised into favourable and unfavourable intermediate-risk groups.

Table 1.1: National Comprehensive Cancer Network (NCCN) risk group definition for localised prostate cancer

Risk Group	PSA (ng/mL)	Gleason Score	T Stage
Low	<10	< 7	≤T2a
Intermediate Favourable Unfavourable	10 - 20	7 3+4 <50% biopsy cores positive 4+3 ≥50% biopsy cores positive	T2b – T2c
High	>20	8- 10	T3a
Very High		Primary score 5 > 4 cores 4 or 5	T3b/4

1.2.3.1. Radiotherapy for prostate cancer

Radical EBRT is a highly effective treatment for localised prostate cancer, traditionally delivered in fraction sizes of 1.8 – 2 Gray (Gy) in 37 fractions, over 7.5 weeks. Randomised trial evidence has demonstrated improved biochemical disease-free survival from dose escalation[38-40]. Using conformal EBRT, an escalated dose of 74 - 79.2Gy in 1.8 - 2Gy fractions, compared to 64 - 70Gy, resulted in a significant improvement in biochemical control with reported 5-year freedom from biochemical failure rates of 64 - 80% [38,41-43]. However, the benefit of dose escalation comes with an increased risk of toxicity, particularly due to the location of prostate gland, in close proximity to the rectum, bladder and neurovascular bundle. There is evidence demonstrating an increase in acute gastrointestinal (GI) and genitourinary (GU) toxicity together with an increase in late rectal toxicity, with 3D conformal radiotherapy[38]. The development of advanced radiotherapy techniques such as intensity modulated radiotherapy (IMRT) has enabled dose escalation to the prostate and lower rates of acute and late GI toxicity[38,44].

1.2.3.2. Radiobiology of prostate cancer

A greater understanding of the radiobiology of prostate cancer has led to the increased use of hypofractionation. A number of studies have indicated that prostate cancer cells have a low alpha/beta ratio of <2 Gy[45-47], lower than that of surrounding dose-limiting structures such as the rectum. Therefore, prostate tumours are thought to be more sensitive to larger fraction size, thereby allowing a higher radiation dose to be delivered without increasing toxicity to surrounding structures.

1.2.3.3. Moderate hypofractionation

Moderate hypofractionation at a dose of 60 Gy in 20 fractions over 4 weeks, in combination with ADT, has now been adopted as standard practice within the UK. Substantial evidence from randomised trials has confirmed this schedule to be non-inferior to conventional fractionation[48-50].

In the landmark CHHIP trial over 3,000 men were randomised between conventionally fractionated radiotherapy at a dose of 74 Gy in 37 fractions, and two moderately hypofractionated schedules of 60 Gy in 20 fractions or 57 Gy in 19 fractions[49]. Most patients had intermediate-risk disease and were on androgen deprivation therapy (ADT). In all risk groups, the 20-fraction schedule was non-inferior to conventional fractionation, but this could not be claimed for the 19-fraction schedule. The 5-year biochemical/clinical failure free rate was 88.3%, 90.6% and 85.9% for the 74 Gy, 60 Gy and 57 Gy groups, respectively. Levels of ≥ grade 2 (G2) acute GU toxicity, as defined by the Radiation Therapy Oncology Group (RTOG) toxicity scoring criteria (Appendix 3), were similar between groups occurring in 46 – 49% of patients and although the rate of ≥G2 acute GI toxicity was higher in the hypofractionated groups at 38%, compared to 25% in the conventional group (p=<0.00001), the difference had settled by 18 weeks post-radiotherapy. In addition, late ≥ G2 GI toxicity was not significantly different between groups, with a 5-year cumulative incidence of 13.7%, 11.9% and 11.3% for 74 Gy, 60 Gy and 57 Gy groups, respectively, and 5-year prevalence of 1.3 – 2.3%. The 5-year cumulative GU toxicity rate was slightly, but not significantly, higher in the 60 Gy group at 11.7%, compared to 9.1% in the 74 Gy group

and 6.6% in 57 Gy group. The rate of ≥G2 sexual symptoms was similar in all treatment arms.

The PROFIT and HYPRO trials both demonstrated no significant difference in long-term biochemical relapse-free survival (bRFS)[48,50]. In PROFIT, 1,206 intermediate-risk patients, not receiving ADT, were randomised between a higher conventional dose of 78 Gy in 39 fractions and moderately fractionated radiotherapy, 60 Gy in 20 fractions, with a bRFS of 85% in both arms[48]. In HYPRO 78 Gy in 39 fractions was compared with a higher biologically equivalent hypofractionated dose of 64.6 Gy in 19 fractions. Acute ≥G2 RTOG rectal toxicity was higher in the hypofractionated cohort at 42% compared with 31.2% (p=0.0015) but no difference was found at 3 months. There was no significant difference in late GI toxicity but the cumulative incidence of ≥grade 3 (G3) GU toxicity was significantly higher in the hypofractionated arm (19% vs 12.9%, p=0.021)[50-52].

1.2.4. SBRT in low- /intermediate- risk prostate cancer

1.2.4.1. Rationale and evidence

The favourable radiobiology of prostate cancer together with robust evidence for moderate hypofractionation provide a strong rationale for considering more profound hypofractionation in the form of SBRT. Prostate SBRT, usually delivered in 5 fractions over 1 - 2 weeks, has a clear advantage for patients in terms of treatment time compared to moderately hypofractionated radiotherapy over 4 weeks, or conventionally fractionated radiotherapy over 7.5 weeks. Given the high number of

patients with localised prostate cancer, this will have wider resource benefits and create additional treatment capacity in radiotherapy units. SBRT is now a standard treatment option for patients with low or intermediate-risk prostate cancer within the US[53]. However, in the UK, it is currently only available to NHS patients in the context of a clinical trial, pending robust evidence confirming SBRT to be, at least, as effective and well tolerated as standard treatment.

There is now a large body of published data (Appendix 1), mainly from the US, demonstrating efficacy and toxicity rates following SBRT to be comparable with standard treatment modalities in low- and intermediate-risk prostate cancer[6,54-65]. However, studies are predominantly non-randomised, with varied study methodology, making it difficult to draw valid conclusions. Many earlier studies were retrospective analyses of single-centre cohorts, and a number had a short period of median follow-up at the time of publication. Ultimately, data from randomised trials are required to effectively compare SBRT with conventional treatment.

1.2.4.2. Randomised trials

Although not strictly SBRT, the results from the HYPO-RT-PC phase III multi-centre trial provide the only long-term randomised trial data to date, demonstrating efficacy to be equivalent to conventionally fractionated radiotherapy[66]. Over 1000 patients, mainly with intermediate-risk disease (11% high-risk), were randomised between a highly hypofractionated schedule of 42.7 Gy in 7 fractions and a conventionally fractionated schedule of 78 Gy in 39 fractions, both without ADT. The 5-year bRFS rate was equal in each arm at 84%. Compared with conventional radiotherapy, there

was a higher rate of ≥G2 GU toxicity in the hypofractionated arm at the end of radiotherapy (28% versus 23% p=0.057) and at 1 year post treatment (6% versus 2%, p=0.0037), but otherwise no significant difference between arms in terms of GI or late GU toxicity.

A further four randomised trials have published early toxicity data, demonstrating acute toxicity to be at least no worse than conventionally fractionated or moderately hypofractionated radiotherapy (CFMFRT)[11,67-69]. The largest of these is the Prostate Advances in Comparative Evidence (PACE) trial which will be discussed in detail in section 1.2.4.3. In the RTOG 0938 trial, 255 low-risk patients were randomised between SBRT, 36.25 Gy in five fractions, and a hypofractionated schedule of 51.6 Gy in 12 fractions[67]. There was no significant difference in urinary, bowel or sexual quality of life (QOL) scores between arms at 1 year and low rates of physician-reported GI/GU toxicity, although only G3 toxicity was reported. The HEAT trial is currently recruiting, aiming to randomise 458 low-/intermediate-risk patients between SBRT 36.25 Gy in 5 fractions, and 70.2 Gy in 26 fractions[68,70]. Early results from 54 patients were published in abstract at 11.5 months median follow-up and did not show a significant difference in physician-reported toxicity, although there was significantly less patient-reported urinary symptoms in the SBRT arm. A smaller Hong-Kong based trial randomised 64 patients between SBRT 36.25 Gy in 5 fractions, and IMRT 78 Gy in 38 fractions, reporting similar rates of ≥G1 GU toxicity at 1 year. However, it found that the SBRT patients experienced significantly less ≥ G1 GI toxicities (SBRT vs IMRT: 64% vs 84%, p=0.041)[69].

1.2.4.3. Prostate Advances in Comparative Evidence (PACE) trial

The PACE trial is a UK-based, international, multicentre, phase III trial, sponsored by the Royal Marsden Hospital (RMH), eligible for patients with low- or favourable intermediate-risk prostate cancer[3,71]. The original study design consisted of two parallel randomisation processes as shown in Figure 1.5. PACE B has now closed to recruitment, having opened in 40 centres in the UK, Ireland and Canada. The primary endpoint is to determine whether prostate SBRT is non-inferior to CFMHRT for freedom from biochemical or clinical failure. PACE A recruitment has been slower to recruit, mainly due to limited patient acceptability of a surgery versus radiotherapy randomisation. In view of this, a protocol amendment was implemented to allow a reduction in recruitment target by changing to a quality-of-life (QOL) endpoint. PACE C has subsequently opened to include patients with intermediate- or high or high-risk disease, randomising between standard radiotherapy and SBRT, and will be discussed in section 1.2.5.2.

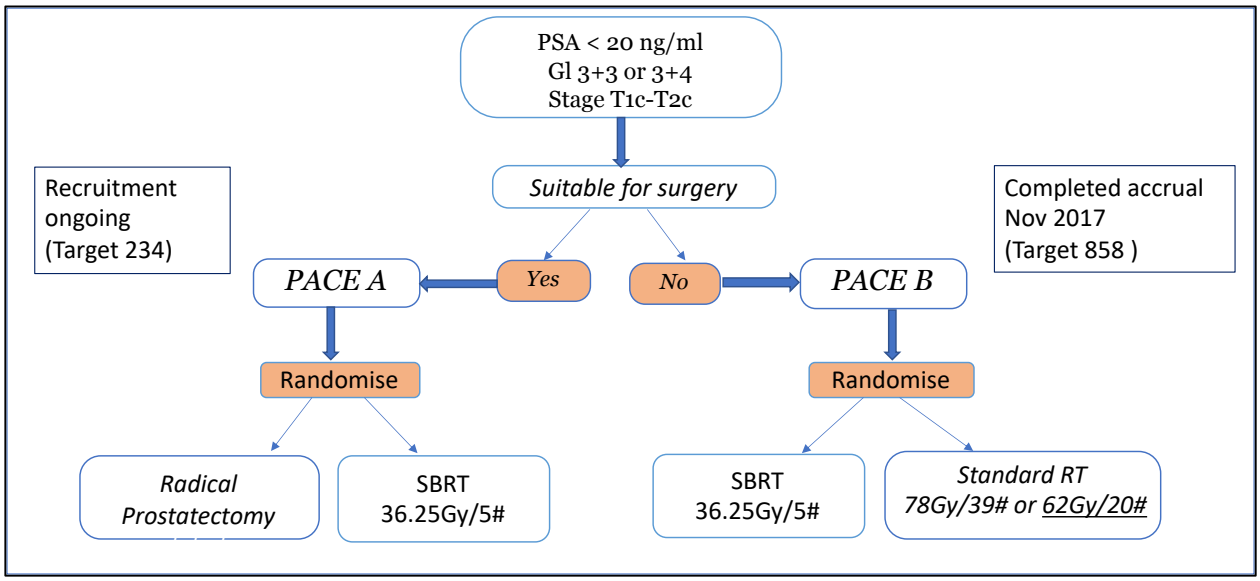
PACE A and B only include patients not receiving ADT. SBRT delivery is prescribed at a dose of 36.25 Gy in 5 fractions to the PTV, aiming to deliver 40 Gy to the CTV, using either CyberKnife or linac-based techniques. Patients in the standard arm of PACE B received either moderately hypofractionated radiotherapy, 62 Gy in 20 fractions or conventionally fractionated 78 Gy in 39 fractions[3].

Acute toxicity results from PACE B have been published by Brand et al, including 874 patients with a median follow-up of 12 weeks[11]. Intermediate-risk patients made up most of the cohort (91% CFMHRT and 93% SBRT). Acute RTOG ≥G2 GU toxicity was

demonstrated in 23% of SBRT patients compared with 27% of CFMHRT patients, and 10% developed ≥G2 GI toxicity in the SBRT arm compared to 12% in the CFMHRT arm, with no statistically significant difference. These initial results confirm that prostate SBRT compares favourably in terms of toxicities with conventional radiotherapy in the 3 months following treatment.

Within the PACE B SBRT arm, 41% of patients were treated on CyberKnife versus 59% with gantry-based SBRT. Notably, significantly less ≥G2 GU toxicity (12% vs 31%, $p<0.0001$) was recorded in the CyberKnife group. The RTOG 0938 trial in which 78.5% were treated with gantry-based SBRTand 21.5% on CyberKnife reported no significant difference in QOL measures between platforms, although this study may not have been sufficiently powered to detect such a difference. Longer-term data will, therefore, be highly informative, since at, present, there is no evidence confirming superiority of either technique.

Figure 1.5. Trial schema for PACE A and PACE B



Schema demonstrating the eligibility and randomisation arms for PACE A and PACE B trials. PSA, prostate specific antigen; Gl, Gleason score; T, tumour; SBRT, stereotactic body radiation therapy; RT, radiotherapy; #, fractions.

1.2.4.4. Non-randomised multi-institutional trials

Until randomised trial data matures, the evidence for SBRT in low-/intermediate risk prostate cancer is predominantly based on results from two multi-centre prospective trials, together with a large metanalysis and pooled data analyses which include multiple single-centre prospective studies[6-10].

The largest multi-centre prospective trial was led by Meier et al and involved over 300 low-/ intermediate-risk patients[6]. All patients were treated without ADT and received SBRT using CyberKnife at a dose of 35.25 Gy in 5 fractions, aiming to deliver 40 Gy to the clinical target volume (CTV). This same treatment technique has been adopted within PACE B and the results of this trial, therefore, provide a useful comparison. At 61 months median follow-up, a high biochemical progression-free survival (bPFS) rate of 97% was reported in both risk groups. In addition, toxicity rates (as defined by the Common Terminology Criteria for Adverse Events (CTCAE)) were remarkably low, with no cases of ≥G3 acute toxicity and acute G2 GU and GI toxicity rates of 26% and 8%, respectively. With regards to late toxicity, worst reported GU toxicity of G2 occurred in 12% and G3 in 2% of patients, and very low rates of G2 GI toxicity were reported in only 2% of cases.

A higher biological dose of 38 Gy in 4 fractions was delivered by Fuller et al, in a multicentre trial involving 259 patients from 18 centres[7]. Patients were treated on CyberKnife, and a heterogeneous technique was used for planning, aiming to emulate high-dose rate (HDR) brachytherapy. The 5-year freedom from biochemical recurrence (FFBR) rates were 100% for low-risk, and 88.5% for intermediate-risk

patients. Further separating the intermediate-risk patients into favourable and unfavourable intermediate-risk (Table 1.1), 5-year FFBR rates of 90.7% and 81.0%, were demonstrated. This differentiation is useful in terms of comparison with PACE B which excludes patients with unfavourable intermediate-risk disease. In terms of toxicity, acceptable rates of CTCAE acute ≥G2 GU toxicity of 36.2% and ≥G2 GI toxicity of 6.9% were reported. The cumulative 5-year late G2 GI toxicity was low at 3.4% with no ≥G3 toxicity and the ≥G2 GU toxicity rate of 14.7% is comparable with the results from both Meier et al[6] and the CHHIP trial[49], although one patient with G4 toxicity required cystoprostatectomy for cystourethritis.

A recent metanalysis by Jackson et al included over 6,000 patients from 38 prospective trials[10]. The median follow-up period was 39 months and 23% of patients had been followed-up for at least 5 years. Intermediate-risk patients made up 92% of the total study population and 15% of patients received ADT. Although dose and fractionation varied, the most common prescription dose used was 36.25 Gy in 5 fractions, with dose per fraction ranging from 5 – 10 Gy and number of fractions ranging from 4 – 9. Fourteen studies reported 5-year bRFS, with an overall bRFS of 95.3%. Toxicity was reported in 37 studies, including 32 studies reporting cumulative incidence using either RTOG or CTCAE criteria: acute ≥G2 acute GU and GI toxicity rates were 16% (0.5% ≥ G3) and 6.2% (0.09% ≥ G3), respectively; and late ≥ G2 GU and GI toxicity rates were 13% (0.94% ≥ G3) and 5.4% (0.48% ≥ G3), respectively. These results are encouraging and in keeping with the studies described above, although they do not capture the full variation in results from individual studies.

A pooled analysis of 8 separate prospective trials was published in 2013 by King et al[8]. This included 1,100 patients with a median follow-up of 36 months, of which 88% had low-risk (58%) or intermediate-risk (30%) disease. Patients received SBRT with CyberKnife, at a median dose 36.25 Gy in 5 fractions (range 35 – 40 Gy in 4-5 fractions), and 14% were treated in addition to ADT. Five-year biochemical disease-free survival (bDFS) was 93% for all patients, and 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively.

A later analysis of 10 prospective trials, by Kishan et al provides even longer-term efficacy data, with a median follow-up period of 6.9 years[9]. This analysis included 2,142 patients solely with low- and intermediate- risk disease, and only 5.4% of patients received ADT. Treatment technique varied between CyberKnife or gantry-based platforms and dose fractionation ranging between 33.5 Gy – 40 Gy in 4 -5 fractions. At 5 years the estimated 5-year bRFS was 92.2% and 88.4% for low- and intermediate–risk patients, respectively, and 7-year bRFS 87.2% and 82.4%, respectively. This indicates that SBRT is likely to achieve rates of long-term disease control at least in keeping with more conventional treatment for prostate cancer. No significant association between bRFS and SBRT dose or use of ADT was found.

In conclusion, although there is a now a large volume of data, long-term results from the PACE B are essential before SBRT could be considered standard treatment for patients with low- or intermediate-risk prostate cancer within the UK. In the meantime, these studies provide a useful means of comparison and are further discussed chapter 2 with reference to my results.

1.2.4.5. UK experience

Experience of SBRT in the UK is less established, but rapidly growing. The initial cohort of patients were treated with CyberKnife, 36.35 Gy in 5 fractions, on consecutive or alternate days, at the Royal Marsden (RMH) and Mount Vernon hospitals. Prospective data was most recently published at 2.5 years median follow up[72,73]. Of the 81 patients, 94% had low- or intermediate risk disease. Rates of RTOG acute ≥G2 GU and GI toxicity occurred in 30% and 22% of patients respectively. Late ≥ G2 GU and GI toxicity occurred in 11% and 10% of patients, with grade 3 GU and GI toxicity occurring in 2% and 1%, respectively. In chapter 2 prospective efficacy and toxicity results from the RMH cohort at approximately 5 years median follow-up will be evaluated and, to my knowledge, provide the longest follow-up data of prostate SBRT within the UK.

1.2.5. SBRT in high-risk prostate cancer

1.2.5.1. Rationale

The evidence for SBRT in high-risk prostate cancer is much more limited, although in theory, hypofractionation could be even more advantageous in this group by enabling further dose escalation, in combination with ADT. Concerns about achieving adequate coverage, given the higher risk of disease outside the prostate balanced with the potential increased toxicity, may have deterred development of SBRT in this group.

1.2.5.2. Evidence

There is minimal evidence demonstrating efficacy of SBRT in high-risk prostate cancer. Recruitment is ongoing to the PACE C trial, which opened in 2019, comparing SBRT with moderately hypofractioned radiotherapy in patients with intermediate- or high-risk localised prostate cancer (excluding patients with T3b/ T4 disease, Gleason ≥ 4+5, or PSA ≥30). Patients are randomised between SBRT, 36.25 Gy in 5 fractions, and moderately hypofractionated radiotherapy, 60 Gy in 20 fractions[74]. The selected dose for the standard arm is 60 Gy rather than 62 Gy (as used in PACE B) since patients are treated with ADT and based on the PROFIT trial results demonstrating 60 Gy in 20 fractions to be equivalent to 78 Gy in 39 fractions in terms of disease control[48]. A further identified multi-centre trial, ASSERT is now closed to accrual and results are awaited. In this trial SBRT, 36.25 Gy in 5 fractions, is compared with a more conventionally fractionated schedule of 73.68 Gy in 28 fractions, in intermediate-/ high-risk patients but results[75].

As demonstrated in Appendix 1, a number of studies include a small percentage of high-risk patients within a mixed cohort[64,76,77]. For example, the pooled multi-institutional analysis, by King et al, included 11% high-risk patients and demonstrated encouraging results with a 5-year bPFS of 81% in this group[8]. In some trials, including the HYPO-RT-PC randomised trial, in which 11% high-risk patients were also included, separate biochemical control and toxicity rates were not reported for each risk group[66]. However, no significant interaction was found between failure-free survival and clinical factors including Gleason score, T stage, PSA, and risk group.

A retrospective study of 213 patients, by Vuolukka et al, included 52% high-risk patients[76]. At 64 months median follow-up, the bRFS for the high-risk group was 80% compared to 100%, and 87.5 % for patients with low- and intermediate-risk disease, respectively (p=0.004). In patients with Gleason score ≥8, the bRFS rate was 66.7% compared with 92.5% and 84.2% for those with Gleason score 6 and 7, respectively (p = 0.001). The study with the longest follow-up which also includes high-risk patients is a retrospective study by Katz et al involving 515 patients treated with SBRT, 35 – 36.25 Gy in 5 fractions[77]. The 38 patients with high-risk disease had an 8-year disease-free survival of 65% compared to 93.6% and 84.3% for low- and intermediate-risk patients, respectively. Gleason score was the only significant factor associated with biochemical failure, and no impact from radiation dose or ADT found.

The largest trial specifically evaluating efficacy and safety of SBRT in the high-risk group is a multicentre phase II trial led by King et al, aiming to recruit 220 patients[78]. SBRT is delivered to the prostate at a dose of 40 Gy in 5 fractions over 2 weeks, with concomitant ADT and SBRT to the pelvis (25 Gy in 5 fractions), given at the discretion of the treating clinician. Preliminary results from 73 patients have been published in abstract form, at a median follow up of 13.8 months[79]. Sixty three percent received ADT and 32% received nodal irradiation. Overall, treatment was well tolerated with no grade 3 toxicity and 2.7% biochemical failure but longer follow up is required to evaluate the efficacy of treatment.

1.2.6. Considerations in the management of high-risk patients with prostate SBRT

There are a number of factors relevant to the expansion of SBRT in high-risk prostate cancer which need to be considered.

1.2.6.1. Androgen deprivation therapy

At least a short course of neoadjuvant and concomitant androgen deprivation therapy (ADT) is often given as standard treatment alongside conventional radiotherapy. However, evidence in low- and favourable intermediate-risk patients is unconvincing, particularly now in the context of dose-escalated radiotherapy[80,81]. Consequently, many of the current prospective SBRT trials, such as PACE A and B, do not include ADT. In the pooled analysis by King et al, the use of ADT was relatively low, given in 14% of the total population and in 38% of the high-risk group[8]. Fifteen percent of patients included in meta-analysis by Jackson et al were on ADT but this was not found to be significantly associated with bRFS[10].

Zelefsky et al have completed recruitment to a multicentre phase III randomised trial, comparing SBRT alone or in combination with ADT in intermediate-risk patients (radiological T3a disease not excluded)[82]. SBRT, 40Gy in 5 fractions was given with or without 6 months of Degaralix. The results of this trial will be of considerable value, with the primary outcome to determine the number of patients with a positive biopsy at a planned time point of 24 – 30 months following SBRT.

In high-risk prostate cancer, the evidence for ADT in combination with high-dose radiotherapy is greater, as demonstrated by results from the DART trial, supporting the use of long-term ADT in these patients[83]. Where specified, ADT is often administered in SBRT trials for high-risk patients, either as mandated or at the discretion of the treating clinician. In PACE C, all patients receive at least 6 months of ADT, and in ASSERT, ADT was given alongside SBRT for 6 months and 18 months in intermediate- and high-risk patients, respectively[75]. In the retrospective trial by Vuolukka et al, which included 110 high-risk patients, 88% of patients in the high-risk group received ADT, compared to 28% and 48% of patients in the low- and intermediate-risk groups, respectively[76]. ADT administration was found to significantly correlate with biochemical control, with a bRFS of 96.1 % in those receiving ADT compared to 81% in those treated with SBRT alone ($p = 0.003$). The duration of ADT varied substantially, with 41.8% of those high-risk group receiving 24 months or longer.

1.2.6.2. Dose and fractionation

The prostate SBRT dose used in published studies ranges between 33.5 Gy and 50 Gy in 4 or 5 fractions, but 36.25 Gy in 5 fractions is most commonly prescribed. Zelefsky et al demonstrated that doses ranging from 32.5 to 40 Gy in 5 fractions were well tolerated, in patients with low-/ intermediate-risk prostate cancer[84]. There was no severe urinary or rectal toxicity reported, and no significant difference in the incidence of acute and late G2 toxicity was detected between the 4 dose levels (32.5 Gy, 35 Gy, 37.5 Gy and 40 Gy). The higher doses were found to be associated with a lower incidence of a positive biopsy at 2 years post treatment and improved biochemical

control with a 5-year biochemical recurrence rate of 15% and 6% following 32.5 Gy, and 35 Gy, respectively but no recurrence in the 37.5 Gy and 40 Gy groups.

Dose escalation has been shown to improve biochemical disease-free survival and delays the need for systemic therapy following conventionally fractionated radiotherapy[38-41]. Pollack et al demonstrated lower rates of biochemical failure and distant metastases in patients with intermediate- and high-risk prostate cancer receiving 78 Gy, compared to 70 Gy in 2 Gy fractions[41]. Retrospective data by Zelefsky et al, suggest that doses as high as 86.4 Gy are associated with improved outcomes in high-risk patient, even in combination with hormones[40]. However, any benefit from dose escalation has to be weighed against the increased risk of toxicity[38,39].

Further dose escalation in SBRT has been evaluated in low-/intermediate-risk patients. The Timmerman group completed a dose escalation study, delivering SBRT up to a dose of 50 Gy in 5 fractions: however, a significant increase in high-grade toxicity was recorded at this level[85,86]. Of the 62 patients in total who received 50 Gy, 6.5% developed ≥G3 GU toxicity and 9.9% developed ≥G3 GI toxicity, including 5 patients who required a colostomy. Potters et al treated 26 patients at 3 dose levels, 40Gy, 45Gy and 50 Gy, in 5 fractions[87]. At a median of 67.2 months follow-up (3 years in the 50 Gy cohort), the PSA nadir was significantly lower following 45 Gy and 50 Gy, with biochemical failure occurring only in 2 patients treated with 40 Gy. No statistically significant difference in toxicity was detected between the groups, although higher rates of late ≥G2 GU and GI toxicity were recorded in patients receiving 50 Gy group.

Given the increased toxicity risk, the argument for further dose escalation in unconvincing, at least in lower risk patients. Even assuming a conservative α/β value of 2, an SBRT dose of 36.25 Gy in 5 fractions has a biologically effective dose (BED) of 168 Gy, which is higher than conventional fractionated radiotherapy, 78 Gy in 39 fractions (BED 156 Gy), yet slightly lower in terms of late rectal toxicity (124 Gy versus 130 Gy, α/β of 3). However, increasing the dose to 50 Gy in 5 fractions markedly increases the tumour BED to 305 Gy but at the cost of increasing normal tissue BED to 216 Gy hence increasing the risk of significant rectal toxicity.

The use of heterogeneous planning techniques can enable dose to be escalated in areas not adjacent to sensitive structures. In the PACE trial and the multi-centre trial by Meier et al, SBRT plans aim to cover at least 95% of the PTV with the 36.25 Gy prescription dose, while delivering 40 Gy to at least 95% of the CTV[6,11]. Stephans et al, employed a technique aiming to deliver 50 Gy in 5 fractions to a high-dose PTV (HDPTV) which included PTV > 3mm from either urethra, bladder, or rectum; and 36.25 Gy in 5 fractions to the remaining low-dose PTV (LDPTV)[88,89]. Outcomes from 35 patients, including 18 with high-risk disease, have been published at 46 months median follow-up, demonstrating a 3-year FFBF rate of 88%[90]. Treatment was tolerated well, aside from one patient who suffered G4 GU and GI toxicity due to a prostatic infection, although did have other risk factors including uncontrolled diabetes and very large prostate of > 200 cc.

1.2.6.3. Simultaneous integrated boost

Dose-escalation, limited to sites of disease within the prostate, may improve efficacy particularly in high-risk patients, while minimising toxicity. There is evidence from retrospective studies that local recurrence following radiotherapy most often occurs at the site of the dominant tumour[91,92]. The FLAME phase III randomised trial investigated the benefit of combining conventionally fractionated radiotherapy, 77 Gy in 35 fractions to the prostate, with an integrated boost of up to 95 Gy to MRI-defined tumour, in patients with intermediate-/ high-risk prostate cancer[93]. The 5-year bRFS rate has recently been reported which was significantly higher in the focal boost arm at 92% compared to 85% in the standard arm, without worsening toxicity or quality of life[94].

A number of SBRT studies are therefore investigating the use of a simultaneous integrated boost (SIB) to dominant intraprostatic lesions (DIL), as defined on imaging[95]. The largest of these is the Hypo-FLAME trial, in which 100 intermediate-/ high-risk patients received prostate SBRT, 35 Gy in 5 weekly fractions, with an SIB up to 50 Gy (median dose 44.7 Gy). No acute ≥G3 toxicity was demonstrated and acceptable rates of G2 GU and GI toxicity in 34% and 5% of patients, respectively, was observed[96].

Morris et al, have reported acceptable rates of acute toxicity, combining a urethral-sparing and SIB technique in 44 low-/intermediate risk patients[97]. Forty Gy in 5 fractions was delivered to the prostate, 36.25 Gy to urethra, anterior rectal wall and bladder base and a SIB of 42.5 Gy – 45 Gy to MRI-defined DIL. Similarly, the RMH-

based SPARC trial aims to deliver 36.25 Gy in 5 fractions to the PTV with a SIB of up to 47.5Gy in 5 fractions, in high-risk patients[98]. In 8 patients, a D95% >47.5 Gy to the DIL was achieved in 37.5% of plans. The rate of ≥G2 acute GI toxicity was relatively high at 37.5%, but no ≥G2 late GI events occurred. Herrara et al increased the SIB dose up to a maximum of 50 Gy in a phase I dose escalation study. The maximum tolerated dose (MTD) was not reached following treatment of 9 patients and a further 11 patients received 50 Gy SIB, with acceptable rates of acute toxicity[99].

1.2.6.4. Overall treatment time and fractionation

SBRT is often delivered over consecutive days or over longer periods of time, from alternate day treatments to once weekly fractions. There is no conclusive evidence of significant detriment by treating over consecutive days. Within the PACE trial, either consecutive or alternate day fractionation is permitted and results from the first UK cohort, reported by Henderson et al, showed no significant difference in grade 2 acute toxicity rates between alternate day and daily fractionation[73]. King et al demonstrated significantly lower rates of late G1/2 GU and GI toxicity of 17% and 5%, respectively, in patients treated with alternate day fractionation, compared to 56% and 44%, respectively, for patients treated over consecutive days[54]. However, there was no significant difference in G3 toxicity, and median follow-up was short at 2.7 years.

The Canadian-based, PATRIOT trial randomised 152 patients to receive prostate SBRT, 40 Gy in 5 fractions, either over 11 days or 29 days[100]. Results at 13.1 months median follow-up, demonstrated the 29-day arm to be superior in terms of patient-reported acute bowel and urinary toxicity, although no significant difference in late

toxicity was found between the two schedules. A similar European trial demonstrated no difference in toxicity or QOL measures at 18 months follow-up between patients receiving SBRT with 36.25 Gy in 5 fractions, on alternate days, compared to a weekly schedule[101].

The evidence confirming the benefit of hypofractionation in prostate cancer, combined with a greater understanding of the radiobiology and potential high sensitivity to larger fraction size, has led to the investigation of more extreme hypofractionation. In the setting of high-dose-rate brachytherapy (HDR-BT), Hoskin et al demonstrated acceptable rates of biochemical control and side effects at 3 years post treatment, after delivering either 3 fractions of 10.5 Gy or 2 fractions of 13 Gy[102]. They also demonstrated acceptable levels of toxicity after single dose HDR-BT, although did note higher rates of urinary toxicity compared to a 2-fraction schedule and in those patients treated with 20 Gy compared to a 19 Gy single-fraction[103].

The eHYPO trial are evaluating 3-fraction SBRT at a dose of 40 Gy in 3 fractions, with maximum urethral dose of 33 Gy, on alternate days[104]. Early results from 59 patients demonstrated low levels of acute toxicity[105]. The 2STAR trial includes 30 low-/intermediate-risk patients delivering SBRT, 26 Gy in 2 weekly fractions. At median follow-up of 49.3 months, biochemical failure was reported in 5.2% of patients. No acute G3 toxicity was reported, with acute ≥G2 GU and GI toxicity occuring in 40% and 3.3%. Late ≥G2 GU and GI toxicity occurred in 43.3% and 13.3%, respectively with G3 toxicity in 2 patients[106].

Single-fraction SBRT is being assessed in a randomised trial, PROSINT, by Greco et al[107]. Patients are randomised between SBRT either with 45 Gy in 5 fractions or a 24 Gy single fraction. The primary aim is to determine toxicity up to 5 years post treatment, and to evaluate physiological changes on post-treatment MRI and pathologic response on biopsy at 2 years follow-up. ONE-SHOT is a single–arm trial, in which a similar technique is employed delivering 19 Gy in one fraction to the prostate/ pSV, and a lower dose of 17 Gy to a urethral planning risk volume (PRV)[108]. Early results have demonstrated the feasibility of this technique in 6 patients although 50% developed acute G2 GU toxicity.

In conclusion, pending long-term results from the aforementioned trials, there is not sufficient evidence to recommend further dose-escalation in SBRT even for high-risk prostate cancer. Therefore, for the planning studies in chapter 4 I have continued to use a prescription dose of 36.25 Gy in 5 fractions.

1.2.6.5. Clinical target volume

The accuracy of clinical target volume (CTV) delineation is particularly vital in SBRT given the high-level precision techniques involved in the planning and treatment process. The risk of geographical miss is greater in view of the smaller margins and steep dose gradient. As with conventional radiotherapy, the CTV in prostate SBRT includes the whole prostate gland and a varying proportion of the seminal vesicles (SV), depending on the clinical risk of SV involvement (SVI).

The clinical treatment volume differs between and within SBRT studies. Some include the prostate alone and others include the prostate and either the proximal (pSV) or full extent of the SVs. In the PACE trial, CTV delineation is aided by using a planning MRI, fused with the planning CT. In PACE A and B, the CTV for low-risk patients consists of the prostate alone and, for intermediate-risk patients, the prostate in addition to the proximal 1cm of the SVs are included[11]. In PACE C, the proximal 2cm of the SVs are included in the CTV[74].

1.2.6.6. Seminal vesicle irradiation

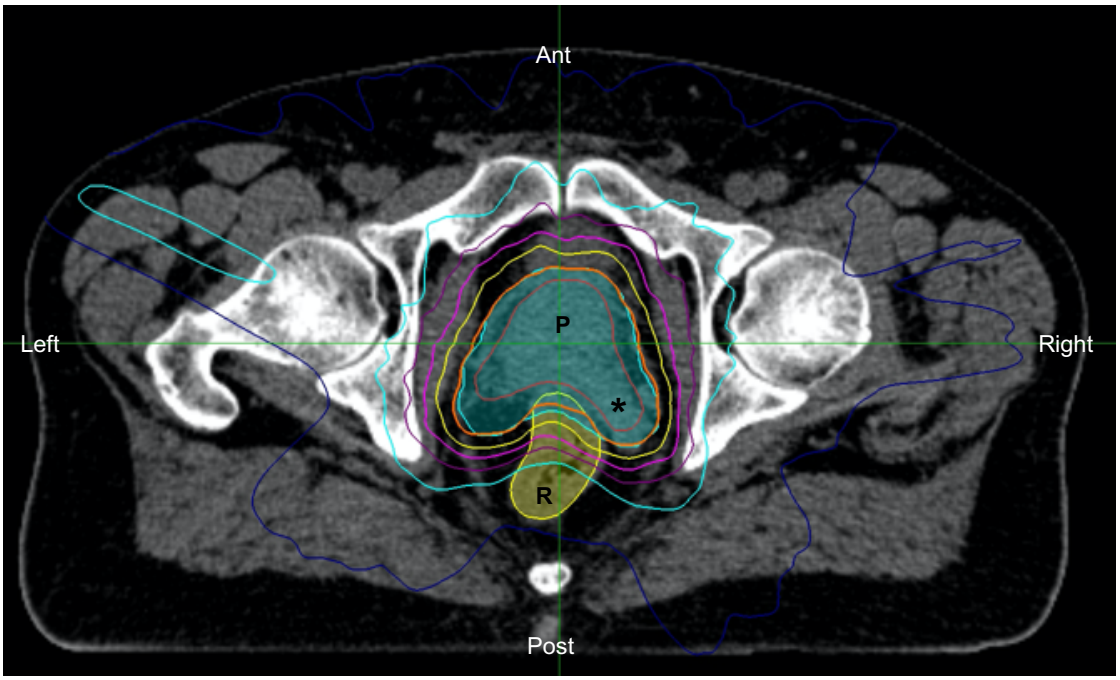
Seminal vesicle involvement (SVI) is a poor prognostic indicator in prostate cancer and, therefore, at least a proportion of the seminal vesicles (SV) are often included in the CTV for prostate radiotherapy. The SV function is to produce the majority of male ejaculate, joining with the vas deferens to form the ejaculatory duct, opening in the prostatic urethra[109]. They consist of long coiled tubes which lie superiorly and posteriorly to the prostate gland in close proximity to the bladder and rectum and often curve around the anterior rectal wall.

These aspects of SV anatomy create a particular challenge for radiotherapy planning (Figure 1.6) since their inclusion results in further posterior-lateral expansion of the target volume, potentially contributing to increased rectal dose and toxicity[15,16]. Studies of patients receiving conformal radiotherapy demonstrated that exclusion of SVs from the target volume led to a significant reduction in rectal dose as well as bladder and femoral head dose to a smaller degree[110]. For example, in the series by

Diaz et al, 20% of the rectal volume received >86% of the total dose in conformal plans where SV were included, compared to 68% when the SVs were excluded[16].

Historically, overcautious SV irradiation may have taken place due to the inadequacy of SVI detection on standard imaging. Prediction has improved over time with the availability PSA and Gleason score together with Partin's tables and Roach formula; and more recently the development of higher quality imaging with multiparametric MRI (mpMRI)[16,111]. SVI incidence has decreased with the increasing use of PSA testing, as shown in a study of 18,505 patients from a radical prostatectomy (RP) database. In patients diagnosed in the more recent PSA period (2001 – 2011), 3.9% had confirmed SVI, compared with 12.7% of patients pre-PSA availability[112]. In a retrospective review of 527 patients having RP between 2012 – 2015, 10% were found to have SVI on histopathology. Sensitivity for SVI detection was confirmed to be 75.9 –85.4% with pre-operative mpMRI, depending on the experience of the radiologist[113]. In another retrospective review of 159 RP patients with pathologic T3b disease, 32.7% were predicted to have SVI on preoperative mpMRI. The rate of biochemical recurrence was higher in those with radiologically diagnosed SVI in 38.5% of cases compared to 23.4% of cases in those with no SVI on imaging[114].

Figure 1.6: Cyberknife plan demonstrating right seminal vesicle wrapping around the rectum



Axial slice from a CyberKnife plan demonstrating the right seminal vesicle curving around the rectal wall as indicated by the black star. Ant, anterior; Post, posterior; P, prostate; R, rectum. Clinical target volume (CTV) is the red line and planning target volume (PTV) in cyan. Isodose lines are demonstrated surrounding the PTV: prescription isodose (orange); 60% isodose (yellow); 50% isodose (magenta); 40% isodose (purple); 30% isodose (cyan); 20% isodose (blue).

These results do not support the avoidance of SV irradiation in all patients with no evidence of involvement on mpMRI, although could be considered in selected patients. Prostate irradiation alone has not been shown to deliver an SV dose considered adequate for microscopic disease control. Parker et al treated 25 patients with conformal radiotherapy at a dose of 75.6 Gy in 42 daily fractions, including the prostate gland alone as the CTV, with a PTV margin of 10 mm/ 7 mm posteriorly[115]. Dose volume histograms (DVH) were calculated for the full SVs, and for separate 6mm SV segments divided through the axial plane, demonstrating that even the most proximal 6mm SV received a dose of less than 50 Gy in approximately 30% of patients.

The rate of SVI in low-risk patients has been reported to be less than 2%, and it is therefore reasonable to omit SV irradiation in such cases[116]. However, patients with intermediate- or high-risk disease, with one or more risk factors (PSA >10; Gleason ≥7; >T2a; or percentage of positive biopsy >50), are at greater risk of SVI and, therefore, at least a proportion of SVs are often included in the CTV[15]. The extent of SV that should be included remains relatively contentious. Pathological studies have suggested the median length of SV involvement to be around 1 cm, as measured from the prostatic insertion point[117,118]. Kestin et al demonstrated >1 cm SV involvement in 7%, and >2 cm in 1%, of all patients, including 4% of high-risk patients[117].

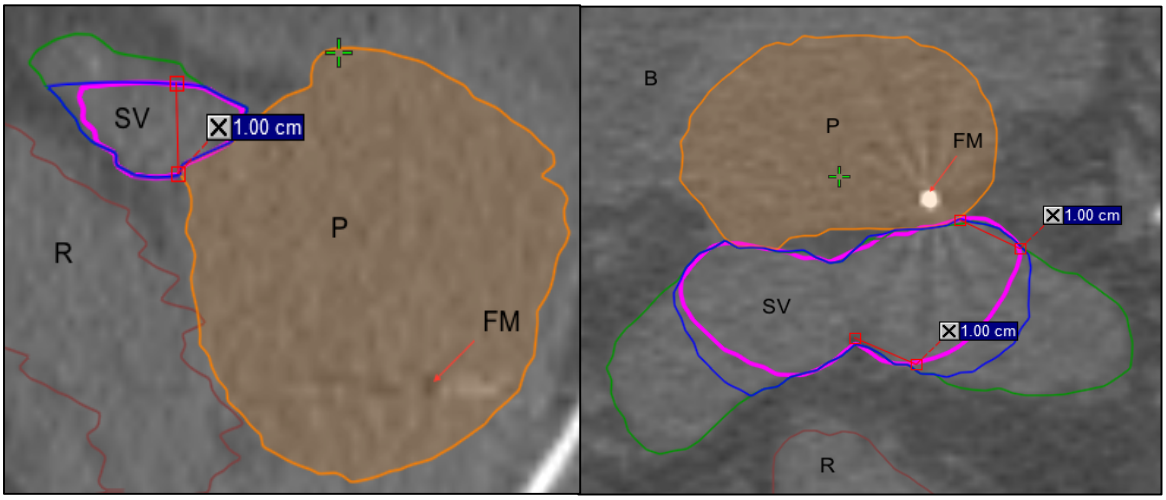
Based on these data, guidelines by the European Organisation for Research and Treatment of Cancer (EORTC) recommend inclusion of 1 cm SV for intermediate-risk, and 2 cm for high-risk patients, as measured vertically from the SV insertion point (Figure 1.7)[119]. The Radiation Therapy Oncology Group (RTOG) intensity modulated radiotherapy (IMRT) trial RTOG0815 protocol includes 1 cm pSV for intermediate risk

patients, measured both vertically and radially (Figure 1.7) which is similar to the definition used within PACE B[120].

Qi et al demonstrated that these methods may not accurately represent the true anatomical pSV (Figure 1.8)[14]. Using reconstructed CT imaging to measure along the central SV axis in 114 patients, they found that the EORTC and RTOG methods inadequately covered the “anatomical” 1 cm pSV in 62.3% and 71.0%, respectively, while the EORTC method inadequately covered the anatomic 2 cm pSV in 17.5% of cases. There is clearly a lack of consensus on the method of pSV delieation and, therefore, the aim of the latter part of chapter 3 is to develop a reproducible method for pSV delineation to improve outlining consistency in clinical practice and for use in multicentre trials such as PACE.

The evidence indicates that the CTV for SBRT in high-risk patients should include at least 2 cm SV, however as discussed this will have implications in terms of planning, with the risk of increased toxicity. Therefore, in the PACE C trial, separate dose levels are employed. In the SBRT arm, the prostate and 1cm pSV remain within the high dose PTV, receiving 36.25 Gy in 5 fractions, with 40 Gy to CTV as per PACE B; while the prostate and 2cm pSV are included within a lower dose PTV receiving 30 Gy in 5 fractions[82]. In the standard arm 60 Gy in 20 fractions is delivered to the high-dose PTV and 47 Gy in 20 fractions to the low-dose PTV. This is based on the CHHIP trial in which a three dose-level approach (Table 1.2)[121]. The lower PTV dose is the dose considered to be sufficient for treating microscopic disease and is equivalent to the dose recommended for salvage radiotherapy to the prostate bed (using α/β of 1.8)[122].

Figure 1.7: Examples of proximal seminal vesicle (pSV) contouring as defined by EORTC and RTOG guidelines.



Sagittal (left) and axial (right) slices from a CT planning scan, demonstrating the 1 cm proximal seminal (pSV) by the European Organisation for Research and Treatment of Cancer (EORTC) guidelines[119] (blue) and Radiation Therapy Oncology Group (RTOG0815) intensity modulated radiotherapy (IMRT) trial protocol[120] (magenta). The red rulers indicate the proximal 1 cm seminal vesicles (SV) measured from the prostatic insertion point. SV, seminal vesicles; P, prostate; B, bladder; R, rectum; FM, fiducial marker.

Figure 1.8: Disparity between reconstructed anatomically defined proximal seminal vesicles and trial protocol delineation methods.

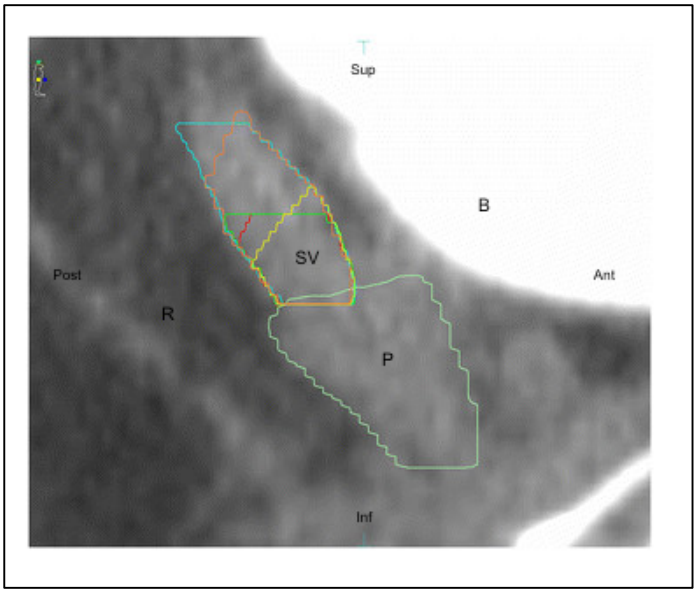


Illustration taken from Qi et al[14]. A sagittal CT slice demonstrating the disparity between their CT reconstructed "anatomic" pSVs, and the pSV contours delineated using EORTC and RTOG methods. Anatomical pSV 1 cm (yellow), 2 cm (orange); EORTC 1 cm (green), 2cm (blue); RTOG 1 cm (red). There is a portion of SV missed anteriorly by the EORTC and RTOG methods and excess SV included posteriorly. Annotations added: Sup, superior; Inf, inferior; Post, posterior; Ant, anterior; P, prostate; SV, seminal vesicle; B, bladder; R, rectum.

Table 1.2: The three-dose level technique used in the CHHIP trial.

Dose Level	**1**	**2**	**3**
CTV	Prostate/pSV + 0.5 cm in LR/IR (Prostate/SV + 0.5 cm in HR)	Prostate + 0.5 cm	Prostate
PTV	CTV + 5mm	CTV + 5 mm/0 mm	CTV + 5 mm/0 mm
Dose	48 Gy/ 20 fractions	57.6 Gy/ 20 fractions	60 Gy/ 20 fractions

Table summarising the three dose levels used within the moderately fractionated arm (60 Gy in 20 fractions) of the CHHIP trial. CTV, clinical target volume; PTV, planning target volume; pSV, proximal seminal vesicles; SV, seminal vesicles; LR, low-risk; IR, intermediate-risk; HR, high-risk.

A pre-trial SBRT planning study, evaluated the feasibility of such an approach within PACE C[123]. Using the dose levels described in the previous paragraph, 5 PACE B patients were retrospectively planned for SBRT with VMAT, achieving a mean coverage of >95% for all dose levels. Two out of five plans met all dose constraints, and the others were acceptable within the allowable dose variations. However, in one case the distal SV PTV dose had to be compromised due to bowel proximity.

This approach would not be suitable for patients with macroscopic SV involvement (stage T3b), in which such a dose reduction would be insufficient. There is limited evidence regarding the optimal approach for managing T3b disease. A multi-institutional retrospective analysis of 276 patients with T3b disease, concluded that dose-escalation with conventionally fractionated IMRT, up to a median of 76 Gy (range 70 – 80 Gy) to the involved SV could be achieved while respecting OAR dose constraints in over 85% of cases[124]. In 64% of patients only the proximal 1/3 had SVI, whilst in 20% there was involvement of the proximal 2/3 and 16% involvement of the

full SV 41% had bilateral involvement to some extent. In this series, 26% of patients also had pelvic lymph node involvement on MRI and 90% of all cases received pelvic radiotherapy. The predicted 5-year risk of biochemical/ clinical recurrence was reported 24.8%, although median follow-up was short at 26 months, and patients received a median of 36 months ADT. The number of involved pelvic lymph nodes was the only significant prognostic factor in terms of recurrence and late GI toxicity, while dose to the non-involved SVs was the only significant predictor of acute GI toxicity.

1.2.6.7. Pelvic irradiation

Prophylactic pelvic node irradiation is often considered in patients with high- or very high-risk prostate cancer, since they are at higher risk of harbouring micro-metastatic disease within the pelvis. However, there is currently no conclusive evidence confirming a benefit in terms of disease survival, but some evidence of an association with increased risk of bowel toxicity[125,126]. In a more recent randomised trial (POP-RT) by Murthy et al improved 5-year biochemical failure- and disease-free survival were demonstrated following from the addition of prophylactic pelvic radiotherapy (50 Gy in 25 fractions), but no difference in overall survival[127]. Although ≥G2 late GI toxicity was higher (8.2% versus 4.5%), the difference was not statistically significant, however there was significantly higher late GU toxicity with pelvic radiotherapy (20% versus 8.9%).

In the PIVOTAL trial, 124 high-risk patients were randomised between prostate-only IMRT with 74 Gy in 37 fractions; and prostate and pelvic lymph node IMRT, with 74

Gy in 37 fractions to the prostate, and 60 Gy in 37 fractions to pelvis[128]. At 37.6 months median follow-up, the largest difference in ≥G2 GI toxicity was reported at 6 weeks follow-up, occurring in 26% of those receiving pelvic radiotherapy, and 7% in those receiving prostate radiotherapy alone. At 2 years, the cumulative ≥G2 GI toxicity rate was 24% for the prostate and pelvis group, compared to 16.9% in the prostate only group, with no significant difference in bladder toxicity between the groups.

A dose escalation IMRT study demonstrated that escalating the pelvic dose from 50 Gy to 60 Gy in in 37 fractions was acceptable in terms of toxicity and reported an overall 5-year biochemical/ clinical failure free rate of 71%, which was significantly higher in the 60 Gy group at 70%, compared to 38% in 50 Gy group[129]. In addition, two moderately hypofractionated schedules, delivering 47 Gy to the pelvis in 20 fractions, over either 4 or 5 weeks, achieved comparably high 5-year biochemical control rates of 80% for the 4-week, and 78% for the 5-week schedule. The 4-week schedule was associated with the highest rates of acute toxicity, reporting 66% ≥G2 GI and 61% ≥ G2 GU toxicity, however symptoms settled by 18 weeks post-treatment, and both schedules were associated with acceptable levels of late toxicity. PIVOTALboost is a four-arm randomised trial which is currently investigating the benefit of prophylactic pelvic radiotherapy and/or a focal high-dose intraprostatic boost in patients with higher risk prostate cancer[130]. A moderately hypofractionated dose of 47 Gy in 20 fractions, over 4 weeks, is given to those receiving pelvic radiotherapy in addition to the standard dose of schedule of 60 Gy to the prostate.

One retrospective study of 97 high-risk patients, compared outcomes in 52 patients treated with SBRT monotherapy (35 – 36.25 Gy in 5 fractions), with 45 patients

receiving conventionally fractionated pelvic radiotherapy (45 Gy), followed by an SBRT prostate boost of 19-21 Gy in 3 fractions[131]. There was no significant difference in ADT use between the groups. The 6-year bRFS was 69%, with no significant difference between the groups, although GI toxicity was significantly higher following pelvic radiotherapy (13.3% G2 GI toxicity), with no cases of G2 GI toxicity reported in the SBRT group.

A number of trials are investigating the use of pelvic SBRT in high-risk patients. In the trial by King et al, pelvic SBRT at 25 Gy in 5 fractions could be delivered to high-risk patients at the discretion of the treating clinician[79]. Preliminary results demonstrated nodal irradiation was delivered in 32% of cases without significant effect on early toxicity, although the numbers are too small to draw any accurate conclusions.

In the FASTR trial, 16 high-risk patients received gantry-based SBRT to the prostate (40 Gy in 5 weekly fractions) and pelvic nodes (25 Gy in 5 weekly fractions), in combination with 12 months ADT[132,133]. Unfortunately, the trial was terminated due to higher-than-expected GI toxicity, with ≥G3 toxicity occurring in 4 (25%) patients at 6 months. Conversely, the SATURN demonstrated no G3 toxicity among 30 patients, at 25.7 months follow-up, using the same dose fractionation to the pelvic nodes[134]. However, acute and late G2 GU toxicity rates were still relatively high at 46.7% and 52%, respectively. Acute G2 GI toxicity was minimal but 32% reported late G2 GI symptoms. Higher rates of ≥G3 GI toxicity may have occurred in the FASTR trial in comparison to SATURN due to the following reasons: the inclusion of 1cm pSV within the high-dose volume rather than prostate alone; the use of a larger high-dose PTV margin of 5mm compared to 3mm; and a higher PTV dose of 40 Gy compared to 33.25

Gy (based on previous results demonstrating rectal V38 to be strong predictor for significant PR bleeding)[135]. In addition, CBCT alone was used for target verification, without fiducial markers as used in SATURN.

SPORT is a multicentre randomised trial, delivering prostate SBRT, 36.25 Gy in 5 fractions, in combination with ADT, with or without elective nodal irradiation, 25 Gy in 5 fractions[136]. Results from the feasibility study of 30 patients demonstrated acceptable toxicity rates at 30 months median follow-up, although evidence of increased GU and GI toxicity in the pelvic SBRT arm[137]. The PRIME trial, is currently recruiting also including node-positive, non-metastatic patients, stratifying patients by nodal status and ADT. All patients are randomised between prostate SBRT, 36.25 Gy in 5 fractions, and a moderately hypofractionated schedule of 68 Gy in 25 fractions[138]. Depending on randomisation, node-positive patients additionally receive pelvic SBRT, 25 Gy in 5 fractions +/- a nodal boost of 30–35, or 50 Gy in 25 fractions to the pelvis +/- a nodal boost of 60- 66 Gy in 25 fractions.

Since the role of prophylactic pelvic radiotherapy in high-risk prostate cancer remains unanswered, the CTV used in chapter 4 includes the prostate and SV alone. The feasibility of SBRT planning in high-risk prostate cancer remains relevant even in the context of pelvic radiotherapy.

1.2.6.8. PTV margins

The use of smaller planning target volume (PTV) margins is one of the fundamental aspects of SBRT. The PTV margin accounts for uncertainties in the treatment planning process (systematic errors) including image registration and target delineation, as well as variations in day-to-day treatment (random errors) related to patient set-up and organ motion/ deformation. Margin recipes are used to calculate margins by taking these uncertainties into account. One example is the formula derived by Van Herk: CTV-PTV margin = $2.5\Sigma + 0.7\sigma$ (Σ = standard deviation (SD) of all systematic errors; σ = SD of all random errors)[139].

The use of smaller margins in low-/ intermediate-risk prostate cancer is substantiated by the volume of data demonstrating long-term efficacy and low toxicity rates. There is some variation among SBRT studies but the majority of larger CyberKnife studies, including PACE, apply a PTV margin of 5mm is applied to the CTV, which is reduced to 3mm posteriorly, due to the proximity of the rectum[8,57,58,65]. However, there is some theoretical concern regarding the use of similar margins in high-risk patients. In one study by Katz et al, a larger PTV margin of 8mm was applied on the side of high-risk disease[58]. As previously described, the CTV for prostate SBRT includes the prostate +/- pSV, which does not account for potential microscopic disease outside the prostatic capsule. Hence, this uncertainty needs to be taken into account by the PTV margin. High-risk patients are at greater risk of extracapsular extension (ECE) and it is important to consider the potential impact on PTV margin size.

In an analysis of 371 prostatectomy specimens, Chao et al, demonstrated risk-group to be highly predictive of both ECE risk and distance of ECE beyond the capsule[140]. Extracapsular extension was present in 19% of low-risk patients increasing to 35% in patients with one unfavourable feature (baseline PSA ≥ 10 ng/ml, Gleason score ≥ 7, or clinical stage ≥ T2b), and to 71% in those with three unfavourable features. Patients with clinical stage T3 were excluded from the study. The overall median ECE distance was 2.4 mm and was within 5.2mm for 90% of cases, most commonly in the posterolateral aspect of the prostate. ECE was present in approximately half of the patients with ≥ 2 unfavourable features, extending beyond 4mm in 21%. This led the investigators to recommend consideration of up to 5mm CTV expansion in the posterolateral regions to account for ECE, although their results are not in keeping with all studies. For example, an older study by Davies et al reported a median ECE distance of 0.5 mm in a similar patients group[141].

As the concern is related to potential extracapsular microscopic disease, the currently used SBRT margins are thought to be sufficient in delivering adequate dose to these areas. In 41 SBRT patients treated with CyberKnife 35 – 36.25 Gy in 5 fractions and margins of 5 mm /3 mm posteriorly, Ju et al retrospectively measured the distance between the prostatic capsule and the 33 Gy isodose line, which was taken to be the dose sufficient to treat microscopic ECE[142]. In 73 – 100% of cases, the 33 Gy isodose line was ≥5mm from the prostatic capsule, including the posterolateral regions, although coverage directly posteriorly, towards the rectum, was less, where the extent of invasion is limited by the recto-prostatic fascia. The average distance from the capsule, in the posterolateral direction, was 11.23 mm, 7.74 mm, 7.26 mm at the prostatic base, mid-prostate, and apex, respectively.

Toxicity has reduced following the development of image-guided radiotherapy (IGRT) which has enabled the use of smaller margins[143]. Image-guided radiotherapy is conducted using pre-treatment imaging, ideally registered to implanted intraprostatic fiducial markers, correcting for inter-fraction displacement. Variation in PTV margins between studies is mainly dependent on the availability of intra-fraction motion monitoring and correction.

The CyberKnife has the additional advantage of being able to track and compensate for intra-fraction motion, every 30 – 60 seconds, and, hence, the impact of target motion is likely to be small. Xie *et al.* measured intrafraction motion in 21 CyberKnife patients demonstrating the largest prostatic shift to be in the anteroposterior (AP) direction over a mean distance 1.8 mm +/- 1.44 mm, compared to 1.55 mm +/- 1.28 mm and 0.87 mm +/-1.17 mm along the superior-inferior (SI) and left-right (LR) axis, respectively[144]. Motion ≥ 2 mm was detected in 4.4% of cases at 30 seconds and 7.5% 60 seconds, respectively, and ≥5 mm motion in 1.2% and 1.9% of cases, respectively. Choi et al analysed intra-fraction motion on CyberKnife in 71 prostate patients performing imaging at 5-8 beam intervals on average[30]. None of the patients had >2 mm of motion in any axis, and >1 mm in 2.8%, 1.4% and 21.1% in the SI, LR, and AP axes, respectively, with the average magnitude of motion being 0.15 mm ± 0.31 mm, 0.12 mm ± 0.19 mm, and 0.73 mm ± 0.32 mm. They found no association between intra-fraction motion and disease control, however there was found to be a significant correlation between the magnitude of motion and the incidence of ≥G2 rectal or bladder toxicity.

Studies of gantry-based SBRT, using real-time tracking systems such as Calypso® System (Varian Medical Systems, Inc., Palo Alto, CA), have employed similar small margins[145,146]. Curtis et al, demonstrated acceptable target coverage 93.1% of the time using 3mm margins, and 99.4% of time using 5mm margins, over a mean fraction length of 7 minutes and 21 seconds[162]. In 17 patients, over 550 fractions, Langen et al, found the prostate to be displaced by >3 mm for 13.6% of the time, and >5mm for 3.3% of the time, over a mean treatment time of 10 minutes[148].

Including a greater proportion of SV for high-risk patients has further implications in terms of applied PTV margins. Image guidance in prostate SBRT is based on the position of the prostate, usually identified by intraprostatic fiducial markers. This does not often include accurate localisation of the SVs which are difficult to identify even with cone-beam CT in gantry-based SBRT. In practice, prostate coverage is often prioritised given the larger extent of tumour volume.

Larger margins may be required to account for SV motion, having been shown to move independently from the prostate in a number of studies analysing daily pre-treatment imaging[149-151]. Significant displacement of the proximal SVs (pSV), relative to the prostate was reported by Lim Joon et al, in a study of 30 IMRT patients[151]. Fiducials were inserted into the prostate and bilateral SVs, with inter-fractional shifts recorded using daily orthogonal imaging. Relative to the prostate, the pSVs were displaced by an average of 0 - 0.38 mm laterally, 0.8 – 1.13 mm superiorly and 1.51 – 1.81 mm posteriorly.

Variability in SV motion has been shown to be higher at an increasing distance from the prostate. Stenmark et al demonstrated 5mm margins to be adequate for treating the prostate and 1cm pSV, but larger margins required to achieve adequate coverage of the full SVs[152]. Using intraprostatic fiducial matching and daily CT imaging, IMRT plans including 1cm pSV with a 5mm PTV margin were found to achieve 95% pSV coverage in 95% of cases. However, plans that included the full SVs with a 5mm margin, achieved 95% SV coverage in only 55% of cases. They found that an 8mm margin was needed to achieve 95% coverage of the full SV in 95% of cases.

Intra-fraction SV motion has been shown to increase over the duration of the treatment in a small study by Gill et al, using cinematic MRI[153]. Motion was most marked in the superior-inferior, anterior-posterior directions, and was not strongly correlated with prostate motion. The mean range of displacement (between 2.5 and 97.5 percentile) at 3, 5, 10 and 15 minutes was 4.7 mm, 5.8 mm, 6.5 mm, and 7.2 mm, respectively, in the SI direction (compared to 3.3 mm, 4.4 mm, 5.1 mm and 5.3 mm for the prostate), and 4 mm, 4.5 mm, 6.5 mm, and 7 mm in the AP direction (compared to 3.6 mm 4.2 mm, 5.3 mm, and 5.3 mm for the prostate).

Oehler et al conducted a study of 20 patients treated with VMAT and image guidance using intraprostatic fiducial markers with both CBCT and KV imaging taken before each fraction[153]. Additional CBCT was performed after treatment to assess intra-fraction motion. They recorded similar magnitude of inter-fraction and intra-fraction motion of 0.9 – 1.4 mm, and minimal difference in fiducial position using CBCT or KV imaging. Using the Van-Herk formula[139], PTV margins of 5-8 mm for the prostate in

low-risk disease and 6-11 mm for the SV in intermediate-/high-risk disease were calculated.

Deformation of the prostate in relation to fiducial markers and organ motion is thought to be minimal[144,154,155]. In comparison, deformation of the SVs is more substantial with one study observing the largest deformation in CTV to be at the anterior and posterior aspect of the SVs, mainly secondary to organ motion[50,154,155]. Evidence regarding the impact of SV volume variability is limited but factors such as the use of ADT and frequency of ejaculation may have an effect[156]. A small retrospective study demonstrated some variation in SV volume between radiotherapy fractions using cone beam CT, with change in volume of up to 78%[157].

These studies suggest that separate SV margins are required if using prostate for localisation. For the purpose of my planning study in chapter 4, I have elected to use a 6mm CTV – PTV margin for the distal seminal vesicles and 5mm/ 3 mm (posterior) for the prostate/ pSV which is in keeping with the study findings above.

1.2.6.9. Volume

A large prostate volume can create further challenges for SBRT. Brachytherapy studies have demonstrated increased late GU toxicity to be associated with prostate volume[158,159]. Pham et al demonstrated that patients with a prostate size of over 60 cc have significantly higher rates of G3/4 late GU toxicity compared to those with smaller prostates, although there was some association with improved biochemical control[158].

There is less data in the context of external beam radiotherapy, but two studies have demonstrated an association between prostate volume and GU toxicity. Aizer et al demonstrated significantly higher rates of G3 GU toxicity following conventionally fractionated IMRT, in patients with prostate volume >50 cc[160]. Similarly, Pinkawa et al demonstrated that the patients in their prospective cohort with a large prostate (≥44 cc) had a lower urinary quality of life (QOL) at baseline and more significant deterioration post radiotherapy compared to those with smaller prostates[161]. Notably, patients on ADT had lower QOL scores despite having a smaller prostate volume.

In view of this association, some SBRT studies have included a maximum prostate volume in their eligibility criteria. Zelefsky et al, for example, only included patients with a prostate volume ≤ 60 cc in their dose escalation study[84]. Potters et al demonstrated an association between G2 toxicity and prostate volume (p=0.02), with increased toxicity in those with prostate volume ≥ 60 cc[87]. Repka et al found prostatic volume was found to be a significant predictor of acute urinary toxicity, with 12% toxicity rate in patients with a prostate volume less than the median of 36 cc, compared with 33% in those with prostate volume >36 cc[162]. One study, by Janowski et al included 57 patients with larger prostates ranging between 50 – 139.7 cc, treated with SBRT (80% treated with 36.25 Gy). Although low rates of G3 GU toxicity, a 2-year ≥ G2 GU toxicity incidence as high as 49.1% was reported[163].

A small increase in CTV volume results in a more substantial increase in PTV volume, with a greater possibility of significant overlap with rectum and bladder. Therefore, cases with larger prostates can be more complex to plan and achieve adequate target coverage while meeting dose constraints to OARs. Since the CTV for high-risk patients

will be larger by including a greater extent of SV, this will have a further impact on PTV volume, particularly if a larger margin is applied to account for SV motion. In addition, the location of the seminal vesicles, in close proximity to rectum and bladder, together with the curvature of the distal SVs around the rectum, will potentially add to the magnitude of OAR overlap.

As previously discussed, a limitation of the CyberKnife is the length of the overall treatment time which includes the time required for the robot to deliver multiple small beams to the target, as well as the time required for imaging and position correction. CyberKnife plans which include larger and/or complexly shaped PTVs will often require a greater number of beams to achieve an acceptable plan, thereby increasing the treatment time and number of monitor units required. As discussed in section 1.2.2.3, the use of the multi-leaf collimator (MLC) may provide a particular advantage in treating patients with high-risk prostate cancer and/ or larger prostates and this is evaluated in chapter 4. In addition, this benefit could also be applied to other urological malignancies such a primary renal carcinoma.

1.2.7. Primary renal carcinoma

Renal cancer is the 7th most common cancer in the UK with approximately 13,100 new cases and 4,500 deaths per year[18]. Incidence rates have increased by more than a third in the past decade, mainly due to the increased use of imaging with over 50% of cases diagnosed incidentally and most presenting with localised disease[164]. Around 36% of cases are diagnosed in patients aged 75 and over and have an association with obesity, hypertension and chronic kidney disease[18,164].

Surgery is the gold-standard treatment for patients with localised disease either with radical or partial nephrectomy if technically feasible[165]. However, given the high rate of presentation in the elderly population, surgery may be unsuitable in several cases due to comorbidities affecting renal and cardiovascular function[166]. Active surveillance is a suitable option for small renal masses which have a low risk of developing metastatic disease and around one third show no growth after 3 years of observation[167,168]. Larger tumour size (≥2 cm) is associated with poorer prognosis and those patients are, therefore, more likely to require delayed intervention in the event of tumour growth[169].

Thermal ablation with radiofrequency ablation (RFA) or cryoablation (CA) is an option for treating small renal lesions in patients not suitable for surgery: however, local control is inferior to partial nephrectomy. A meta-analysis of 1,375 lesions reported local control rates, at 18.7 months follow-up of 87.1% and 94.8%, for RFA and CA, respectively[170]. Both techniques have limitation in terms of tumour size with higher rates of local recurrence seen following treatment of larger tumours (>4 cm) - local

recurrence rates of up to 14.3% for RFA and 23% for CA[171]. In addition, there exists a significant risk of complications including urinary leak, strictures and haemorrhage which is more common in larger tumours.

The role of radiotherapy in localised renal cancer is currently limited as it is traditionally thought of as a radioresistant tumour. However, evidence suggests that there may be a wide spectrum of radiosensitivity, and potentially could be overcome with higher dose per fraction using high precision techniques such as VMAT or SBRT[20]. Preclinical studies have demonstrated marked tumour response from an ablative dose of radiotherapy, thought to be partly achieved by immune response and microvascular disruption[20,172]. Radiotherapy to renal tumours is challenging due to the highly radiosensitive adjacent structures, namely small and large bowel and renal parenchyma. In addition, the kidney has been shown to be a mobile structure, requiring the use of large margins[173,174].

The use of high precision techniques involved in SBRT could allow the delivery of ablative radiotherapy doses while minimising dose to surrounding normal tissues. This is a particularly attractive treatment option for elderly and frail patients as it avoids the risks of more invasive treatment and hospitalisation. There is, therefore, increasing interest in the use of SBRT in primary renal carcinoma. A number of studies have demonstrated SBRT in primary renal cancer to be relatively well tolerated with local control rates comparable to other nephron-sparing treatment and an acceptable impact on renal function[22-24,175-178].

A meta-analysis by Correa et al. identified 26 studies, 11 of which were prospective trials[21]. Three hundred and seventy-two patients with a median age of 70.4 years were included (most of whom were considered inoperable) with a mean tumour diameter of 4.6 cm (range 2.3 – 9.5 cm). Eighty percent of patients had localised disease and others received SBRT for primary tumour in metastatic settings. The dose fractionation varied between studies but, 30 - 40 Gy in 3-5 fractions or 26 Gy in 1 fraction, were most commonly prescribed. With 28 months median follow-up, local control was reported to be 97.2%, ranging between 70% and 100%. The local failures were all reported in those receiving lower doses, which had to be reduced in some cases to meet dose constraints. Of the 23 trials reporting toxicity, SBRT was found to be well tolerated, with 1.5% ≥G3 (CTCAE) toxicity rate, and 8.8% G2 mainly consisting of nausea, fatigue or skin toxicity. There was mean reduction in estimated glomerular filtration rate (eGFR) of 7.7 ml/min and 2.9% of patients, with pre-existing renal dysfunction, required dialysis.

A pooled analysis by The International Radiosurgery Oncology Consortium for Kidney (IROCK) included 223 patients from 9 centres, with a median follow-up of 2.6 years[178]. One hundred and eighteen patients received single-fraction SBRT, at median dose of 25 Gy (range 14 -26 Gy) and 105 received multiple fractions at a median dose of 40 Gy (range 24 – 70 Gy) in 2 – 10 fractions. Local control rates were 97.8% at both 2 years and 4 years follow-up. Cancer-specific survival and progression-free survival were 95.7% and 77.4%, respectively at 2 years and 91.9% and 65.4%, respectively, at 4 years. Large tumours and multi-fraction SBRT were associated with poorer outcomes. Treatment was well tolerated with 1.3% ≥G3 toxicity, and acceptable mean eGFR reduction of 5.5 ml/min, with 26.5% experiencing an improvement in renal

function. There was no significant difference between fractionation in terms of toxicity, apart from some increased nausea in the single-fraction group.

A further analysis by the same group specifically focused on those patients with larger tumours (≥4 cm, median tumour diameter 4.9 cm)[23]. Ninety-five patients from 9 centres were included, the median age of which was 76 years, including 81% with ECOG performance status 0/1 and 29.5% with a solitary kidney. Local relapse was 2.9% which compares favourably with outcomes from thermal ablation[171]. Cancer-specific survival was similar to the previous study at 96.1% at 2 years and 91.4% at 4 years, with increasing tumour size associated with inferior cancer-specific survival. There was no ≥G3 toxicity recorded and 7.4% G2 toxicity rate. Thirty three percent of patients had a deterioration in chronic renal impairment and 3.2% required dialysis.

Correa reported outcomes from a small retrospective study evaluating SBRT for larger primary renal tumours but in the metastatic setting[179]. Eleven patients, with a median tumour diameter of 9.5 cm, were treated in 5 fractions of 25 Gy – 40 Gy. Treatment was generally well tolerated and, at median follow-up of 3.9 years, 6 out of 7 patients with follow-up imaging had evidence of local control. In a further prospective dose-escalation study by the same author, patients were planned to be recruited to dose levels 25, 30 , 35 and 40 Gy in 5 daily fractions, reaching a maximum tolerated dose (MTD) of 35 Gy when two G3 toxicities were reported[175]. At a medium follow-up point of 5.3 months all patients had progressed in terms of systemic disease, but there was evidence of local disease control, with a 17.3% median disease in tumour size. Median tumour size was 8.7cm, ranging between 4.8 – 13.8 cm. The initial PTV had a medium

volume of 763 cc (range 265 – 1234 cc) which had to be compromised by a median of 4% to exclude small bowel.

Limitations of these analyses include the absence of pre- and post-treatment comorbidity assessment, retrospective data collection with possible under-reporting of toxicity and short follow-up. Multi-centre prospective trials are therefore vital to evaluate the true benefit of SBRT for primary renal cancer. Recruitment is underway for RADSTAR which is a prospective randomised pilot trial of SBRT versus radiofrequency ablation for the management of small renal masses[180]. FASTRACK II is a multi-institutional phase II trial which includes two SBRT fractionation schedules (treatment delivery with gantry-based SBRT or CyberKnife) depending on tumour size[181]. Patients with tumours ≤4 cm in maximum diameter receive a single fraction of 26Gy; and those with tumours > 4 cm in maximum diameter receive 42Gy in three fractions. They are aiming to recruit 70 patients with the primary objective to detect efficacy from SBRT after 5 years follow-up.

The location of primary renal cancers, in close proximity to radiosensitive normal tissues, makes it difficult to deliver an ablative dose of radiotherapy without compromising target coverage. This problem is heightened in cases with larger tumour volumes, resulting in an increased risk of underdosage, thereby contributing to poorer local control. In order to achieve such a high level of conformity on CyberKnife, a larger number of beams may be required which will add to the planning and treatment time. In comparison to the Iris variable collimator (section 1.2.2.2), multi-leaf collimation (MLC) could improve CyberKnife planning by allowing the use of fewer, larger beams which can be shaped to avoid surrounding structures. A comparison of Iris and MLC

planning in SBRT for primary renal cancer is investigated in chapter 5 followed by a discussion regarding optimum dose and the management of large primary renal tumours.

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Chapter 2: Five-year outcomes following Stereotactic Body Radiotherapy (SBRT) with CyberKnife in localised prostate cancer - UK experience

Sections of the following chapter were presented as:

- Stereotactic body radiotherapy for prostate cancer: Long-term outcomes from one of the first UK centres.

  Morrison K, Henderson D, Tree A, Khoo V, van As N

  Oral presentation: UK SABR Consortium Annual Conference, Nov 2018.

2.1. Introduction

There is a strong rationale to support the use of stereotactic body radiotherapy (SBRT) in localised prostate cancer, both in terms of radiobiology and on a practical level. A large volume of data now exists from outside the UK (Appendix 1), demonstrating SBRT to be safe and effective in the management of low- and intermediate- risk prostate cancer[1-5]. However, there remains a lack of randomised data comparing SBRT with conventional treatments, which is being addressed within the UK-based, multicentre, PACE trial[6]. Acute toxicity results from PACE B have recently been reported, demonstrating no significant difference in genitourinary (GU) or gastrointestinal (GI) toxicity between SBRT and conventionally fractionated or moderately hypofractionated radiotherapy[7]. Since it will be some time before long-term toxicity and efficacy data becomes available, results from single-centre UK studies will be highly informative and provide the opportunity to ensure outcomes are consistent with conventional radiotherapy and SBRT studies, worldwide.

The Royal Marsden Hospital (RMH) began delivering prostate SBRT with the CyberKnife® Robotic Radiosurgery System (Accuray Incorporated) in 2011. Since that time point, prospective efficacy and toxicity data has been collected within a service evaluation of patients treated with prostate SBRT, outside of the PACE trial. In collaboration with Mount Vernon Hospital, acute toxicity data from this first UK cohort was published in 2015, demonstrating treatment to be well tolerated, with acceptable rates of acute toxicity[8,9]. To date, this is the only published prospective study of prostate SBRT within the UK. Between 2016 and 2019 I continued the data collection and recruited further patients to the study. In this chapter I will present the results of

my analysis at 5 years median follow-up, to establish long-term effectiveness and toxicity rates.

2.2. Hypothesis

Cyberknife-based SBRT is a safe and effective means of treating low- and intermediate-risk prostate cancer as indicated by high rates of long-term biochemical control and low incidence of acute and late toxicity, consistent with other studies.

2.3. Aims

- To determine the freedom from biochemical/ clinical progression (FFBP) rate in patients with localised prostate cancer treated with SBRT on CyberKnife at 5 years median follow up.
- To determine rates of acute and late toxicity and relate these to volumetric data and CyberKnife plan dosimetry.

2.4. Methodology

2.4.1. Patient cohort

This study included patients receiving prostate SBRT with CyberKnife within a service evaluation at the Royal Marsden Hospital (RMH) between 2011 – 2018. Patients with histologically confirmed, localised low- or intermediate- risk prostate cancer as defined by the National Comprehensive Cancer Network (NCCN) risk group definition (Table 1.1) were included, without concomitant androgen deprivation therapy (ADT). The rationale for not using in ADT in this patient cohort was previously discussed in section 1.2.6.1. Patients with high-risk features (Table 1.1) could be included, at the discretion of the treating physician, in conjunction with ADT.

Patients were required to have been adequately staged with diagnostic pelvic magnetic resonance imaging (MRI), and a bone scan in high-risk patients to exclude metastatic bone disease. All patients were discussed and suitability for treatment confirmed at the local specialist SBRT multidisciplinary team meeting (MDT). Patients were excluded if they had any contraindication to radiotherapy, including medical conditions such as inflammatory bowel disease, previous abdomino-pelvic radiotherapy, bilateral hip replacements; or to intraprostatic fiducial marker insertion such as urinary sepsis, coagulopathy or on anticoagulation in which the risks of withholding were significant.

2.4.2. Planning and treatment technique

Patients were provided with a patient information sheet (PIS) and consented for treatment and fiducial marker insertion. Intraprostatic fiducial marker insertion was mandatory to facilitate accurate tracking of the prostate on CyberKnife. Four gold markers, ideally including at least one pair of linked markers, were inserted into the prostate under ultrasound guidance, either transrectally or transperineally, with appropriate prophylactic antibiotic cover.

A computed tomography (CT) planning scan was conducted at least 7 days following fiducial insertion. Patients were scanned and treated with a comfortably full bladder. They were required to drink 325 mls of fluid 45 minutes prior to the scan and each fraction of treatment, aiming for ≥ 150 cc bladder volume. Bowel preparation consisted of daily enemas commenced two days prior to and until the day of their CT and then recommenced 2 days prior to the first treatment fraction and administered before each fraction of radiotherapy. Planning MRI was performed for co-registration with the planning CT to aid accurate target volume delineation.

Planning CT and MR images were uploaded to Eclipse (Varian Medical Systems, USA) for clinical contouring, which was completed by an SBRT research fellow, either Dr A Tree, Dr D Henderson, or myself. Each case was reviewed and approved by the treating consultant, Dr N van As or Dr V Khoo, prior to planning. The clinical target volume (CTV) for low-risk patients included the prostate alone, and for intermediate-risk patients included the prostate and the proximal 1cm of the seminal vesicles. The planning target volume (PTV) was created using a CTV expansion of 5 mm, reduced

to 3mm posteriorly. The organs at risk (OAR) were contoured as follows: rectum, bladder, bowel, femoral heads, penile bulb, and urethra if adequately visualised.

All patients were treated using the CyberKnife robotic radiosurgery platform, with intrafraction motion tracking, at a prescribed dose of 36.25 Gy in 5 fractions over 5 – 11 days. The planning requirements were consistent with those used in the PACE trial and the OAR dose constraints are summarised in Appendix 2. The main objective was to deliver the prescribed dose of 36.25 Gy to at least 95% of the PTV, and 40 Gy to at least 95% of the CTV, prescribing to the 75 – 85% isodose (minimum 77% isodose where urethra not visualised).

2.4.3. Recording relapse

The Prostate Specific Antigen (PSA) level was recorded every 3 - 6 months for 5 years, and annually thereafter, until 10 years follow-up was reached. Biochemical progression was defined using the Phoenix criteria[10]:

PSA increase of ≥2 ng/mL above post treatment nadir. Benign PSA bounce, which is known to be a frequent occurrence in previous brachytherapy and SBRT studies, was defined as a PSA rise of at least 0.2 ng/ml before returning to the previous nadir, or below[11-15]. For this reason, patients with a documented PSA rise within 24 months of treatment required 3 consecutive rises before being classed as biochemical progression. For patients with confirmed biochemical progression, the onset and extent of clinical relapse was recorded.

2.4.4. Recording toxicity

Physician-reported GU and GI toxicity was recorded using the Radiation Therapy Oncology Group (RTOG) toxicity criteria[16] (Appendix 3), which was completed by the clinician assessing the patient in follow-up clinic, or during telephone consultation by myself or previous SBRT research fellow. Patient-reported GU toxicity and erectile dysfunction were evaluated by requesting patients to complete the International Prostate Symptom Score (IPSS) and International Index of Erectile function (IIEF) questionnaires (given to the patient at the time of their clinic appointment or sent out and returned by post or email). The IPSS, developed by the American Urological Association (AUA) is based on the answers to 7 questions concerning urinary symptoms and one question concerning quality of life[17] (Appendix 4). Each answer is graded 0 to 5, with total score ranging from 0 to 35 (asymptomatic to very symptomatic). The IIEF addresses the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) (Appendix 5). It is a validated questionnaire that is readily self-administered in research or clinical settings[18].

The time points for toxicity and PSA assessment are summarised in (Table 2.1). Acute toxicity data was recorded during the initial 12 weeks following commencement of treatment: at baseline; at 1-2 weeks (end of treatment); then at 2 - 4 weekly intervals. Late toxicity was recorded at 3 monthly intervals for the first 2 years, and 6 monthly years 3- 5.

Table 2.1: Follow-up assessment intervals

		Follow-up post treatment									
Assessment	Baseline	1 – 2 weeks (EOT)	2 – 4 weekly	Week 12	Month 6	3 monthly	Month 24	6 monthly	Year 5	Annually	Year 10
PSA	x			x	x	x	x	x	x	x	x
RTOG GU	x	x	x	x	x	x	x	x	x		
RTOG GI	x	x	x	x	x	x	x	x	x		
IPSS	x	x	x	x	x	x	x	x	x		
IIEF	x				x	x[a]	x	x[b]	x		

Summary of follow-up aseessment time-points and frequency. EOT, end of treatment; PSA, prostate specific antigen; RTOG, Radiation Therapy Oncology Group; GU, genitourinary; GI, gastrointestinal; IPSS, International Prostate Symptom Score; IIEF, International Index of Erectile Function; x[a], 6monthly; x[b], annually.

2.4.5. Plan analysis

Data was retrospectively collected from each plan to include: volume measurements for PTV, bladder and rectum; CTV (V40 Gy) and PTV coverage (V36.5 Gy); dose to OAR (Appendix 2).

2.4.6. Outcome measures and statistical analysis

The primary efficacy objective was to determine the rate of freedom from biochemical or clinical progression (FFBP) at 5 years follow-up. The main toxicity objective was to determine the incidence of physician reported ≥ grade 2 RTOG acute and late GU and GI toxicity within 5-years follow-up.

Data prospectively collected 2011 - 2019 was analysed in February 2019. Statistical analysis was conducted using Prism (© 1994 - 2021 GraphPad Software, LLC). Median follow-up was calculated using the inverse Kaplan-Meier method and summary statistics were used to describe patient characteristics and PSA response. The Kaplan-Meier method was used to estimate FFBP at 5 years. A further retrospective analysis of PSA levels was conducted in May 2021 to corroborate results with the benefit of longer median follow up.

Physician-reported acute and late GU and GI toxicities were categorised as worst reported RTOG grade and expressed as a percentage of the total number of patients. Prevalence of toxicity was recorded for each time point and Kaplan-Meier method applied to estimate cumulative incidence rate censoring patients at time of death or

last follow-up. IPSS and IIEF scores were displayed as summary statistics at each time point of data collection.

Descriptive statistics were used to analyse and compare treatment plan dosimetry indices, applying Mann-Whitney U test to assess for significant difference between groups, and Spearman's correlation coefficient to assess for correlation between toxicity and plan indices.

2.5. Results

2.5.1. Patient characteristics and follow up

Sixty-two patients were treated between August 2011 and March 2018, the characteristics of which are summarised in Table 2.2. The median age was 69 years, and the majority of patients were categorised as intermediate risk (82%). Of the six high-risk patients included, three were classed as high-risk solely based on a baseline PSA level marginally above 20 ng/ml. Nine (14.5%) patients received hormone therapy. 49 (79%) patients would have fitted the eligibility criteria for the PACE B trial, i.e. with low- or favourable intermediate-risk disease, and without the use of hormones. All patients received the prescribed SBRT dose of 36.25 Gy in 5 fractions. Twenty-seven patients (43.5%) were treated over alternate days and 35 (56.5%) treated over consecutive days.

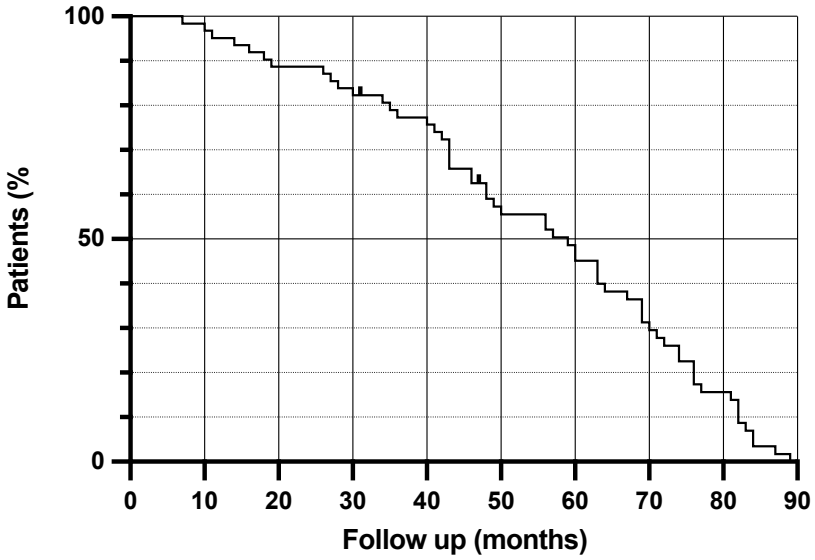
At the time of analysis, the median follow-up was 59 months (range 7 – 89 months), including 28 (45%) patients with at least 5 years follow-up, as shown in Figure 2.1. Seven patients had less than two years follow up, two of which had been lost to follow-up at 7 and 18 months, respectively. Three patients died between 31- and 47- months post treatment, giving an estimated overall survival rate of 94.14%. In all cases the cause of death was unrelated to the prostate cancer diagnosis or treatment.

Table 2.2: Patient characteristics.

Patient characteristic	Parameter (n=62)
Age (years)	69 (54 – 82)
Pre-treatment PSA (ng/ml)	9 (1.9 – 28)
< 10	35 (56.5%)
10 – 20	22 (35.5%)
>20	5 (8%)
Gleason Grade	
Gl 3+3=6	14 (22.5%)
Gl 3+4=7	44 (71%)
Gl 4+3=7	3 (5%)
Gl 4+4=8	1 (1.5%)
T stage	
T1c	4 (6%)
T2a	23 (37%)
T2b	10 (16%)
T2c	23 (38%)
T3a	2 (3%)
Risk category	
Low	5 (8%)
Intermediate	51 (82%)
High	6 (10%)
Hormone Therapy	
No	53 (85.5%)
Yes	9 (14.5%).
Prostate volume (cc)	53 (17 -144)
Length of follow-up	
<1 year	3 (5%)
1-2 years	4 (6.5%)
2-5 years	27 (43.5%)
≥ 5 years	28 (45%)

Results are displayed as median (and range), or number of patients (and percentage of total patients). PSA, prostate specific antigen; cc, cubic centimetres.

Figure 2.1: Patient follow-up



Reverse Kaplan Meier curve demonstrating percentage (%) of patient remaining under follow-up at each time point. Patients were censored at time of death. Median follow-up calculated as the point in months where 50% of patients remained on follow-up.

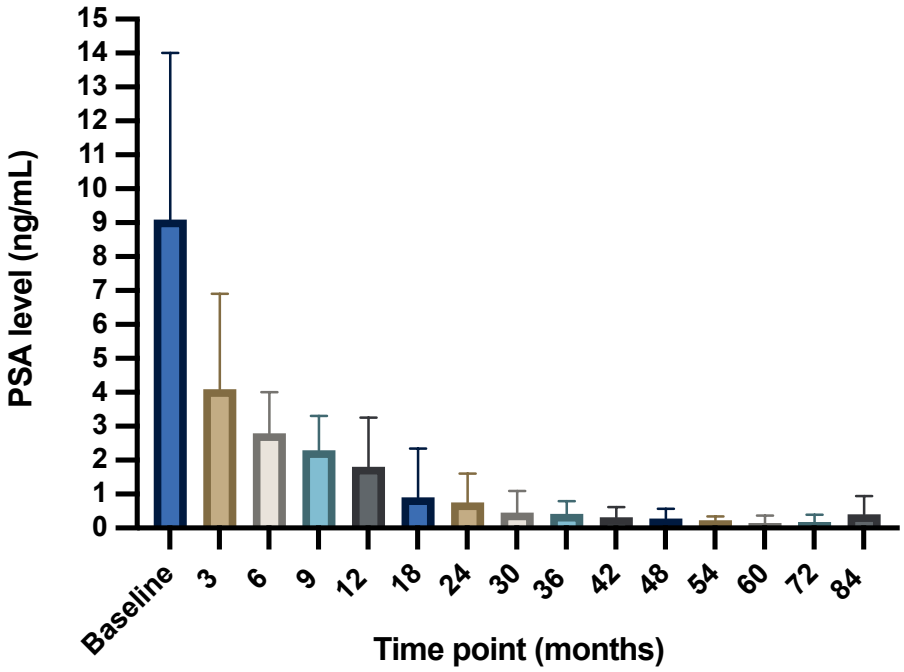
2.5.2. Efficacy

2.5.2.1. PSA response – prospective data analysis at 5 years median follow-up

Figure 2.2 demonstrates PSA response following treatment, in comparison to the baseline PSA. Patients receiving androgen deprivation therapy (ADT) were excluded from the analysis. From a median baseline PSA of 9 ng/ml there was a gradual decrease over time falling to a median PSA of 0.15 ng/ml (Interquartile range (IQR) 0.06 – 0.37) at 5 years. The median PSA nadir was 0.2 ng/ml (IQR 0.09 – 0.47 ng/ml), with a median time to nadir of 48 months (IQR 36 – 60 months). As expected, including patients on ADT resulted in a lower median PSA at 3- and 6-months post treatment, but rose to similar levels by 9 months follow-up.

A benign PSA bounce was recorded in 40% of patients, peaking at a median time of 12 months post treatment (range 6 – 36 months). The median magnitude of PSA rise above the previous nadir was 0.7 ng/ml (IQR 0.3 - 1.1ng/ml). Two patients were recorded as having a 2nd PSA bounce, with a rise of 0.4 ng/ml above previous nadir, one at 36 and the other at 42 months.

Figure 2.2: PSA response



Bar chart demonstrating PSA response (excluding patients on androgen deprivation therapy). Each bar indicates the median PSA (ng/mL) at each time point (months). The error bar indicates the upper interquartile range. PSA, Prostate Specific Antigen.

2.5.2.2. PSA response - retrospective analysis at 7 years median follow-up

The same patients were included in this further analysis, at a median follow up of 81 months. A further two non-prostate cancer related deaths had occurred during this period. Excluding the patients on hormones, the median PSA nadir was 0.17 (IQR 0.05 – 0.42), with median time to nadir of 60 months (IQR 36 – 84 months). The incidence of benign PSA bounce remained at 40%.

2.5.2.3. Biochemical relapse – prospective data analysis at 5 years median follow-up

Biochemical progression was recorded in 4 patients, with a median time to relapse of 33 months (range 18 – 66 months). One patient had low-risk and three had intermediate-risk prostate cancer, including one patient with unfavourable intermediate-risk disease (Gleason 4+3).

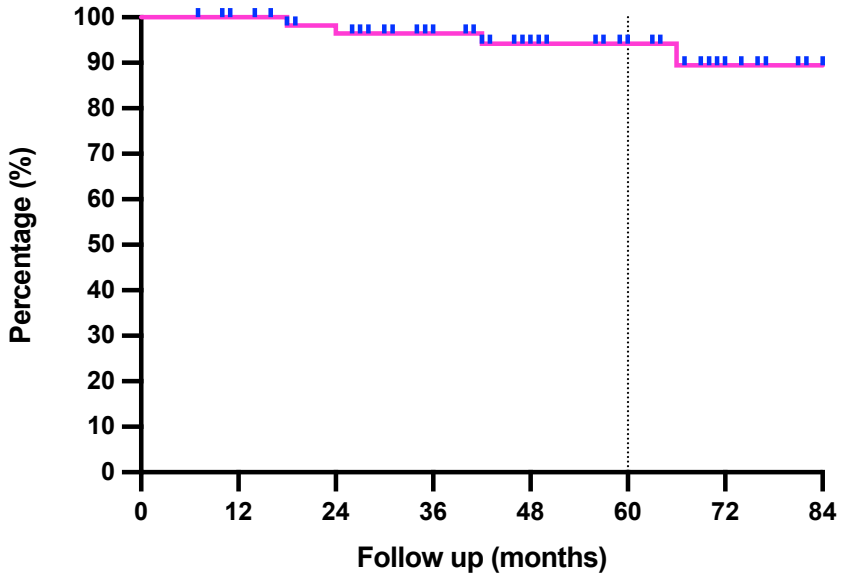
As demonstrated in Figure 2.3, the predicted 5-year FFBP rate for all patients was 94.18%. Excluding patients who received ADT, the rate was 93.88%. Including only patients with low- and favourable intermediate-risk disease, who fit the PACE B eligibility criteria had a 5-year FFBP rate of 95.7%. The 5-year FFBP rate for the intermediate risk group alone was 96%.

2.5.2.4. Biochemical relapse – retrospective analysis at 7 years median follow-up

Four further patients developed biochemical recurrence between 7 and 9 years follow-up, giving a total of 8 (12.9%) patients in this series with biochemical recurrence. Estimated FFBR rates were 94.68%, 91.97 % and 88% at 5, 6, and 7 years respectively (Figure 2.4).

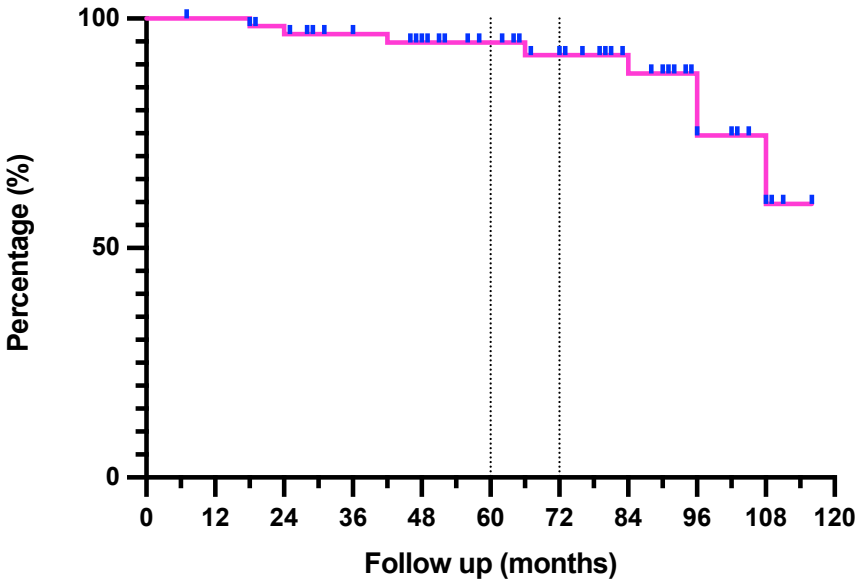
The individual details for each patient with biochemical relapse are summarised in Table 2.3.

Figure 2.3: Freedom from biochemical progression rate at 59 months median follow-up



Kaplan Meier curve demonstrating freedom from biochemical progression (FFBP) rate for all patients at 59 months median follow-up. Patients were censored at time death or last follow-up. The dotted line crossing x-axis demonstrates the predicted 5-year FFBP rate.

Figure 2.4: Freedom from biochemical progression at 81 months median follow-up



Kaplan Meier curve demonstrating freedom from biochemical progression (FFBP) rate for all patients at 81 months median follow-up. Patients were censored at time death or last follow-up. The dotted lines crossing the x-axis demonstrates the predicted 5-year and 6-year FFBP rates.

Table 2.3. Patients with biochemical relapse

Relapse time post treatment (months)	PSA level at relapse (ng/ml)	Radiological pattern of recurrence	Imaging modality	Subsequent treatment	Age at relapse	NCCN Risk Group	T-stage	Gleason score	Baseline PSA (ng/ml)	Hormones	PSA Nadir (ng/ml)	Previous PSA bounce
18	12	Widespread metastatic	Choline PET	ADT	69	Int	T2c	Gl 3+4	18	No	9.0	No
24	5.7	Solitary node	PSMA PET	ADT and SBRT	66	Int	T2b	Gl 4+3	6.8	No	1.7	No
42	4.1	Local and solitary bone	Choline PET	Salvage prostatectomy then SBRT	66	Low	T2a	Gl 3+3	7.6	No	0.93	No
66	3.3	Local. New colorectal cancer	Choline PET	PSA monitoring Surgery/ chemo for colorectal cancer	77	Int	T2a	Gl 3+4	6.3	No	0.48	No
84	3.7	Pelvic and retroperitoneal nodes	PSMA PET	ADT and SBRT	69	Int	T2b	Gl 3+3	14	No	0.64	Yes
96	3.9	Unconfirmed pelvic node +/- local	PSMA PET	PSA monitoring	73	Int	T2a	Gl 3+4	14.5	No	1.3	Yes
96	2.2	Unconfirmed local	PSMA PET	PSA monitoring	74	Low	T2a	Gl 3+3	7.7	No	0.22	Yes
108	2.4	Local	PSMA PET	PSA monitoring	77	Int	T2c	Gl 3+ 4	18	No	0.22	No

Table summarising details of patient with biochemical relapse. PET, positron emission tomography; ADT, androgen deprivation therapy; SBRT, stereotactic body radiation therapy; PSA, prostate specific antigen; Gl, Gleason score.

2.5.3. Toxicity

2.5.3.1. Genitourinary toxicity

Twenty-three (37.1%) patients developed ≥ grade 2 (G2) RTOG acute GU toxicity, including five patients (8%) with grade 3 (G3) symptoms. All patients were recorded has having no RTOG toxicity at baseline. Toxicity consisted mainly of cystitis or obstructive urinary symptoms, which developed during treatment or in the immediate post treatment period. As shown in Figure 2.5, there was a marked improvement in symptoms over time, with almost all ≥G2 toxicity settling by the 12-week point. Two patients developed G3 and G2 haematuria at 8 weeks and 12 weeks, respectively. 10% of patients were on an alpha-adrenoreceptor antagonist at baseline, which was prescribed in a further 35% within 4 weeks of treatment. Seven patients were documented to have stopped this by 12 weeks, but for 50% of patients, the date of discontinuation was unknown.

Within 5 years of follow-up, 14 (22.6 %) out of 62 patients developed late GU toxicity of ≥ grade 2 (16.13% G2 and 6.5% G3). Toxicity data was available in 27 out of the 28 patients with at least 5 years of follow-up. Six (22.2%) of those patients had ≥ G2 worst reported late GU toxicity at some point within the five-year period, but by 5 years only one patient (7.5%) had symptoms. The predicted cumulative incidence rate of late ≥ G2 GU toxicity was calculated at 26.9% (including 8.6% G3 toxicity) as shown in Figure 2.6. The frequency of late ≥ G2 GU toxicity was higher in the population who had a benign bounce in PSA (38.1%), in comparison to those with no bounce (12.5%).

As demonstrated in Figure 2.6 and Figure 2.7, there was a marked increase in G1 and G2 toxicity within the first 2 years, consisting mainly of frequency and/or urgency. G2 haematuria occurred in 4 patients, between 12 – 60 months follow up. G3 late GU toxicity occurred in four (7%) patients, occurring at approximately 4 years follow-up in three out of four cases. Two patients developed urethral strictures requiring dilatation (one patient having previously been catheterised for urinary retention at 18 months follow-up), one had haematuria with clots, and the other required temporary catheterisation for urinary retention. By the 5-year point there were no cases of G3 toxicity, and the only case of G2 toxicity was in the patient who had undergone salvage prostatectomy and is likely to have contributed to his symptoms.

Figure 2.5: Prevalence of acute genitourinary toxicity

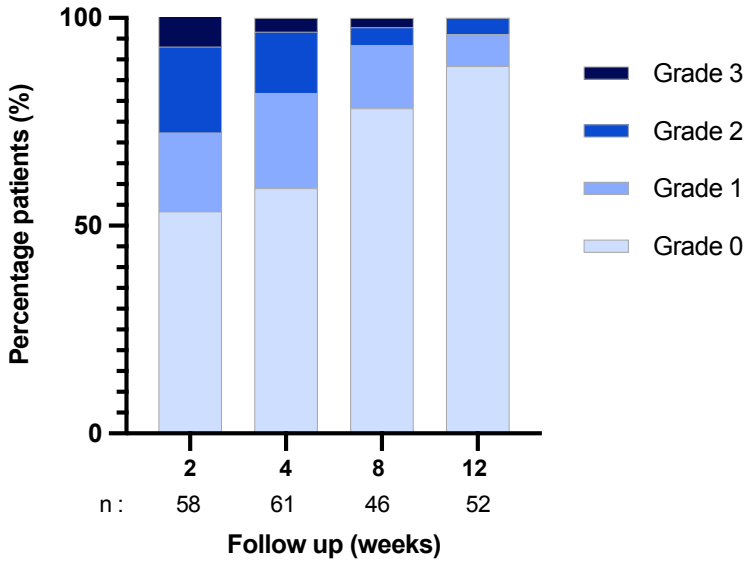
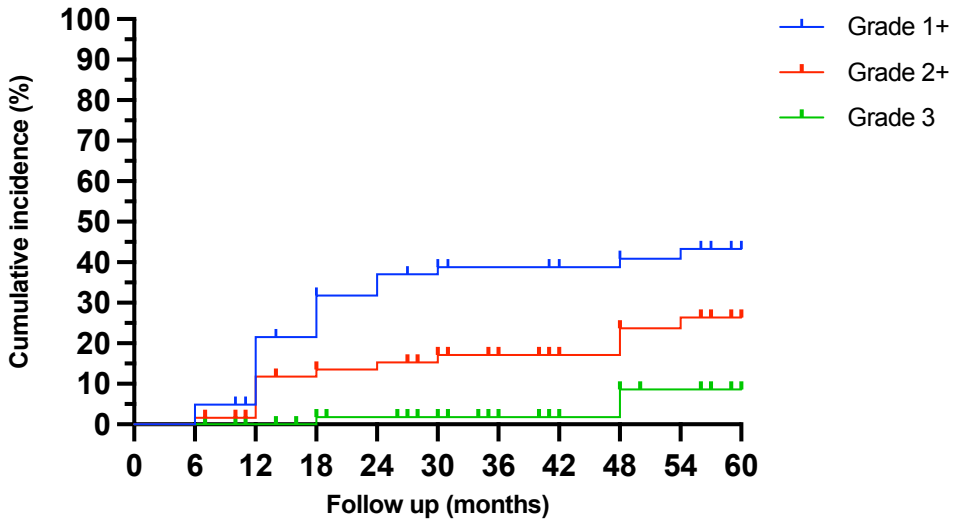


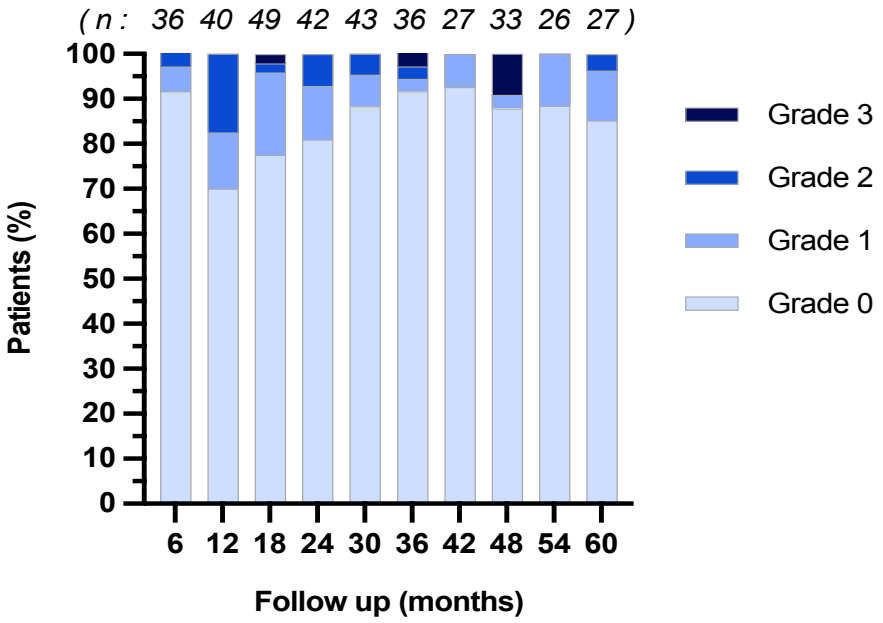
Figure demonstrating the prevalence of acute genitourinary (GU) toxicity at 2, 4, 8 and 12 weeks from commencement of SBRT, as defined by the RTOG toxicity scale. The RTOG score (grade 0 – 3) is colour coded as shown in the legend. n: number of patients with completed RTOG toxicity scores at each time point.

Figure 2.6: Cumulative incidence of late genitourinary toxicity



Kaplin-Meier curve demonstrating cumulative incidence of late genitourinary toxicity. Patients are censored at the time of death or last follow-up. The RTOG score (grade 0 – 3) is colour coded as shown in the legend.

Figure 2.7: Prevalence of late genitourinary toxicity



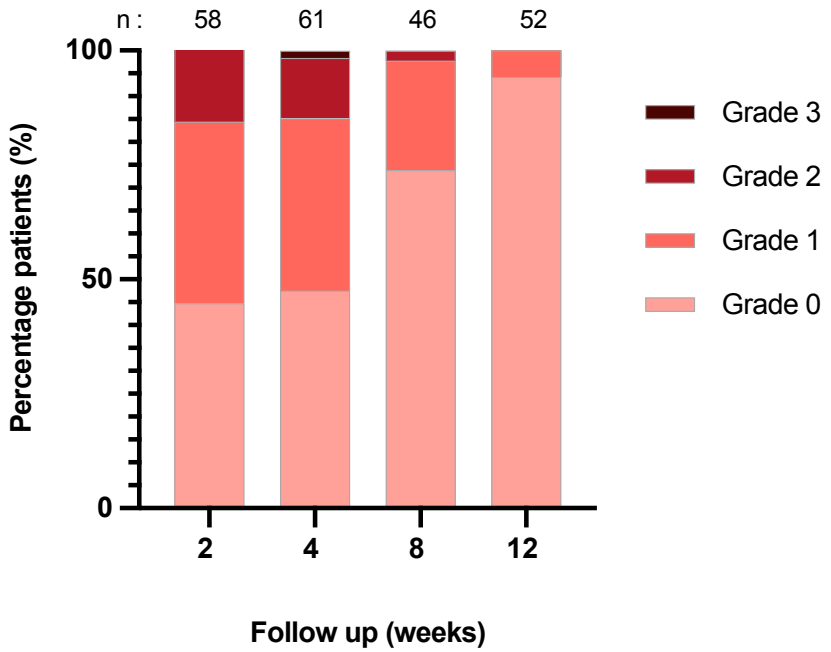
Bar chart demonstrating the prevalence of late genitourinary toxicity at each time point (6 – 60 months), as defined by the RTOG toxicity scale. The RTOG score (grade 0 – 3) is colour coded as shown in the legend. n: number of patients with completed RTOG toxicity scores at each time point.

2.5.3.2. Gastrointestinal toxicity

Sixteen patients (27.4%) developed ≥ G2 worst-reported RTOG acute GI toxicity, with all patients recorded has having no toxicity at baseline. Symptoms developed within the first 4 weeks following commencement of treatment and had all resolved to G1 or below by 12 weeks (Figure 2.8). Symptoms of proctitis and/or diarrhoea requiring medical intervention were the main reasons for G2 toxicity reporting. One case of G3 diarrhoea with faecal incontinence was reported at 4 weeks follow-up.

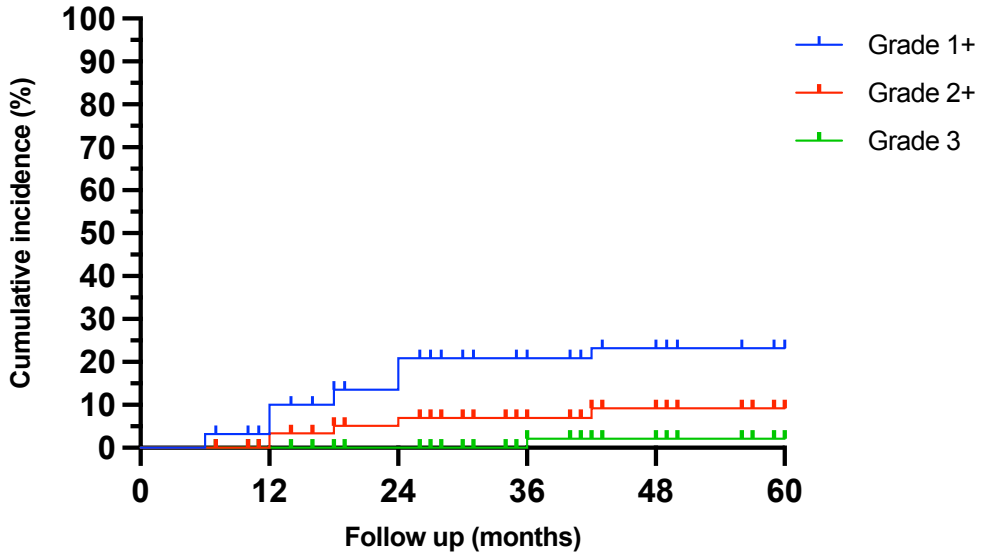
Five patients (8.1%) developed a worst-reported late GI toxicity score of ≥ G2, at some point within 5 years of follow-up, including symptoms of diarrhoea, urgency and one case of rectal bleeding. One patient was classed as having G3 toxicity on account of faecal incontinence. The cumulative incidence and prevalence of late GI toxicity are demonstrated in Figure 2.9 and Figure 2.10, respectively. The predicted 5-year late ≥ G2 GI toxicity rate was calculated as 9.2% ≥ G2 (including 2.1% G3). Of the patients with full 5-year toxicity data (n = 27), 3 patients (11.1%) had a worst-reported GI toxicity score of ≥ 2. At the 5-year point only 2 patients had persistent GI symptoms, but none with ≥G2 toxicity. There was a weak correlation between worst reported grade of acute GI toxicity and the incidence of late GI toxicity ($r=0.36$, $p=0.0038$).

Figure 2.8: Prevalence of acute gastrointestinal toxicity



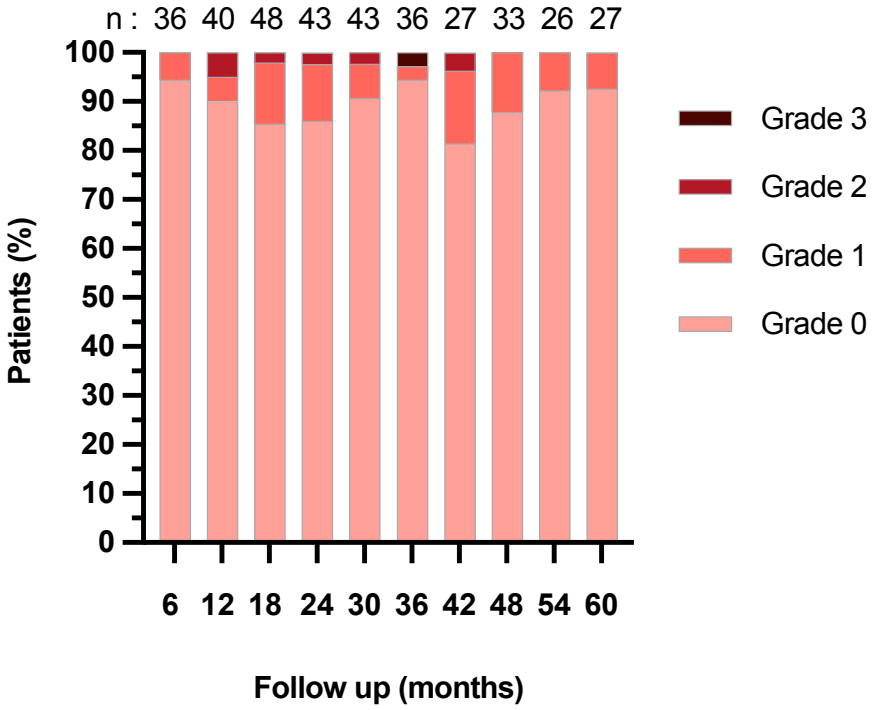
Bar chart demonstrating the prevalance of acute gastrointestinal (GI) toxicity at 2, 4, 8 and 12 weeks from commencement of SBRT, as defined by the RTOG toxicity scale. The RTOG score (grade 0 – 3) is colour coded as shown in the legend. n: number of patients with completed RTOG toxicity scores at each time point. acute gastrointestinal toxicity

Figure 2.9: Cumulative incidence of late gastrointestinal toxicity



Kaplin-Meier curve demonstrating cumulative incidence of late gastrointestinal (GI) toxicity. Patients are censored at the time of death or last follow-up. The RTOG score (grade 0 – 3) is colour coded as shown in the legend.

Figure 2.10: Prevalence of late gastrointestinal toxicity



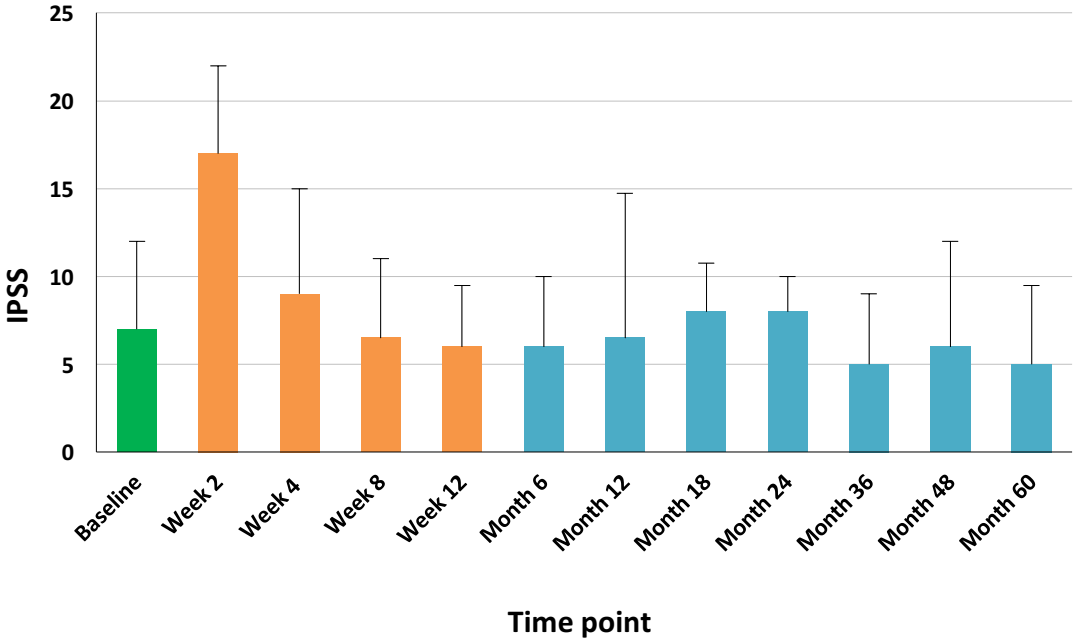
Bar chart demonstrating the prevalence of late gastrointestinal (GI) toxicity at each time point (6 – 60 months), as defined by the RTOG toxicity scale. The RTOG score (grade 0 – 3) is colour coded as shown in the legend. n: number of patients with completed RTOG toxicity scores at each time point.

2.5.3.3. Patient reported outcomes for urinary function (IPSS scores)

Figure 2.11 demonstrates the median IPSS score at each time point, from pre-treatment baseline until 5 years follow-up. The baseline median IPSS score was 7 (IQR 4.0 – 12.0) peaking at 2 weeks post commencement of treatment, to a median score of 17 and maximum of 31. As shown, symptoms had markedly improved by week 4, and by 12 weeks the median IPSS had returned to below baseline at a median score of 6, although this improvement is not a statistically significant reduction. No significant difference in median IPSS scores were detected between groups treated with alternate day fractionation or daily fractionation.

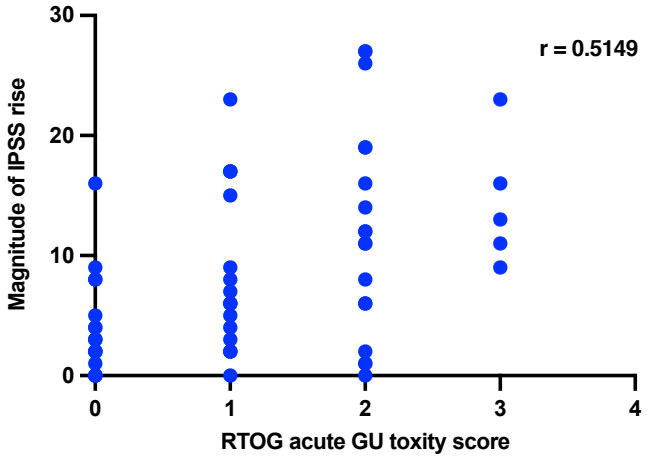
The median recorded maximum IPSS score was 18 (IQR 9.5 – 23), with a median magnitude of rise from baseline of 6 (IQR 2.0 – 13.5). 21 (33.87%) patients had a maximum rise in IPSS of ≥ 10. For the 23 patients with ≥G2 RTOG acute GU toxicity, the median maximum IPSS score was higher at 22 (IQR 19 – 27), with median rise of 12 (IQR 6.0 – 19.00) and median baseline of 9.0 (6.0 – 13.00). 15 (65.2%) of these patients had a maximum rise in IPSS from baseline of ≥ 10, and there was evidence of moderate correlation between RTOG grade and both magnitude of IPSS rise ($r = 0.51$, $p < 0.0001$) and maximum IPSS ($r = 0.63$, $p = <0.0001$), as demonstrated in Figure 2.12 and Figure 2.13. There was however no evidence of correlation between baseline IPSS and acute GU toxicity. As shown in Figure 2.11, the median IPSS remained relatively stable over the course of the 5-year follow-up, with a slight rise between 12 and 24 months. This is consistent with the RTOG score data which demonstrated a rise in G1 and G2 GU symptoms during the same period. However, there was very weak correlation between IPSS rise and late GU toxicity.

Figure 2.11: International Prostate Symptom Scores (IPSS)



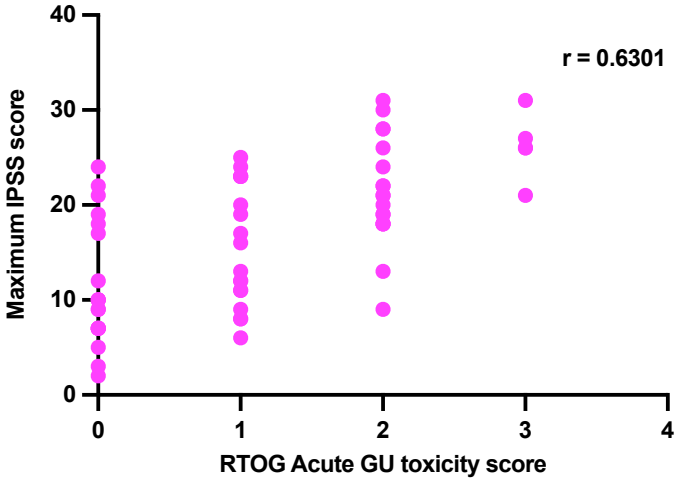
Bar chart demonstrating the median International Prostate Symptom Score (IPSS) score at each time point from pretreatment baseline (green), through the acute 12 week follow-up period (orange), and the late follow-up period (blue), up to 5 years. The error bar indicates the upper interquartile range.

Figure 2.12: Correlation between IPSS rise and acute genitourinary toxicity



Scatter plot demonstrating the correlation between acute RTOG genitourinary (GU) toxicity and magnitude of rise in International Prostate Symptom Score (IPSS) within first 12 week follow-up period. r, Spearman's Correlation Coefficient.

Figure 2.13: Correlation between maximum IPSS and acute genitourinary toxicity

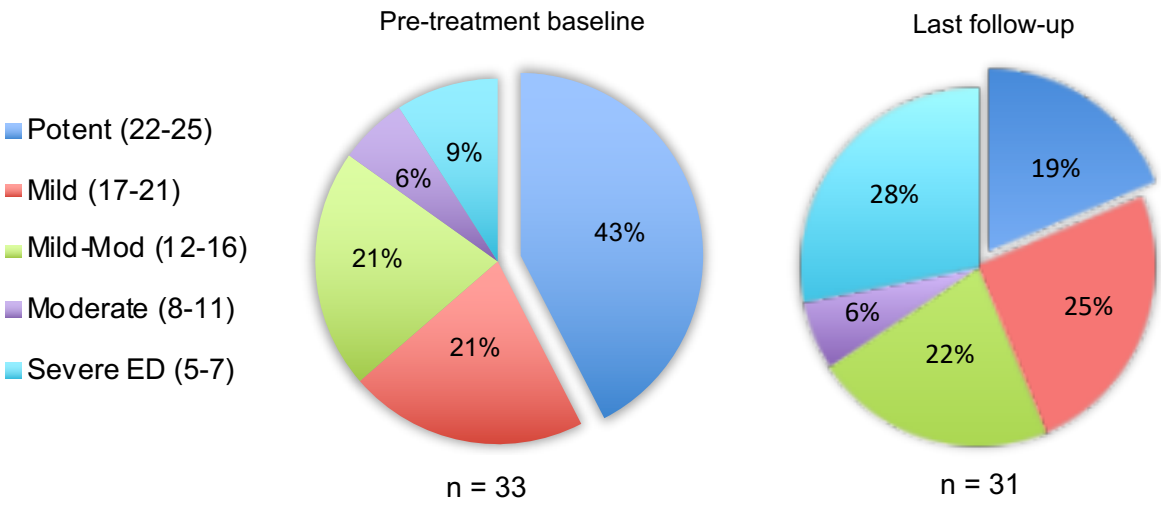


Scatter plot demonstrating the correlation between acute RTOG genitourinary (GU) toxicity and maximum International Prostate Symptom Score (IPSS) during the first 12 week follow-up period.. r, Spearman's Correlation Coefficient.

2.5.3.4. Patient reported outcomes for erectile dysfunction

Baseline IIEF questionnaires (Appendix 5) were completed in 41 (66.1%) patients. Eight patients on androgen deprivation therapy (ADT) were excluded from this analysis. The baseline scores of the remaining 33 patients are summarised in Figure 2.14, demonstrating that 14 patients (43 %) were considered to be potent at baseline (IIEF score 22-25). Follow-up IIEF questions were completed in 31 patients. 18 patients (58.1%) maintained the same level of erectile function compared to baseline including 6 (46.15%) of the 13 patients who were potent at baseline. At the time of last follow-up, 19% of patients were potent at the time of last follow-up, with an increase in severe erectile dysfunction to 28%.

Figure 2.14: Erectile function



Pie charts demonstrating International Index of Erectile function (IIEF scores) at baseline and at last follow-up. Patients receiving concomitant androgen deprivation therapy (ADT) were excluded from this analysis. Each segment represents the percentage (%) of patients with each degree of erectile function as defined by the IIEF score grouping shown and colour coded in the legend. n, number of completed IIEF questionnaires

2.5.4. The effect of volume, dose and fractionation on toxicity rates

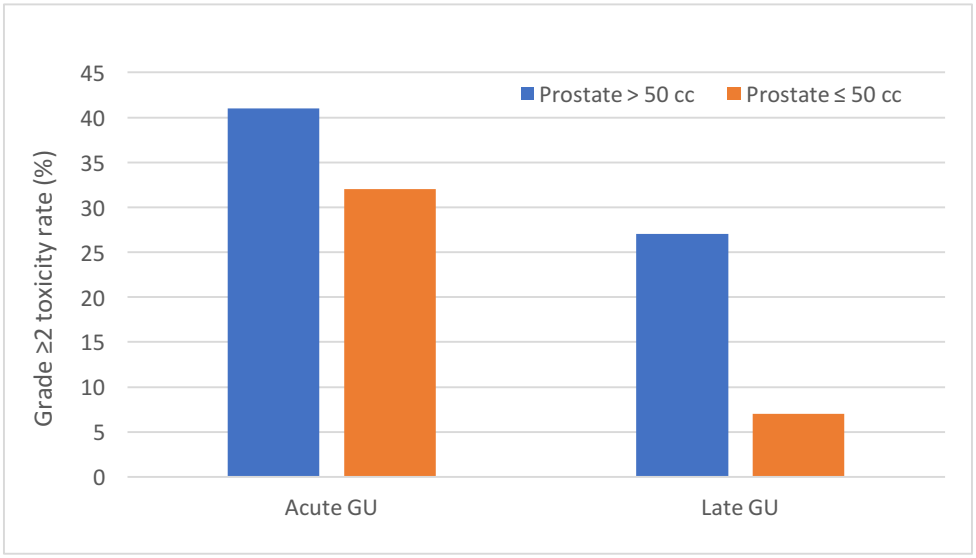
The target volume and dosimetry data for all patients is summarised in Appendix 6, categorised according to worst reported RTOG acute and late GU and GI toxicity.

2.5.4.1. The effect of target and OAR volume

The median prostate volume in my study was 53 cc, ranging between 17 and144 cc. 34 patients in this series had a prostate volume >50 cc, and 28 patients had a prostate volume ≤50 cc. The acute ≥G2 GU toxicity rate was 9% higher in the patients with prostate volume >50 cc (Figure 2.15). The late ≥G2 GU toxicity was as much as 20% higher in patients with prostate volume >50 cc although it does not represent a statistically significant difference (p = 0.13).

The median PTV was smaller in patients with no acute GU toxicity (87.12 cc, IQR 78.18 – 114.2 cc) in comparison to those with ≥G2 toxicity (120.4 cc, IQR 91.89 – 135.6 cc) but not statistically significant. Consistent with the prostate volume results, patients with a PTV volume > 100 cc had a 6% (p=0.17) and 9% (p=0.18) higher rate of acute and late GU toxicity, respectively, and a 17% higher rate of acute ≥G2 GI toxicity compared to patients with PTV ≤ 100 cc, but again not a significant difference (p=0.35).

Figure 2.15: Effect of prostate volume on genitourinary toxicity



Bar chart demonstrating ≥ grade 2 RTOG toxicity rates, comparing patients with prostate volume >50 cc and patients with prostate volume ≤50 cc. GU, genitourinary.

As shown in Appendix 6, the median bladder volume for those with acute GU toxicity was larger (294 cc, IQR 182.3 – 378.3 cc) than those with ≥G2 toxicity (171 cc, IQR 130.4 – 346.8). In this series, similar to PACE B, we aimed for a bladder volume of ≥150cc, which was met in 46 cases at the time of the planning scan. Of the 16 patients with a bladder volume of <150 cc, the incidence of acute ≤G2 GU toxicity was much higher at 63% compared to 28% in patients with a bladder volume ≥150 cc, although not quite reaching statistical significance (p=0.057).

The median volume of bladder to receive 18.1 Gy (V18.1 Gy) was the only dosimetric value where a significant difference was detected between those with G0 (19.5%, IQR 12.48 – 29.10 %), and those with ≥G2 acute GU toxicity (28%, IQR 19.2 – 37.1 %, p=0.015). No significant difference was detected for any parameter between those with no toxicity and those ≥G2 late toxicity. The median urethral V44 Gy was lower in patients with no late urinary toxicity, however the numbers of patients in which the urethra had been contoured was too low to detect a significant difference.

No significant difference in dosimetry was detected between those with no acute GI toxicity and those ≥G2 GI toxicity. The median rectal V36 Gy, V 29 Gy and V18.1 Gy were higher in men with ≥G2 toxicity, and the median V 36 Gy was higher in the 5 patients with late ≥G2 GI toxicity 5 patients but no significant difference was detected.

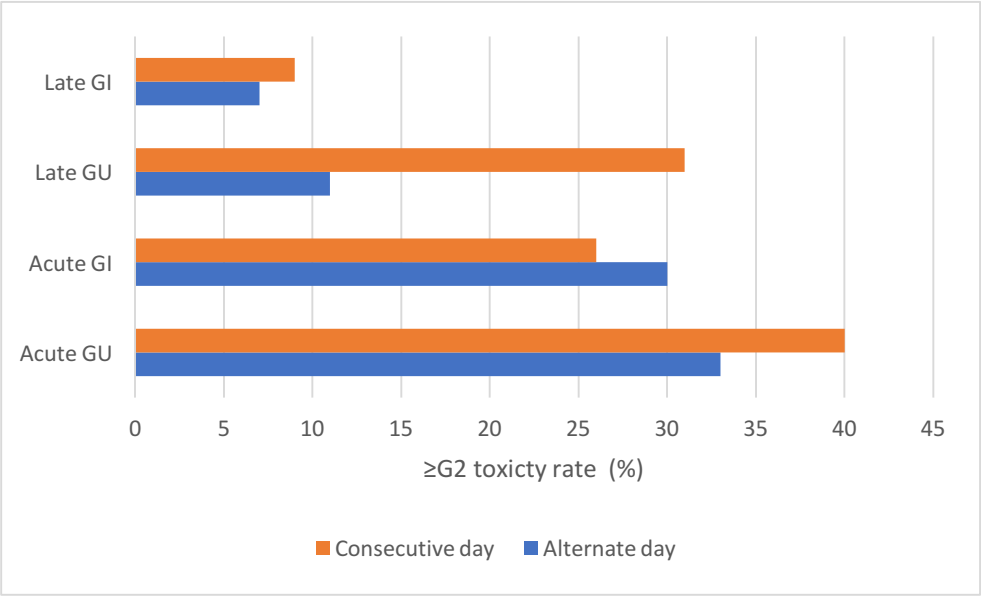
2.5.4.2. Effect of daily versus alternate day fraction

The toxicity rates of patients treated with daily SBRT over 1 week compared to patients treated with alternate day treatment over 2 weeks is demonstrated in Figure 2.16. No statistically significant difference in acute or late ≥ G2 toxicity was detected however there was a marked difference in the rates of late GU toxicity, occurring in 31% of patients treated with daily fractionation compared to 11% of patients treated over alternate days ($p = 0.09$).

2.5.4.3. Effect of prostate volume and consecutive day versus alternate day fractionation

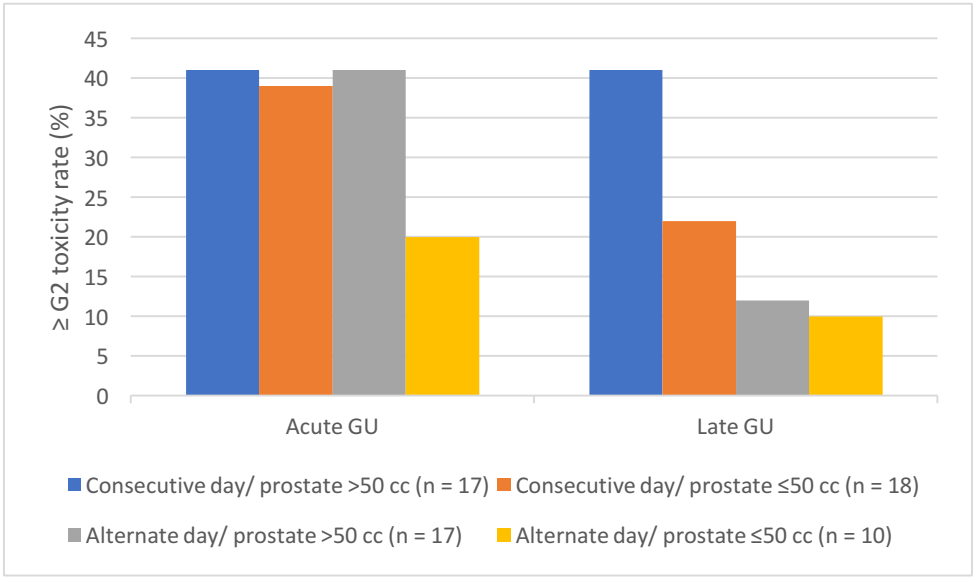
The combination of a large prostate >50 cc and daily fractionation resulted in a significantly higher rate of late ≥GU toxicity (Figure 2.17). Patients with a large prostate, in which SBRT was delivered on consecutive days, had a 41% late ≥G2 GU toxicity rate, compared to patients with a small prostate, receiving SBRT over alternate days, in which late ≥G2 GU toxicity only occurred in one patient (10%, $p=0.044$). In addition, the patients with large prostates had an almost 30% higher rate of late ≥G2 GU toxicity rate if treated over consecutive days rather than on alternate days ($p = 0.019$). The difference in late toxicity from the use of alternate day fractionation was not significant in patients with small prostate ≤ 50 cc and there was no significant difference found in acute toxicity between the groups.

Figure 2.16: The effect of fractionation on toxicity



Bar chart demonstrating ≥ grade 2 RTOG toxicity rates, comparing patients treated with alternate day fractionation versus patients treated with daily fractionation. GU, genitourinary; GI, gastrointestinal.

Figure 2.17: The effect of prostate volume and fractionation on genitourinary toxicity



Bar chart demonstrating ≥ grade 2 RTOG toxicity rates, comparing patients treated with alternate day fractionation versus patients treated with daily fractionation. GU, genitourinary; GI, gastrointestinal.

2.6. Discussion

My results support the implementation of SBRT, for the management of low- and intermediate-risk prostate cancer within the UK. To date, as far as I am aware, this is the only series within the UK reporting long-term data following prostate SBRT. I have confirmed 5-year efficacy and toxicity outcomes to be consistent with data from other studies, internationally. This is further supported by acceptable rates of physican-reported acute and late toxicity, and favourable patient-reported data with regard to urinary and sexual function.

2.6.1. Efficacy outcomes

2.6.1.1. Freedom from biochemical progression

Results from the prospective data, at 5 years median follow-up, demonstrated an overall 5-year freedom from biochemical progression (FFBP) rate of around 94%. This has been corroborated by results from my later retrospective analysis of PSA response, at 81 months median follow-up. There is substantial variation in efficacy reporting between studies. The larger studies, with at least 5 years follow-up, report FFBP or biochemical progression free survival (bPFS) rates of 85-100%[3,19]. The large meta-analysis, by Jackson et al, which included 38 prospective studies, reported an overall 5-yr BPFS rate of 95.3% (95% CI 91.3 – 97.5), and 93.7% at 7 years (95% CI 91.4 – 95.5)[1]. I have reported an estimated 7-year FFBP rate of 88%, however longer follow-up is required to validate this, given only 27 patients had reached 7 years follow-up.

The rate of biochemical progression post SBRT is associated with pre-treatment NCCN prostate cancer risk classification. In a pooled analysis of data from 8 institutions, including 1100 patients, the 5-year BPFS rate was significantly different between low- (95%) intermediate- (84%) and high- (81%) risk patients[3,19]. In the recent metanalysis by Jackson et al, there was a lack of data regarding biochemical control by risk group, especially in studies with high-risk patients. Of those studies that reported on separate risk groups, there was a 5-year bRFS of 96.7% for low-risk patients compared to 92.1% with intermediate-risk disease[1]. In my cohort, none of the 6 patients who were classified as high-risk developed biochemical recurrence by the time of last follow-up (median 48 months). Aside from the small number cases, the use of ADT in 3 patients may have had some effect, in addition to the relatively short follow-up period (< 5 years) in 4 cases. The 5-year FFBP rate for the intermediate risk group alone was 96%, but the number of low-risk patients was too low to accurately assess, with 2 out of the 5 patients developing biochemical progression at 3.5 and 8 years follow-up.

2.6.1.2. PSA kinetics

PSA kinetics after SBRT can differ from external beam radiotherapy (EBRT) in terms of expected PSA nadir (nPSA), rates of PSA decline as well as the likelihood and magnitude of PSA bounce[20]. Following conventional EBRT, nPSA of <0.5ng/ml, and time to nadir of >24 months have been shown to be associated with improved biochemical relapse free and distant metastases free survival[21,22]. In comparison, the nPSA tends to be lower following SBRT or high-dose-rate (HDR) brachytherapy [23].

The prognostic role of nPSA after SBRT has not yet been fully validated, however brachytherapy studies have demonstrated an association between a lower nPSA of ≤0.2 ng/ml and long-term efficacy[24,25]. A recent multi-institutional study which included 14,220 patients treated with low-dose-rate (LDR) brachytherapy, demonstrated that in the 77.1% of patients with a 4 year PSA of ≤0.2, the FFR rate was 98.7% at 10 years and 96.1% at 15 years[25]. A multi-institutional retrospective analysis of 1062 SBRT patients, at 66 months median follow-up, found nPSA to be a significant predictor of failure[26]. In that study the median nPSA was 0.2ng/ml, with median time to nadir of 40 months, with 84% and 54% of patients reaching a nPSA of ≤ 0.5 ng/ml and ≤0.2ng/ml, respectively. In my analysis, excluding patients receiving ADT, the median nPSA was 0.17 ng/mL, with median time to nadir of 5 years, which is encouraging. A nPSA of ≤0.5 ng/ml was reached in 84.9%, and ≤0.2 ng/ml in 62.3%.

A further multi-institutional study, including 1908 SBRT patients, analysed the effect on PSA kinetics of different SBRT dose and fractionation schedules (35 Gy/5 fractions, 36.25 Gy/ 5 fractions, 40 Gy/ 5 fractions and 38 Gy/ 4 fractions)[20]. The median nPSA for the whole population was 0.18ng/ml, with no significant difference between the 5 fraction regimens, but markedly lower at 0.01 ng/ml in the 38 Gy 4-fraction group, with a faster rate of decay. This, however, did not equate to improved biochemical control in this group. The median time to nadir was longest in the 40 Gy in 5-fraction group and was associated with a lower probability of biochemical recurrence compared to the other dose groups. As concluded by the authors, this would suggest that escalation above 40 Gy in 5 fractions may not be associated with improved biochemical control and the low nPSA level may simply reflect ablated benign prostate tissue. However,

with a median follow-up of 6 years, longer-term differences in biochemical control associated with a lower nPSA may not have been captured.

A benign PSA bounce, which is well recognised following brachytherapy, is frequently seen after SBRT, and less often after conventional EBRT[11-13,15]. In this series, 40% of patients had at least one PSA bounce, consistent with other SBRT studies reporting a bounce in 15 - 51% of cases[11,14,26-28]. The median magnitude of PSA rise in the literature ranges between 0.5 – 1.0 ng/ml, usually occurring at 9 - 36 months follow-up but has been described up to 7 years after SBRT[11,15,26,28,29]. In my series, the PSA rose by a median magnitude of 0.7ng/ml, peaking at a median time of 12 months (range 6 – 36 months), although in one patient a second bounce was seen as late as 42 months follow up.

Ascertaining the pattern of PSA bounce post SBRT is important it has implications for post-treatment monitoring. Some cases risk being misinterpreted as biochemical failure, as described in a pooled analysis of 4 prospective trials, where 8 % of patients had a PSA bounce of nadir + 2 ng/ml[14]. Proceeding to salvage therapy based on a PSA rise should be considered with caution, and treatment ideally reserved for radiologically confirmed recurrence. As shown in Table 2.3, two patients in this series, with a previous history of PSA bounce, had a PSA level of nadir + 2 ng/ml at their most recent follow-up, fitting the criteria for biochemical recurrence. At 8 years follow-up, this would be more consistent with disease recurrence, however, they continued on PSA monitoring since imaging was not confirmatory.

The mechanism of PSA bounce remains uncertain - potentially due to prostitis, an immune response or unexplained late radiation effect[28]. Several studies have demonstrated an association with radiation dose, young age, increased prostate volume, and lower-risk prostate cancer[11-13,15,28,29]. In this series, 42.86% of bounce-positive patients had a low Gleason score of 6, markedly higher than the total population. In a recent metanalysis, the PSA nadir and time to nadir was higher in bounce-positive patients compared to bounce-negative patients[11]. This fits with my series in which 5 (23.8%) bounce-positive patients had a PSA nadir ≤ 0.1 ng/ml compared to 18 (56.3%) of bounce-negative patients; and the time to nadir was significantly longer in the bounce-positive patients, at a median of 72 months compared to 42 months ($p = 0.0007$).

Current data is inconclusive regarding the prognostic significance of a PSA bounce. Some studies have demonstrated no correlation [12,14,15,26], but more recent studies have demonstrated PSA bounce to be associated with reduced risk of biochemical recurrence[27,28]. This may simply be due to the associated lower-risk disease, and results should be interpreted with caution as studies are highly heterogenous and mainly retrospective in methodology. In my series, none of the patients presenting with biochemical recurrence within 6 years follow-up had a previous PSA bounce, however numbers are too small to assess any association between PSA bounce and FFBR.

2.6.2. Genitourinary toxicity

2.6.2.1. Acute toxicity

Acute GU side effects are common following prostate radiotherapy, typically including symptoms of urinary frequency, weak stream or dysuria, with incontinence and haematuria being unusual in the acute setting. I have reported ≥ G2 acute GU toxicity occurring in 37.1% of cases, including 8% with G3 toxicity. This is less than reported within the 60 Gy/ 20# arm of the CHHIP trial (49%), and is consistent with our previous results published at 2.5 years follow up[9,30]. My results are within range of acute toxicity reported in other SBRT studies, although higher than the overall ≥ G2 GU toxicity rate of 16% reported in the Jackson meta-analysis, and the multicentre trial by Meier et al which reported 26% acute G2 GU toxicity and no G3 cases G3 [4,7].

Acute toxicity results from PACE B demonstrated no significant difference in RTOG ≥ G2 GU toxicity between SBRT and conventional/ moderately hypofractionated radiotherapy, reported as 23% and 27% respectively. However, in the HYPO trial the frequency of acute ≥ G2 GU toxicity was higher in the ultrafractionated group (28%) compared to the conventional radiotherapy arm (23%)[31]. In comparison to conventional EBRT, symptoms following SBRT occur earlier, typically peaking in the first 1-2 weeks following treatment, which is consistent with my data.

2.6.2.2. Late toxicity

In terms of late GU toxicity, 16.13% and 6.5% of patients in my cohort had a worst reported toxicity of G2 and G3 respectively, which is higher than expected in comparison to some studies. For example, in the multicentre trial by Meier et al, which employed the same dose and OAR constraints, 12% of patients experienced worst reported late GU toxicity of G2, and 1.3% G3[32]. Kishan et al reported an estimated 5-year cumulative incidence rates from their pooled analysis of 10 institutions, in which 9 studies had at least 5 years follow up, and SBRT dose ranging between 33.5 Gy – 40 Gy in 4/5 fractions[3]. They reported 11.2% G2 and 1.8% G3 toxicity which is again lower than my results where the estimated 5-year cumulative incidence rate was 18.25% for G2 and 8.6% for G3 toxicity[3]. Some studies, however, have reported higher rates of late ≥G2 GU toxicity, with rates up to 30% or more in some studies[33-35].

My data demonstrates a clear pattern of late GU toxicity. The majority of patients who developed G2 toxicity often had a combination of symptoms including frequency, urgency, dysuria and/ or weak stream within the first 6 – 24 months of follow up, usually settling within 6 – 12 months. This is consistent with the pattern of late urinary flare, which has been previously described after SBRT[36-38] and has long been recognised following brachytherapy in over 20% of patients[39,40]. Symptoms are usually self-limiting and the majority settle with conservative management. The aetiology is not well understood but is thought likely to be inflammatory, with evidence of radiation induced cysto-urethritis on endoscopic examination[37]. Some association with younger age has been demonstrated but no link to baseline IPSS or previous acute urinary

toxicity, and no clear temporal relationship between the onset of urinary flare and benign PSA bounce[37,41].

In my series, the four cases of late G3 toxicity occurred later at a median of 48 months follow-up (range 18 – 48 months), and all symptoms had settled by the following 6-month assessment. Two patients required intervention for urethral/ bladder neck strictures, and a further patient was temporarily catheterised for acute urinary retention. This is in keeping with other studies which report invasive intervention for urinary obstruction to be rare at <5%[42]. I reported ≥G2 haematuria in 5 (8%) patients at median 30 months follow-up. Haematuria is known to occur in around 20% of patients post radiotherapy, the causes of which are multifactorial, but some evidence exists of an association with total dose and volume of the bladder neck and urethra in the high dose region, as well as history of previous transurethral resection of prostate (TURP)[43]. In a study of 208 patients, treated with SBRT 35 - 36.25 Gy in 5 fractions, Gurka et al demonstrated at least one episode of haematuria in 18.3 % of patients at a median of 38 months follow-up. They found no association with anticoagulation use, and typical cystoscopic findings consisted of hyperaemia of the bladder neck and prostatic urethra, with bladder cancer diagnosed in 1.4% of cases[44].

2.6.2.3. The effect of prostate volume

The inclusion of patients with larger prostate volumes in this series may explain the higher rates of GU toxicity compared to some other studies. Zelefsky et al included only patients with a maximum prostate volume of <60 cc[35] and the Meier et al reported a median prostate volume of 43 cc[4], compared to 53cc in my study. In PACE B, 46% of patients had a prostate size of ≥ 40 cc, compared with 72.6% in my series[4,7].

The patients in my series with a prostate > 50 cc in volume had a higher rate of both acute and late ≥G2 urinary toxicity compared to patients with prostate volume ≤50 cc. The difference in late toxicity was most marked, with a ≥G2 toxicity rate of 27% in those with large prostates compared to 7% in those with smaller prostates. Although this was not statistically significant it is of clinical relevance and is in keeping with published studies as discussed in chapter 1.

In the retrospective review by Janowski et al, which included 57 patients with prostate volumes ranging between 50 and 138.7 cc (median 62.9 cc), there was a high 2 year ≥ G2 GU toxicity incidence of as much 49.1%[45]. Repka et al also demonstrated patient-reported acute urinary symptoms in in 12% of patients with a prostate volume less than the median volume of 36 cc, compared to 33% in those with prostate volume >36 cc[46]. In the dose escalation trial by Potters et al, a prostate volume >60 cc was found to be significantly associated with a higher rate of G2 toxicity, with no difference in toxicity between dose levels (40 Gy, 45 Gy and 50 Gy)[47].

2.6.2.4. Effect of bladder dose and volume

In this study I detected a significant difference in the median bladder V18.1 Gy between patients with no toxicity and those with ≥G2 acute GU toxicity. The impact of bladder dose on acute GU toxicity is not well understood, though some association between toxicity and dose to the bladder trigone has previously been demonstrated[48]. Using a dose-surface map technique, Henderson et al were unable to demonstrate an association between bladder trigone dose and ≥ G2 RTOG acute GU toxicity but did demonstrate a correlation between patients with an IPSS rise > 10 and the percent of bladder trigone receiving ≥ 40 Gy [49]. Repka et al also demonstrated some association between IPSS-defined toxicity and dose to 15.5% of the bladder wall, but no association with urethral dose[46]. Using NTCP modelling, Kole et al demonstrated an association between late urinary flare and bladder dose, with a reduced rate of toxicity in those cases with a bladder D12.7% of 33.5 Gy or less [41].

Bladder size may influence acute GU toxicity, since smaller bladder volumes could result in increased bladder mean dose. Byun et al demonstrated[33] which resulted in a small significant increase in bladder mean dose, however, did not demonstrate association with toxicity[33]. In this series I have demonstrated that patients with a bladder volume of <150 cc, which is lower than the minimum bladder volume requirement for prostate radiotherapy at RMH, had a much higher incidence of urinary toxicity.

2.6.2.5. Effect of dose and fractionation

There does not appear to be a clear link between SBRT dose escalation and increased ≥G2 acute GU toxicity[50,51]. In the dose escalation study by Zelefsky et al, the incidence of acute ≥ G2 GU toxicity was not significantly different for each dose level[35]. However, there was evidence of an association between dose and late GU toxicity with a higher incidence of late ≥ G2 toxicity at each dose level of 23.3%, 25.7%, 27.8% and 31.4% for the 32.5 Gy, 35 Gy, 37.5 Gy and 40 Gy dose levels, respectively. The only G3 toxicity was a urethral stricture which occurred in the 40-Gy dose arm. In contrast, the phase 2 study by Fuller et al, in which a higher biologically equivalent dose of 38 Gy in 4 fractions was delivered, reported relatively low cumulative 5-yr grade ≥2 GU toxicity rate of 14.7%[5]. In the phase I/II dose-escalation study reported by Hannan et al, a significant difference in ≥G2 late GU toxicity was not detected between the lowest 45 Gy, and highest 50 Gy dose levels (20% vs 19%), but ≥G3 GU toxicity occurred only in the 50 Gy dose level group (G3 4.9% and G4 1.6% G4)[51].

One of the main findings of my study was the higher rate of late ≥GU toxicity in patients treated with SBRT over consecutive days compared to patients treated with alternate-day fractionation. Patients receiving daily treatment had a 20% higher rate of late ≥G2 GU toxicity. This alone was not found to be statistically significant, however in the group of patients with larger prostates (>50 cc), the difference in late ≥GU toxicity was significantly greater in those treated with daily fractionation, at 41% compared to 12% in those treated on alternate days (p=0.019). This is similar to the findings of King et al demonstrating that patients treated with alternate day fractionation had significantly lower rates of late ≥G1 GU and GI toxicity of 17% and 5%, respectively, in comparison

to patients treated over consecutive days in which 56% and 44% developed late ≥G1 GU and GI toxicity, respectively[52]. No significant difference in acute toxicity was detected between daily- and alternate-day fractionation which is consistent with earlier results reported by Henderson et al[9]. Although, as previously discussed, results from the PATRIOT trial demonstrated some improvement in acute GU toxicity, by treating once weekly, rather than on consecutive days[53].

In comparison to CFMHRT, there are concerns regarding potential higher rates of late GU toxicity with SBRT[54]. The 5-year cumulative ≥G2 toxicity rate within the CHHIP trial 60 Gy/ 20 fraction arm was 11.7%, which is lower than reported in my series; but in the PROFIT trial 22.2% of patients, who received the moderately hypofractioned dose, had worst reported late GU toxicity of ≥ G2[30,55]. A large retrospective study including 1335 SBRT and 2670 IMRT patients, identified from a US service claim database, reported urinary toxicity following SBRT in 43.9% of patients, compared to 36.3% post IMRT[56]. Randomised trial evidence is ultimately required, and long-term results from PACE B are therefore greatly anticipated. In the meantime, results from the HYPO trial are encouraging which demonstrated no significant difference between treatment arms, except at 1 year post treatment when the cumulative late GU ≥G2 rate was 6% for the ultra-fractionated arm and 1% for the conventional arm[31].

2.6.2.6. Patient- reported urinary toxicity

A particular strength of this study has been the use of the IPSS score to evaluate urinary symptoms from the patient's perspective and to confirm consistency with physician reported toxicity, in which the risk of under-reporting is more likely. As my

results have demonstrated, there was only moderate correlation between IPSS scores and RTOG GU toxicity grade. Unfortunately, IPSS scores are not recorded in the majority of SBRT studies for comparison with my results. The PACE B acute toxicity paper did present IPSS data, with no significant difference found between treatment arms. In comparison to my results, the median baseline IPSS, magnitude of IPSS rise and 12- week IPSS were very similar, although the maximum IPSS score was lower in the PACE B SBRT arm at 13 (IQR 8-19) compared to 18 (IQR 9.5 – 23) in my study.

A number of studies have defined acute and late urinary symptom flare as: ≥ 5 rise in IPSS from baseline, peaking at a maximum IPSS score of ≥15[34,37,39]. Using this criteria Repka et al reported acute urinary symptom flare in 22.3% of patients[46]. In my series, according to this criteria, 27 (43.5%) patients developed acute urinary flare, which included all 5 patients who developed RTOG G3 toxicity and 72% of patients with G2 toxicity. In addition to the smaller median prostate volume of 36 cc, the other difference from my study was that all patients were prescribed prophylactic alpha-adrenoceptors prior to treatment. Using the same definition, investigators from the same centre reported late urinary flare in 13 – 21% of patients receiving SBRT, 35 – 36.25 Gy in 5 fractions[37]. At a median time to flare of 9 months, the median magnitude of IPSS flare was 13, returning to baseline by 2 years. In my series, 14 (22.9%) patients fulfilled this IPSS criteria for late urinary flare urinary, although corresponded with only 43% of those with RTOG ≥ G2 late toxicity and in none of the patients with G3 toxicity.

2.6.3. Gastrointestinal toxicity

Acute ≥ G2 GI toxicity, manifested as proctitis and diarrhoea, was evident in 27.4% of my cohort, with one case of G3, due to diarrhoea and faecal incontinence at 4 weeks follow-up. Importantly, symptoms were short lived with the majority occurring during treatment or in the first 1-2 weeks of follow-up and settling within 8 weeks. This compares well with the CHHIP trial results in which 38% of patients in the 60Gy/ 20 fraction arm developed ≥ G2 acute GI toxicity[30]. However, my result is higher in comparison to many other SBRT studies where the frequency of ≥ G2 acute GI toxicity ranges between 0 – 18%[1,3-5,7,57]. Low levels of acute GI toxicity are reported in the Jackson metanalysis: G2 6.1%, G3 0.06% and G4 0.03%[1], and Meier et al reported 8.1% G2 toxicity with no G3 or higher[4]. Within the PACE trial there was no significant difference in RTOG ≥ G2 acute GI toxicity between the two arms: SBRT 10% G2, <1% G3; CFMHRT 11% G2 and 1% G3 . However, using CTCAE criteria, acute GI toxicity was significantly worse in the SBRT arm at 16% versus 8% in the CFMHRT arm[7].

Dose escalation studies have demonstrated an association between increasing dose and acute GI toxicity. Zelefsky et al reported G2 rates of 0, 2.9, 2.8 and 11.4% for 32.5 Gy, 35 Gy, 37.5 Gy, and 40 Gy dose levels respectively, with no grade 3 or 4 toxicity[50]. Hannan et al report G2 rates of 6.7%, 26.7% and 23% for the 45 Gy, 47.5 Gy and 50 Gy dose levels, in addition to 1.6% G3 and 1.6% G4 toxicity in the 50 Gy cohort[51]. This group previously demonstrated a significant correlation between G2 acute rectal toxicity and treatment of >50% rectal wall circumference to ≥24 Gy[58].

Late GI toxicity is much less common than late GU toxicity, which is reflected in my data, with ≥ G2 late GI toxicity occurring in 8.1% of patients. Crucially, all symptoms had resolved by 5 years follow-up. The majority of SBRT studies report very low rates of ≥ G2 late GI toxicity of 2 – 6.4%[1,3-5]. There is no evidence to suggest any difference in comparison to conventional or hypofractioned radiotherapy, as evidenced by the HYPO trial results which reported an estimated 5-year cumulative toxicity of 10% in both arms. My results also compare favourably with the CHHIP trial data in which the ≥G2 GI toxicity rate was 11.9% in the 60 Gy arm , and 13.7% in the 74 Gy arm.

Remarkably, no patients in the dose escalation trial by Zelefsky et al trial developed late ≥G2 GI toxicity. Hannan et al reported low levels of toxicity in patients treated at the 45 Gy and 47.5 Gy, dose level, however at 50Gy, a high level of late GI toxicity was reported, with almost 10% of patients developing ≥G3 toxicity, including 5 patients who required a colostomy[51,58,59]. Kim et al detected a strong association between high grade rectal toxicity and the volume of rectum receiving high-dose radiation[58]. There was a significant correlation between G3 toxicity and rectal wall V50 Gy of > 3cc, and >35% of rectal wall circumference receiving ≥ 39 Gy.

I have reported only one ≥G2 case of late rectal bleeding, but it is a relatively common late GI symptom. Musunuru reported a rate of 19.4% in 258 patients receiving SBRT 35 – 40 Gy in 5 fractions, occurring at a median of 11.7 months from the start of radiation. They found the volume of rectum receiving ≥ 38 Gy to be a strong predictor of high-grade rectal bleeding, and some association with target volume size, PTV margin, radiation dose, history of haemarroids and anticoagulation use[60].

The implantation of a rectal gel spacer to increase distance between rectum and prostate, may reducing rectal toxicity. This was not used in my study but its use has become increasingly common in prostate radiotherapy. A randomised trial involving 222 patients treated with IMRT 79.2 Gy demonstrated a reduction in the mean rectal V70 Gy and a 5 % reduction in late rectal toxicity [61]. Given the small number of patients and short follow-up of 15 months, the benefit of routine use in SBRT remains uncertain, particularly since the rates of late rectal toxicity are already low in the majority of studies. However, this method may provide certain advantages in selected patients.

2.6.4. IIEF scores and sexual function

Only 66% of patients in my series completed IIEF questionaries at baseline, which reduced further during follow-up. This was not unexpected given the sensitive nature of the questionnaire. Comparison of results with other studies was limited, as not always reported and the definition of erectile function by IIEF score differed between studies. I have reported 43% of patients completing baseline IIEF questionnaire were potent (IIEF score ≥ 22) prior to SBRT. At the time of last follow-up 19% of patients remained potent. Dess et al reported IEFF data in 373 patients receiving SBRT 35 – 36.25 Gy in 5 fractions, without ADT. IIEF questionnaires were completed in 99% of patients, using IEFF score of ≥ 16 to define functional erection. 49% had IEFF score ≥ 16 at baseline, reducing to 34% and 30% at 24 and 60 months[62]. Similarly, in my study 67% had a baseline IPSS of ≥ 16 which reduced to 52% and 37% at 24 and 60 months, respectively.

The randomised Phase 3 HYPRO study is the largest study reporting sexual function after hypofractionated radiotherapy. They reported that, at baseline, 70% of patients were able to achieve an erection sufficient for intercourse and that this fell to 35% at 5 years. No significant difference was between conventional and hypofractionafed arms, corroborated by a further study which excluded patients who received short term hormones [31,63,64]. A systematic review by Loi et al included 12 SBRT studies, all using the Expanded Prostate Cancer Index Composite-26 (EPIC-26)[65] to measure sexual quality of life and demonstrated erectile dysfunction in 26 – 55% of previously sexually functioning patients at 5 years[66].

2.6.5. Study limitations

Although my results have been helpful in confirming efficacy rates of SBRT to be consistent with other centres and highlighting potential methods for reduce toxicity, there are limitations which may have impaired effective comparison with other studies. In particular, this is a small study of 62 patients from a single centre, which may have affected the validity of my results in comparison to the larger studies and may explained the higher-than-expected toxicity rates. For example, the use of the Kaplan-Meier method to estimate 5-year cumulative toxicity may be less appropriate in a small study, and risks overestimating toxicity.

In addition, the substantial variation of toxicity reporting between studies complicates any comparison. Firstly, there is likely to be some effect from the use of different scoring criteria. In the recent meta-analysis by Jackson et al, the Common Terminology for Adverse Events (CTCAE) criteria was used in 19 studies and RTOG

criteria in 13 studies[1]. A demonstration of this variation lies in the results from PACE B in which both RTOG and CTCAE (version 4.0) scoring systems were used, with a noticeable discrepancy between toxicity rates. As previously mentioned, the RTOG acute G2 GU toxicity rates were not significantly different, at 23% and 27% for the SBRT and CFMHRT arms, respectively (p=0.16). However, using CTCAE criteria, the toxicity rate was higher for the SBRT arm at 30.8%, compared with 23% for the CFHRT arm (p=0.01)[7]. Similarly for acute ≥ G2 GI toxicity, RTOG defined toxicity rate was 10% for SBRT arm and 12% for CFMHRT arm, compared with the CTCAE defined rate of 16% for SBRT and 8% for CFMHRT. In another example, Meier et al reported 3 cases requiring catheterisation in the acute setting which were classified as G2 using CTCAE version 4.0, but in our study, using RTOG criteria the same patients are likely to have been classified as G3.

The accuracy and consistency of toxicity recording is difficult to ensure in a large multicentre trial with numerous investigators, and in an unblinded randomised trial there is a risk of observer bias which may affect reporting. The design of the case report form may also have had an influence on the higher reported toxicity rates in this study. For example, in our small study, a small number of investigators completed RTOG scoring using a detailed print-out of RTOG criteria (Appendix 3), which in comparison to the more simplified PACE B case report form (CRF), may have increased the likelihood of toxicity reporting.

Discrepancies in the timing and frequency of toxicity data collection, which is often not reported, may also have contributed to differences in toxicity rates between studies. Meier et al recorded acute toxicity at 4 time points: final fraction, 1 week, 1 month, and

3 months post treatment, which is less frequent than our study and, therefore, may have reduced the ability to capture acute toxicity[4]. Hannan et al, reported an acute GI toxicity rate of 23%, defining acute toxicity as symptoms occurring less than 270 days from treatment. This contrasts with the study by Boyer et al, who defined acute toxicity as occurring within 90 days of treatment, and only recorded CTCAE scores at 1 month and 3 months follow-up[51,57].

2.7. Conclusion

- SBRT to the prostate in a UK population at a dose of 36.25 Gy in 5 fractions shows a FFBP rate of 94%, equivalent to other international studies
- PSA kinetics, including PSA nadir, time to nadir and frequency of PSA bounce occurring in 40% of patients were consistent with other studies.
- Acceptable rates of acute GU toxicity (37.1%) were confirmed, but higher than reported in some the larger studies. This may simply be related to differences in toxicity reporting, and potentially influenced by the inclusion of patients with large prostate volumes and/ or volume of irradiated bladder. Importantly, symptoms were short-lived and resolved by 12 weeks follow-up with conservative management in all cases. The use of prophylactic alpha-adrenoreceptor antagonists could be considered to reduce toxicity.
- Late GU toxicity was higher than expected (22.9%), however the majority of symptoms were typical of late urinary flare, occurring within the first 2 years of treatment and settling within 6 – 12 months after conservative management. Prevalence rates may therefore be a more accurate reflection of the severity of late GU toxicity. A significant increase in late toxicity was demonstrated in patients with larger prostate volumes > 50 cc and receiving daily SBRT. Consideration of alternate-day fractionation should therefore be considered in these patients.
- As expected, GI toxicity was less common occurring in 27.4% in the acute setting but settling within 8 weeks of treatment, and 8.1% late toxicity which is consistent with other studies.

- Sexual function data was available from 66% of patients, and of those who were potent at baseline, 46% demonstrated no deterioration in function, consistent with other studies.
- The results of this study add to evidence supporting the use of prostate SBRT, but ultimately the long -term results from the PACE trial will be vital to adequately compare SBRT with conventional treatments.
- As with other reports, the majority of patients in this analysis had low- and intermediate-risk prostate cancer, without the addition of hormones. It therefore does not answer the question of whether SBRT is safe and effective in higher-risk patients, and this is being addressed in the PACE C trial.

2.8. References

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Chapter 3: Quality assurance in Stereotactic Body Radiotherapy planning for localised prostate cancer using data from multiple centres within the PACE B trial.

Sections of the following chapter have been published/ presented as:

- Variability analysis of clinical target volume (CTV) outlining for prostate SBRT within the multicentre PACE trial[1].

  Morrison K, Naismith O, van As N

  Poster presentation, British Urology Group Annual Meeting, Sep 2018

  Abstract in Clinical Oncology 2019: 31(2): e23

- Improving consistency of proximal seminal vesicle (pSV) delineation for prostate SBRT[2].

  Morrison K, van As N

  Poster presentation, ESTRO 38, Milan, Italy, April 2019

  Abstract in

- Clinical target volume definition schema included in PACE C contouring guidelines (Appendix 8)[3].

  The PACE Trial (Prostate Advances in Comparative Evidence)

  Radiotherapy planning and delivery guidelines (PACE-A and PACE-C) 2020

3.1. Introduction

As discussed in chapter 2, stereotactic body radiation therapy (SBRT) is an effective and well tolerated treatment for low- and intermediate-risk prostate cancer. The aim of phase III PACE trial is to address the remaining uncertainty regarding comparability with conventional treatment, randomising patients between SBRT and surgery (PACE A) or standard radiotherapy (PACE B). As discussed in chapter 1 PACE B completed accrual in 2017 having successfully opened in at least 40 centres throughout the UK, Ireland and Canada.

In a large multicentre radiotherapy trial such as PACE B, a robust quality assurance (QA) programme is vital to ensure protocol compliance and optimise the reliable interpretation of results. Protocol deviations in radiotherapy trials are common and have been shown to be associated with inferior clinical outcomes[4,5]. Radiotherapy QA is of particular importance in the use of high precision techniques such as SBRT, which involves advanced planning techniques, accurate image guidance and reduced target volume margins to deliver ultrafractionated radiotherapy while optimising normal tissue sparing. The CyberKnife robotic system employs multiple non coplanar beams to produce a sharp dose gradient and inhomogenous dose distribution[6]. As discussed in chapter 1, it possesses the ability to compensate for intrafractional motion with submillimetre accuracy, relying on fiducial markers to track translational and rotational motion.

These techniques permit the use of reduced target volume margins in order to maximise normal tissue sparing however as a result, there is less a smaller margin for

error and potentially a greater risk of geographical miss. The accuracy of SBRT is therefore highly dependent on the precise delineation of the target volume and organs at risk, at the outset. Inaccuracies at this early stage will lead to systematic error which may have clinical implications in terms of tissue toxicity and tumour control[7]. Recommendations by The Royal College of Radiologists (RCR) state that radiotherapy departments should have a process to enable optimal target volume delineation and peer review[8].

3.1.1 Interobserver contouring variability

Interobserver variability in volume delineation is a well-recognised challenge in radiotherapy planning and an important contributor to systematic error as discussed in chapter 1[9]. Target volume delineation is associated with the greatest potential for variability and observer bias[10] and in prostate radiotherapy, clinical target volume (CTV) delineation is a significant issue[11,12]. Discrepancies are documented to be most marked at the prostatic apex and seminal vesicles, with a greater degree of consistency at the rectal-prostate and prostate-bladder interfaces[12].

Variability in interobserver contouring has led to the increased use of detailed contouring guidelines and protocols both in radiotherapy departments and multicentre trials. Implementation of a contouring protocol can result in a marked improvement in interobserver contouring variability as demonstrated by Mitchell et al following the introduction of the contouring protocol for post prostatectomy radiotherapy taken from the RADICALS trial[13].

The completion of a satisfactory benchmark contouring and planning exercise as a requirement for multicentre trial entry has become more common place. The aim is to reduce interobserver variability and ensure adherence to protocol guidelines. Prior to entry into PACE B, all centres were required to submit a benchmark exercise which was reviewed by the PACE QA team in accordance with the trial protocol.

PACE-C, which was discussed in chapter 1, includes patients with higher risk prostate cancer, randomised between SBRT and moderately hypofractionated radiotherapy. In preparation for PACE-C opening, it was important to review the extent of interobserver contouring variability among centres within PACE B, which may influence the design of the protocol contouring guidelines for PACE C As previously explained in the first chapter, a greater proportion of the seminal vesicles (SV).

3.2. Hypothesis

- There is significant CTV outlining variability between PACE trial centres, most marked in the delineation of the proximal seminal vesicles (pSV).

- It is possible to define a standard method for pSV delineation which will improve consistency within clinical practice and future SBRT trials.

3.3. Aims

- To conduct a review of pre-trial benchmark outlining cases submitted within the PACE trial quality assurance programme for PACE-B entry, evaluating the proportion of outlining deviations and determine specific areas of variability.

- To analyse the degree of CTV outlining variability between centres, with the use of conformity indices.

- To define a standard method for proximal seminal vesicle delineation in prostate SBRT and confirm improvement in interobserver variability.

3.4. Retrospective review of benchmark case feedback proformas

3.4.1. Methods

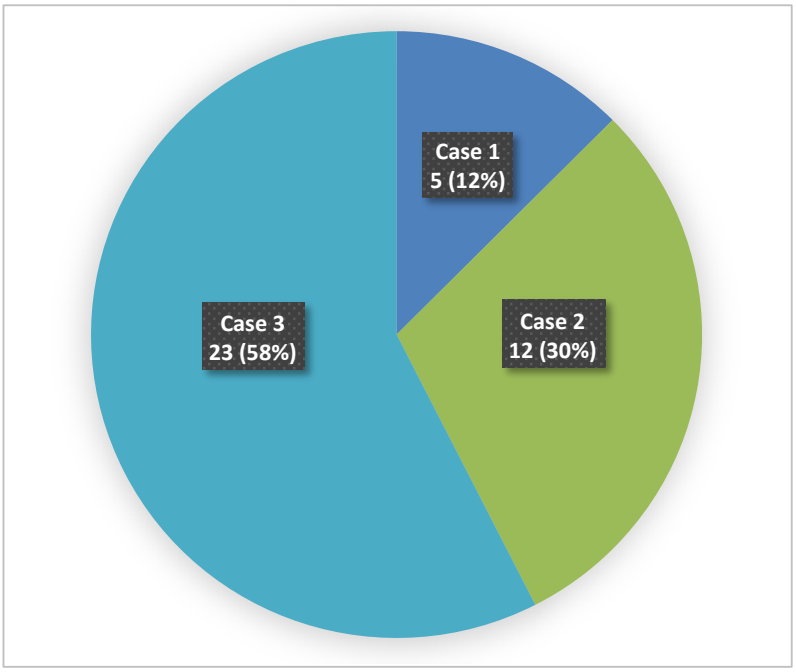
3.4.1.1. PACE B trial benchmark exercise

Before being approved to open PACE B, interested centres were required to submit a completed benchmark contouring and planning exercise. Forty centres had submitted benchmark cases for review by the final date for PACE B entry in August 2017.

Each centre was provided with anonymised CT and MRI images for an intermediate-risk prostate cancer case. The benchmark cases were created using imaging data from previously treated prostate SBRT cases, who had consented for their data to be used for research, education and training. Centres were required to accurately fuse images and contour target volumes and organs at risk (OARs) to include rectum, bladder, bowel, femoral-heads and penile bulb, as defined in the trial protocol. Using the completed structure set they were required to complete separate conformal and SBRT plans, as appropriate.

As demonstrated in Figure 3.1, not all centres received the same benchmark case image set. The decision was made to change the case used on two occasions. Case 1 had a urinary catheter in situ which was a requirement of the original protocol and, therefore, was changed following protocol amendment. Case 2 was changed following review as images were felt to be suboptimal and prone to subjective interpretation. 58% of centres completed the benchmark exercise using the case 3 images.

Figure 3.1: Proportion of centres receiving each benchmark case



Pie chart demonstrating the proportion of centres receiving each benchmark case image set.

3.4.1.2. Benchmark case review process

In my role as SBRT research fellow, I contributed to the clinical outline review between March 2016 until completion of the benchmark exercise in August 2017. Submitted structure sets were uploaded to the Eclipse (Varian Medical Systems, USA) planning system research terminal for contouring review. The review was in the form of a visual assessment conducted by the PACE QA team consisting of the chief investigator, physicist and SBRT research fellow. For each review a feedback proforma was completed and returned to the participating centre, reporting any protocol deviations, recommended changes, and approval status for trial entry. Centres were deemed either: suitable for inclusion in PACE and advised to address any comments in future plans; or not approved at this stage with the opportunity to address any issues and resubmit for further review.

3.4.1.3. PACE B contouring guidelines

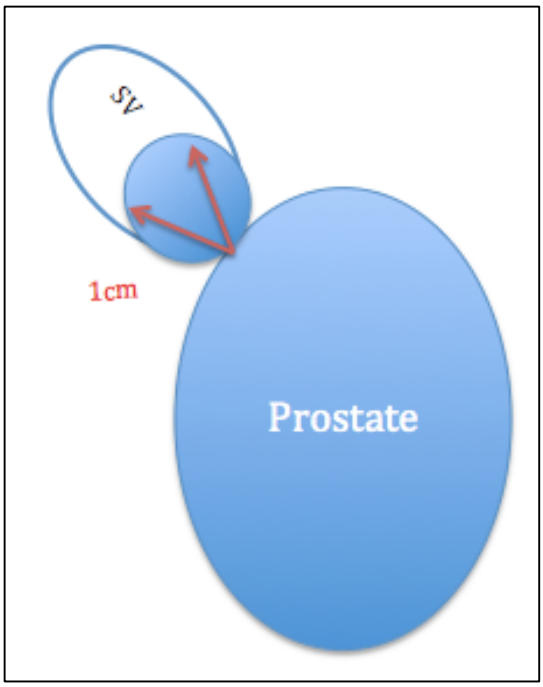
Benchmark cases were reviewed with reference to contouring guidelines within the PACE trial protocol (Table 3.1). The CTV for both standard radiotherapy and SBRT arms, includes the whole prostate +/- 1cm pSV, dependent on the National Comprehensive Cancer Network (NCCN) risk-category (Table 1.1). As demonstrated, CTV contouring guidelines have been refined in protocol amendments over time to improve pSV outlining. Since the version 5 amendment, a schematic diagram was added to illustrate how the 1cm pSV should be defined (Figure 3.2), and version 7 included a more detailed description of how to define the 1cm pSV. The definition for each OAR delineation is summarised in Table 3.2.

Table 3.1: PACE protocol CTV outlining guidelines

Protocol version	Low risk	Intermediate risk
Version 1. Nov 2011	GTV = prostate only CTV = GTV + 1 – 2 mm	GTV = prostate + 1 cm pSV CTV = GTV + 1 – 2 mm
Version 5. June 2015	CTV = prostate only	CTV = prostate plus 1 cm pSV
Version 7. March 2016	CTV = prostate only	CTV = prostate plus 1 cm pSV from insertion point in the superior-inferior plane. To include the middle 1⁄2 – 2⁄3 SV width (i.e. not the tips).

Summary of the CTV outling guidelines from the PACE procotol, demonstrating protocol amendments made to clarify proximal seminal vesicle (pSV) definition . GTV, gross tumour volume; CTV, clinical target volume.

Figure 3.2: PACE B definition of 1cm proximal seminal vesicle delineation



Schematic illustration taken from the PACE trial protocol demonstrating the proximal seminal vesicle (pSV) outlining definition for intermediate-risk patients. CTV shown in blue; SV, seminal vesicles.

Table 3.2: Summary of organ at risk (OAR) delineation

Organ at risk	Definition
Rectum	Solid structure, including lumen and rectal wall, extending from the anus to the rectosigmoid junction.
Bowel	Extending above rectum, within 15 cm of PTV (within 4 cm for gantry based RT). May be outlined as “bowel bag”.
Bladder	solid structure, including the bladder wall and lumen.
Urethra	if visible
Penile bulb	portion of bulbous spongiosum that lies inferior to the urogenital diaphragm.
Femoral heads	exclude femoral neck
Testes	blocking structure

3.4.1.4. Retrospective evaluation of benchmark case reports

Benchmark case reports completed within the PACE trial QA programme were retrospectively reviewed. The following data was recorded:

- The number of centres approved for PACE trial entry following the initial benchmark case submission.

- The number of submissions from each centre before trial entry approval was granted.

- The number of outlining deviations for each case.

- The most common sites of CTV and OAR outlining deviation.

3.4.2. Results

Sixty-seven benchmark QA reports from 40 centres were available for retrospective review, completed between November 2012 and August 2017. As demonstrated in Figure 3.3, 50% of centres were approved for trial entry following their initial benchmark case review. The remaining centres were required to resubmit cases for further review after making recommended changes to clinical outlining. 87.5% were approved for trial entry following review of the 2nd submission. Only one centre was required to make further changes and resubmit before being approved for trial entry.

Figure 3.3: Centre approval following PACE benchmark case submission.

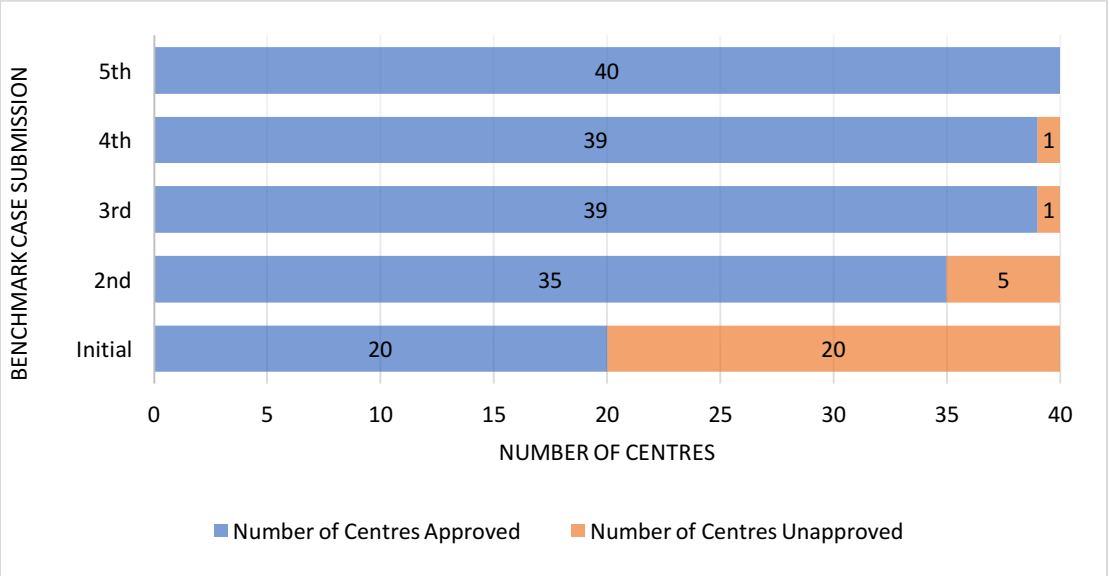


Table 3.3 summarises the clinical outlining deviations documented on the initial benchmark report for each centre. Changes to CTV outlining was recommended in 36 (90%) out of the 40 initial benchmark reports. This was recorded in 19 (95%) of the 20 unapproved centres reports. The most common CTV deviation was proximal seminal vesicles (pSV) contouring, which was recorded in 32 (80%) of 40 reports, and in 18 (90%) of the 20 unapproved cases. Specifically, the excessive inclusion of seminal vesicle within the volume was the most frequently noted CTV outlining issue. Prostate contouring deviations were documented in 25 (62.5%) centres, and in 13 (65%) of unapproved centres. Deviations in OAR outlining (Table 3.4) were more varied, with the highest proportion of deviations at the rectal and bowel sites. The most common documented issue was variability in defining the superior limit of the rectum at the recto-sigmoid junction.

Results from this study confirm that this most common outlining deviation in the PACE B benchmark exercise was in the CTV and particularly pSV outlining. The next part of the study involves a quantitive analysis of contouring variability between centres.

Table 3.3: CTV discrepancies documented on the initial PACE benchmark reports

CTV Structure	Contouring Deviation	Total centres (n=40)	Approved centre (n=20)	Unapproved centres (n=20)
CTV whole		36	17	19
Prostate		25	12	13
	Apex	11	4	7
	Base	8	5	3
	Posterior margin	7	4	3
	Anterior/ lateral margin	7	4	3
Proximal seminal vesicles		32	14	18
	Excessive	18	8	10
	Insufficient	13	6	7
	Inaccurate	7	4	3

Table 3.4: The number of organ at risk discrepancies documented on the initial PACE benchmark feedback reports

OAR Structure	Contouring Deviation	Total centres (n=40)	Approved centre (n=20)	Unapproved centres (n=20)
Rectum		20	9	11
	Inferior border	11	3	8
	Superior border	9	5	4
Bowel		22	12	10
	Inferior border	8	5	3
	Insufficient	9	2	7
	Excessive	10	7	3
Bladder		14	7	7
	Inferior border	7	2	5
	CTV overlap	7	4	3
Penile Bulb		13	6	7
Femoral Heads		18	9	9

3.5. Analysis of CTV contouring variability

3.5.1. Methods

I conducted an analysis of CTV contours from the initial benchmark case submitted by each centre. This included only the 23 centres who completed the exercise using case 3 (Figure 3.1). Twenty-one contours were available for analysis due to technical difficulties uploading the original imaging from two of the centres. The contours from each centre (investigational contours) were compared to reference PACE CTV, prostate and pSV contours which were previously outlined by me, and reviewed by PACE Chief Investigator, Dr van As.

3.5.1.1. Software

DICOM (Digital Imaging and Communications in Medicine) data from each centre were imported into the VODCA (Visualisation and Organisation of Data for Cancer Analysis) software program. The reference PACE CTV contour was outlined, with MRI fusion, using Eclipse contouring software and imported to VODCA for analysis.

3.5.1.2. CTV contours

All CTV contours, including the reference contour, were combined into a single structure set on VODCA (Figure 3.4). The benchmark exercise required centres to submit a combined CTV only and I used a Boolean operator function on VODCA to create separate investigational pSV and prostate structures, by subtracting the

reference prostate contour (Figure 3.5). This ensured consistency, although does not take into account any variability in defining the SV insertion point. VODCA.

3.5.1.3. Conformity indices

The following indices were calculated (Figure 3.6) to quantitively assess investigational structures against the reference structures:

DICE similarity coefficient (DSC): Overall indicator of how well the investigational volume conforms to the reference volume.

Geographical Miss Index (GMI): Measures proportion of the reference volume not included by the investigational volume.

Disconcordance Index (DI): Measures proportion of the investigational volume exceeding the reference volume.

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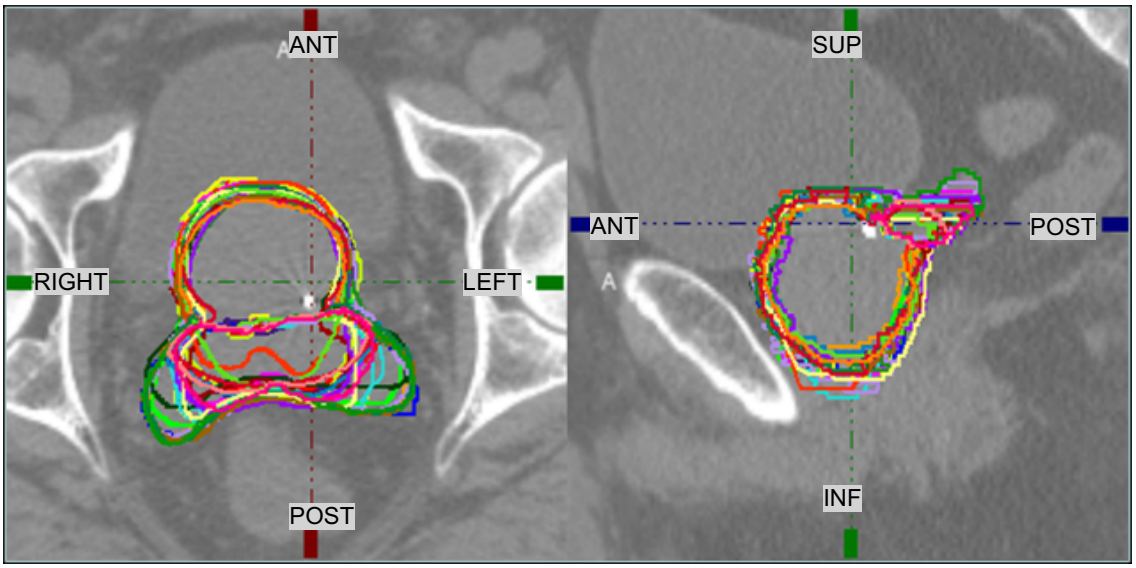
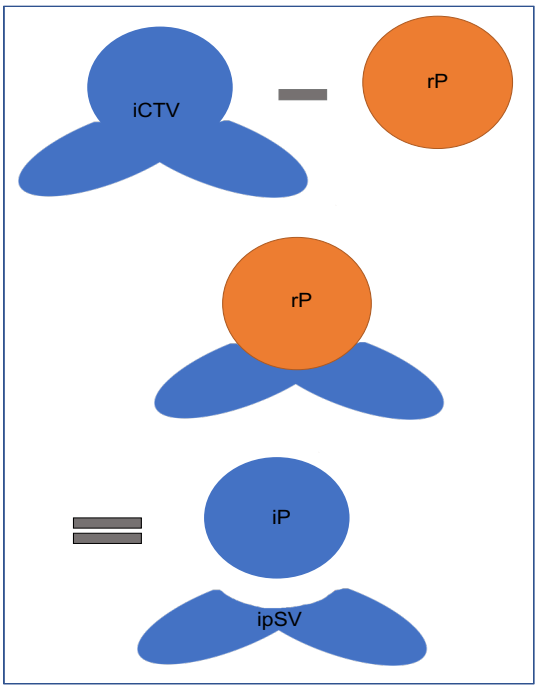
Figure 3.4: Investigational contours from PACE B benchmark exercise



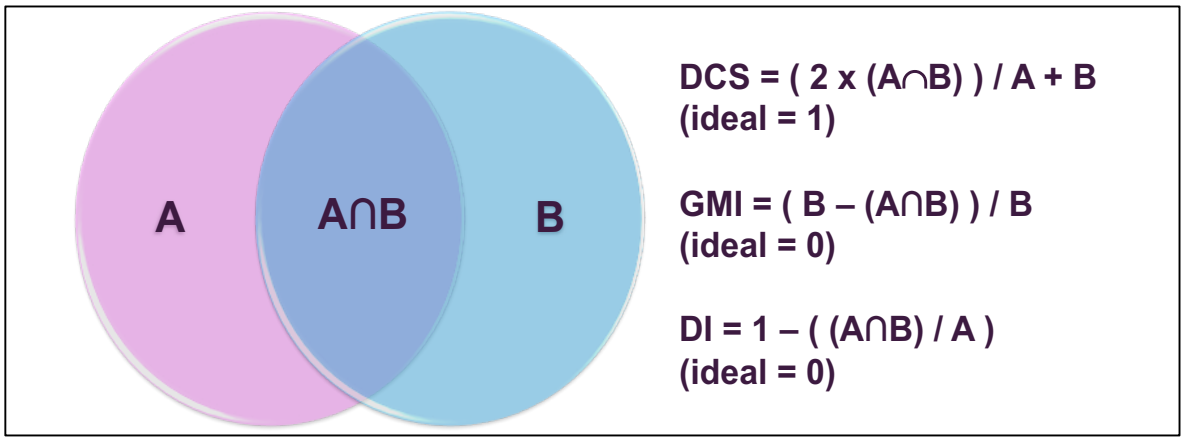
Screenshot of axial and sagittal CT slices taken from VODCA (Visualisation and Organisation of Data for Cancer Analysis) computer program, demonstrating 21 investigational CTV and pSV outlines centres participating in the PACE trial benchmark quality assurance (QA) exercise. Ant, anterior; Post, posterior; sup, superior; Inf, inferior.

Figure 3.5: Boolean operator function to creating investigational prostate and pSV structures



Schematic diagram demonstrating the Boolean operator function. The investigational proximal seminal vesicle (ipSV) volume is defined by subtracting the reference prostate (rP) volume from the investigational CTV (iCTV).

Figure 3.6: Conformity indices



Schematic diagram and equations used to calculate DICE similarity coefficient (DCS), Geographical Miss Index (GMI) and Disconcordance Index (DI). A, investigational contour; B, reference contour; A∩B, intersection of investigation contour and reference contour.

3.5.1.4. Comparison and statistical methods

CTV and pSV contours for each centre were directly compared to the reference PACE CTV and pSV contours. Simple volume measurements (cc) and calculation of conformity indices were used to compare differences in volume and position[14-17].

The Prism version 9 (© 1994 - 2021 GraphPad Software, LLC) package was used to conduct the statistical analysis. Shapiro-Wilk test was used to test for normality, reporting normally distributed variables with mean and 95% confidence interval, and variables without normal distribution reported with median and interquartile range (IQR). The Mann-Whitney U non-parametric test was performed to detect statistically significant differences in median CI values between prostate and pSV contours. The Spearman's correlation coefficient (r) was used to detect the significance of correlation between pSV volume and conformity indices.

3.5.2. Results

The volume and conformity index results of 21 investigational structures sets, as compared to the reference contours are summarised in Table 3.5.

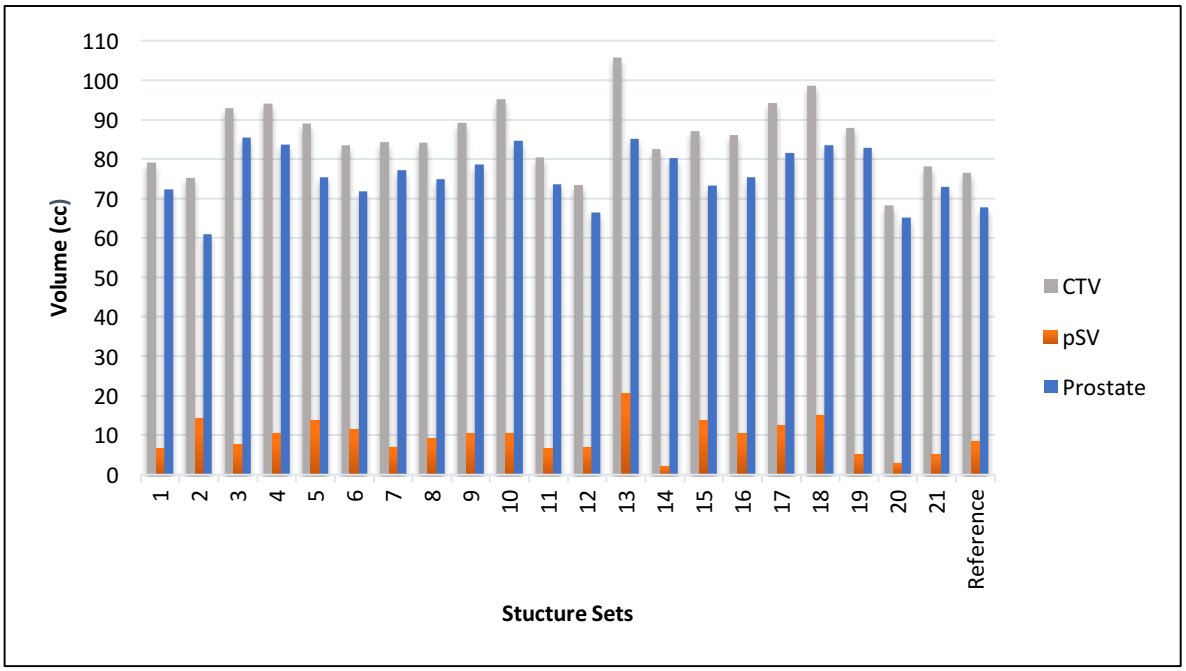
Figure 3.7 demonstrates the volumes (cc) of the reference, and each investigational CTV, prostate and pSV contour. The investigational CTV volumes ranged between 68.31 – 105.7 cc, with a mean volume of 86.16 cc (95% CI 82.11 – 90.21 cc), larger than the reference CTV volume of 76.4 cc. The investigational prostate volumes ranged between 60.43 – 85.43 cc, with mean volume of 76.43 cc (95% CI 73.29 – 79.58 cc); and pSV volumes ranged between 2.21 – 20.59, with mean volume of 9.72 cc (95% CI 7.75 – 11.75 cc). The mean volumes for both the investigational prostate and pSV contours were greater than the reference contours which measured 67.8cc, and 8.7 cc for prostate and pSV, respectively.

Table 3.5: Volume and conformity index results

Structure	Measurement	Volume	DSC	GMI	DI
CTV	Reference	76.4	1	0	0
	Mean	86.16	0.88	0.06	0.16
	Median	86.10	0.88	0.06	0.17
	Range	73.52 – 105.7	0.82 -0.91	0.01 – 0.15	0.07 – 0.23
pSV	Reference	8.7	1	0	0
	Mean	9.72	0.70	0.25	0.27
	Median	10.36	0.72	0.18	0.30
	Range	2.21 – 20.59	0.39 – 0.86	0.03 – 0.76	0.03 – 0.62
Prostate	Reference	67.8	1	0	0
	Mean	76.43	0.90	0.04	0.15
	Median	75.46	0.90	0.03	0.15
	Range	60.93 -85.43	0.87 – 0.93	0.01 – 0.09	0.04 – 0.22

Volume and conformity indices of the investigational CTV, pSV and prostate contours in comparison to the reference PACE contours. CTV, clinical target volume; pSV, proximal seminal vesicles; DSC, DICE similarity cooefficient; GMI, geographical miss index; DI, Disconcordance Index.

Figure 3.7: Volumes of investigational and reference structures

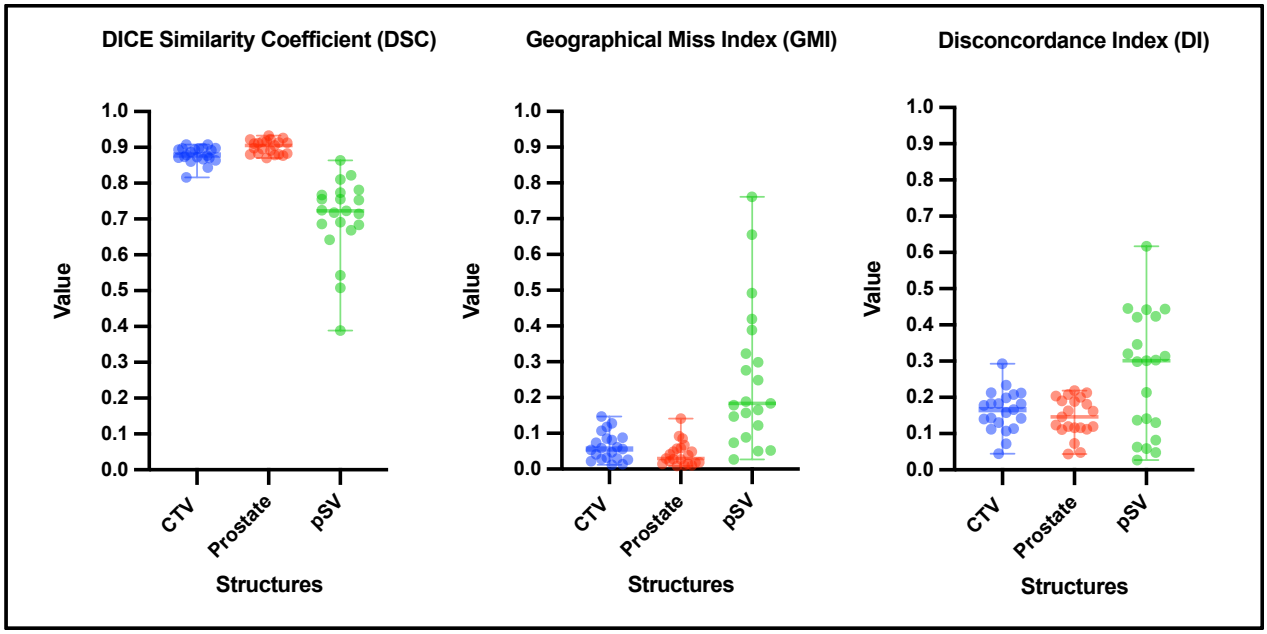


CTV, clinical target volume; pSV, proximal seminal vesicles

As clearly demonstrated in Table 3.5 and Figure 3.8, the median DCS for the pSV outlines is significantly lower at 0.72 (IQR 0.68 – 0.77, $p < 0.0001$) compared to the prostate outlines, and DSC markedly varies between centres to as low as 0.39 in one case. This confirms considerable interobserver variability for pSV outlining compared to overall CTV and prostate in which the median DCS is 0.88 (IQR 0.87 – 0.90) and 0.91 (IQR 0.88 – 0.92). Both values are close to one, confirming relative agreement in outlining between centres.

For the CTV and prostate contours, the median GMI was calculated as 0.06 (IQR 0.03 – 0.09) and 0.04 (IQR 0.02 – 0.06) respectively, close to the ideal value of zero, indicating low geographical miss. The GMI for the pSV contours was also low but slightly higher than the prostate contours, with a median value of 0.18 (IQR 0.11 – 0.36, $p <0.0001$). The median DI values were 0.17 (IQR 0.12 – 0.2) and 0.15 (IQR 0.11 – 0.2) for CTV and prostate contours respectively. The median DI for the pSV contours was higher at 0.3 (IQR 0.11 – 0.42) the DI, ranging between 0.027 – 0.617, indicating that, overall, centres were more likely to over-contour the pSV in comparison to the reference contours.

Figure 3.8. Comparing CTV, prostate and proximal seminal vesicle interobserver variability



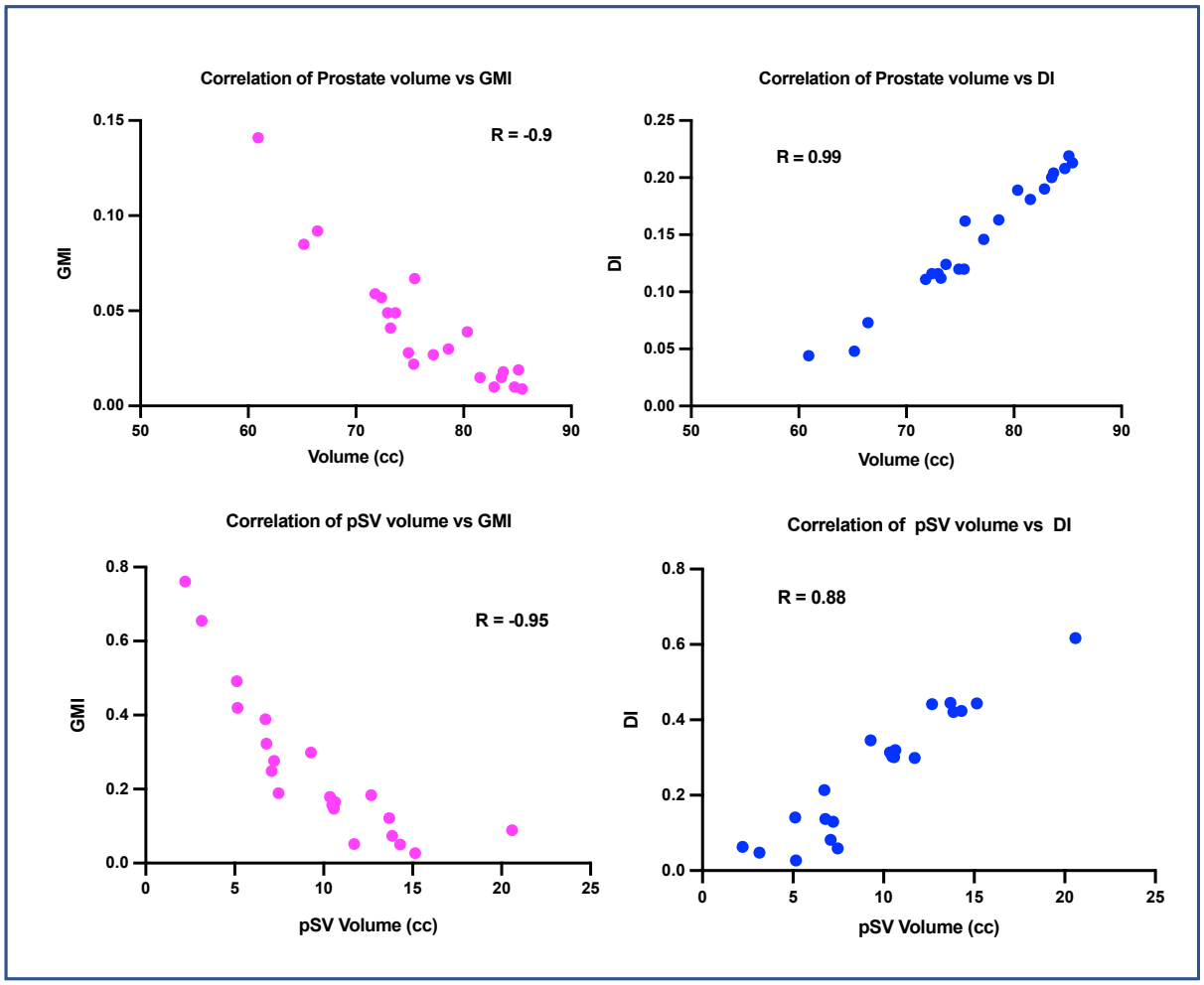
Scatter charts with individual conformity index values plotted for clinical target volume (CTV), prostate and proximal seminal vesicle (pSV). The dots represent each investigational contour and error bars represent the median value.

The relationship between volume (cc) and conformity indices for the prostate and pSV contours is demonstrated in Figure 3.9**.** For both structures, the GMI is inversely related to volume (cc), which is as predicted, since smaller volumes are associated with greater risk of geographical miss. Conversely, the DI correlates well with increasing prostate and pSV volumes, since the chance of increasing excess tissue with large volumes is increased.

As shown in Figure 3.9, a small change in pSV volume has a greater effect on GMI and DI. The prostate volumes range between 60.93 – 85.43 cc with a difference of 24.5 cc, while the pSV volumes range between 2.21 – 20.59 cc which is a lower absolute difference of 18.38 cc, although proportionally a greater increase in volume. The prostate GMI and DI range difference is 0.08 and 0.18, respectively, while the pSV GMI and DI range difference is larger at 0.73 and 0.59. Therefore, in the context of pSV delineation, even slight non-concordance with reference contours has a greater impact on conformity index results.

My results demonstrate significant interobserver variability in pSV outlining and highlights the need an improved method of delineation which I evaluate in section 3.6.

Figure 3.9: Conformity indices versus volume



Scatter charts demonstrating geographical miss index (GMI) and Disconcordance index (DI) against volume of prostate and proximal seminal vesicles (pSV). R, Spearman correlation coefficient.

3.6. Defining a new method to improve the consistency of pSV contouring

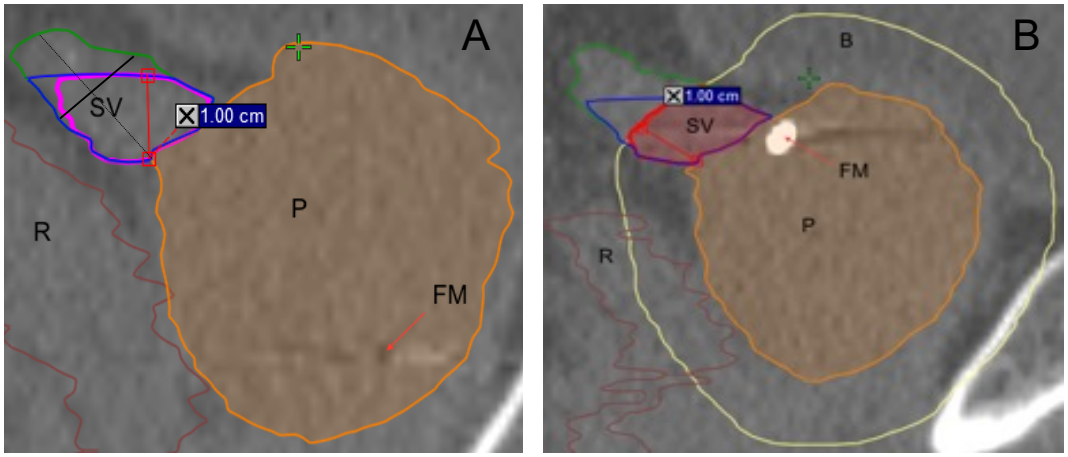
3.6.1. Method

3.6.1.1. Establishing a method of pSV delineation

As discussed in chapter 1, I conducted a literature review to establish methods of pSV delineation used in radiotherapy studies. There was no clear consensus and, in most studies, the method of delineation was not documented. Similar to the PACE B protocol, EORTC guidelines recommend inclusion of 1 cm SV for intermediate-risk patients, as measured vertically from the SV insertion point, and RTOG IMRT trial protocols include 1cm pSV, measured both vertically and radially[18,19]. I tested both methods as shown in Figure 3.10, and as suggested by Qi et al (Figure 1.8), both methods did not achieve adequate coverage anteriorly, with over-coverage posteriorly[20]. This was in relation to a perpendicular line drawn at 1cm along the central axis of the seminal vesicles from the insertion point at the prostate.

I attempted to recreate the method for pSV delineation as described by Qi et al which involves using reconstructed planning CT images to measure along the central SV axis[20]. Although this may produce contours more consistent with SV anatomical variations, the process was time-consuming and not easily reproducible. I have therefore investigated the use of a semi-automated method for delineation, which is easily reproducible, and conforms better to the SV anatomy in comparison to the EORTC method as shown in Figure 3.10.

Figure 3.10: Methods of proximal seminal vesicle delineation (pSV)



Sagittal slices from a CT planning scan. (A) demonstrating 1 cm proximal seminal vesicles (pSV) as defined in EORTC guidelines (blue) and RTOG IMRT RTOG0815 and RTOG0126 trial protocols (magenta). The red ruler indicates 1 cm measured vertically from the prostatic insertion point. The black lines indicate 1cm measured on the central axis. (B) demonstrating 1cm proximal seminal vesicles (pSV) as defined by a semi-automated method of delineation(red) in comparison to the EORTC method (blue). SV, seminal vesicle; P, prostate; R, rectum; FM, fiducial marker.

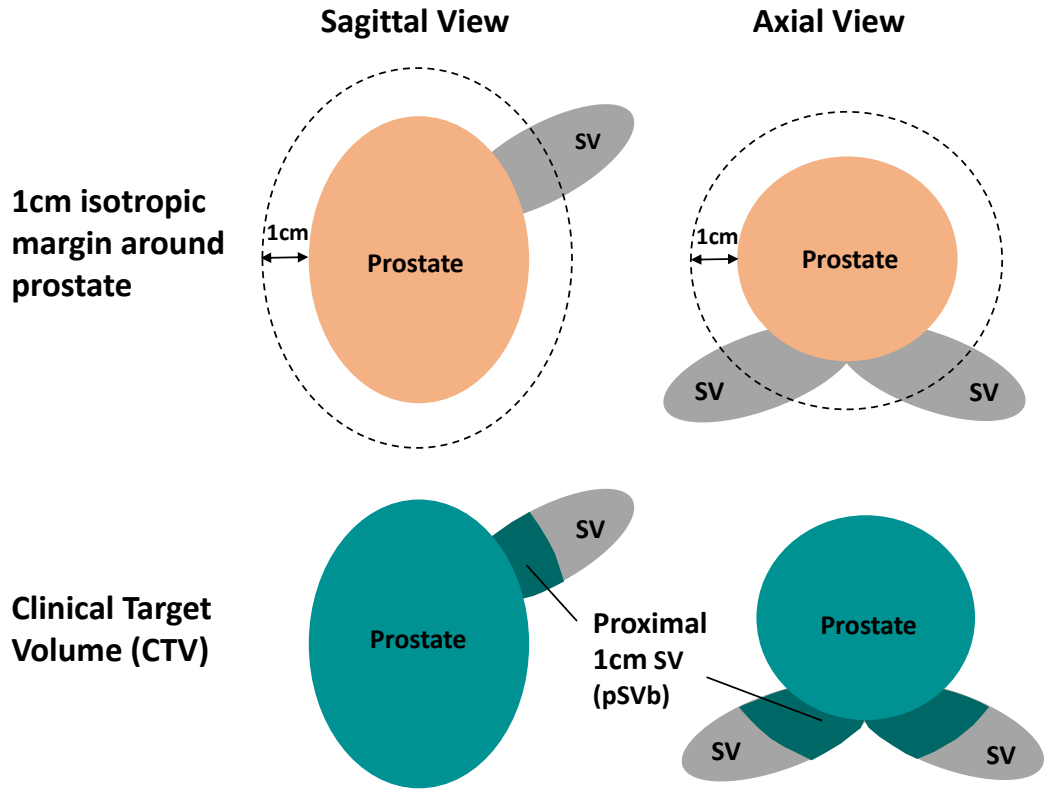
3.6.1.2. Semi-automated method for pSV delineation

This method involves the use of a computer-generated isotropic margin around the prostate volume to define the pSV (Figure 3.11):

- The prostate and seminal vesicles are contoured separately, and a 1cm isotropic margin around the prostate applied.

- Using the Boolean operator function a new pSV structure is created consisting of the intersection between SV and prostate+1cm structures.

Figure 3.11: Diagram of semi-automated method for pSV outlining



3.6.1.3. Study participants

I organised a contouring station at the British Urology Group (BUG) national uro-oncology conference 2018, inviting clinical oncologists, with experience in prostate radiotherapy, to attend during the conference and participate in a contouring exercise.

3.6.1.4. Software and training

The contouring exercise was conducted using RayStation® 7 on two laptops provided by the Raystation team. Prior to the session, anonymised CT and MR imaging for an intermediate-risk prostate cancer case were uploaded and co-registered on Raystation prior to the session. The same image set from the benchmark exercise in section 3.5 was used for this study. A Raystation representative was in attendance through-out the sessions on the first day to provide technical and assistance in setting up the equipment.

3.6.1.5. Contouring exercise

Each participant attended the contouring station at an allocated time slot and was provided with written instructions (Appendix 7). They were first requested to complete separate structure contours for prostate and full seminal vesicles (SV). In the interest of time, partial prostate contours were provided, extending from apex to mid-gland, and participants were required to complete the superior section. They were then asked to create a further structure to incorporate only the proximal 1cm portion of the seminal vesicles, using their own method of delineation (method A, pSVa).

For each structure set, applying the Boolean operator function on Raystation, I was able to generate a new pSV structure using the semi-automated method described in Figure 3.11 (method B, pSVb).

3.6.1.6. Analysis of data

For each method, the investigational contours were again compared to the reference contours. Volume measurements and conformity indices were calculated as previously described (Figure 3.6). Results for methods A (pSVa) and B (pSVb) were compared, using paired t-test to measure statistical significance (significance level set at p=≤0.05).

Statistical analysis was conducted using Prism version 9 (© 1994 - 2021 GraphPad Software, LLC) package. Shapiro-Wilk test was used to test for normality. Volume measurements are normally distributed and are reported with mean and 95% confidence interval. The conformity index values are normally distributed, with the exception of the pSVa GMI, and are therefore reported with median and interquartile range (IQR). To detect significant differences in median CI values between pSVa and pSVb contours, the paired t-test and Wilcoxon matched-pair non- parametric test were conducted as appropriate.

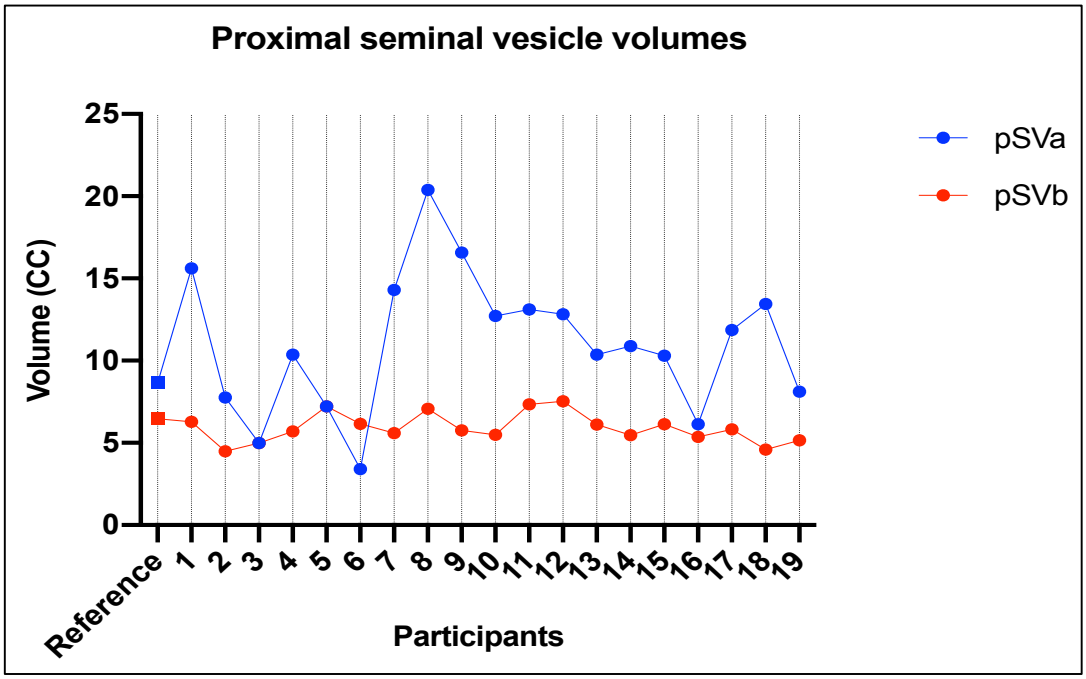
3.6.2. Results

Twenty-one clinicians attending the conference participated in the contouring exercise. Contours from two participants were incomplete and were therefore excluded from the analysis. In one case this was due to a technical error on Raystation which resulted in the participants contours not being saved.

Nineteen investigational structure sets were analysed. Figure 3.12 demonstrates the volume of each individual pSV contour volumes, for each contouring method. The volume of the pSVa contours, defined using the participants own method (method A), ranged from 3.41 to 20.39 cc. The mean volume was 11.07 cc (95% CI 9.04 – 13.11 cc), which was greater than the reference contour, measuring 8.65 cc. The pSV (pSVb) contours, defined using the semi-automated method (method B), ranged less in volume, measuring 4.49 – 7.54 cc. The mean volume was 5.91 cc (95% CI 5.49 – 6.34 cc) compared to the reference contour of 6.46 cc. The mean pSVa volume was significantly higher than for pSVb ($p < 0.0001$).

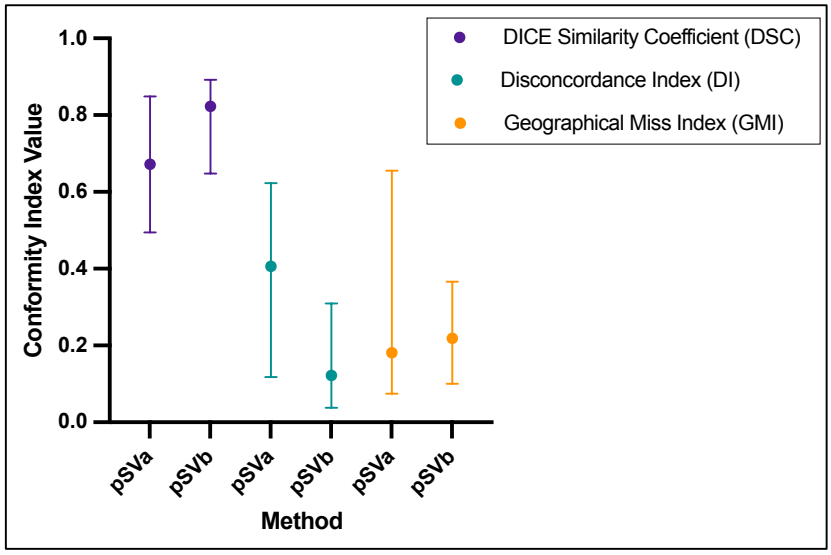
Figure 3.13 demonstrates the range and median values for each conformity index, comparing pSV contours defined using method A (pSVa) and method B (pSVb). For the pSVa contours, the DSC ranged between 0.49 – 0.85 for method A, and 0.65 – 0.89 for the pSVb contours for method B. The pSVb median DSC was higher at 0.82 (IQR CI 0.78 – 0.84), compared to 0.67 (IQR 0.64 – 0.72, $p = <0.0001$) for pSVa. This confirms that the pSV contours defined using method B, demonstrated increased concordance with the reference contour in comparison to method A.

Figure 3.12: Variability of pSV volumes between two outlining methods.



Graph demonstrating pSV volumes for each participant, comparing contours defined using method A (pSVa) and method B (pSVb).

Figure 3.13: Range and median conformity index values, comparing method A (pSVa) and method B (pSVb) contours



There was no significant difference in median GMI (p=0.81) demonstrated, although The GMI range for pSVa was greater at 0.12 – 0.62 compared to 0.07 – 0.21 for pSVb, however the median GMI was low for both methods at 0.18 (IQR 0.11 – 0.29) and 0.22 (IQR 0.16 – 0.24) for pSVa and pSVb respectively, with no significant difference detected. The DI ranged between 0.07 – 0.66 for pSVa and 0.10 – 0.45 for pSVb. The median DI was lower for pSVb at 0.12 (IQR 0.09 – 0.21), compared to method A (pSVa) at 0.41 (IQR 0.19 – 0.44, p=<0.0001). This indicates that with method B, pSV contours were less likely to include excessive volume in comparison to the reference contours.

My results clearly confirm that the use of the semi-automated method for 1cm pSV delineation results in less interobserver variability and reduces the risk of excessive contouring. which may have a benefit in terms of toxicity. My recommendation is for this method to be used in clinical practice and in the context of a trial protocol. This method has now been included in the outlining guidelines for PACE C (Appendix 8)[3].

3.7. Discussion

The aim of this study was to identify clinical outlining variability amongst centres entering the PACE B trial, and to develop a method for proximal seminal vesicle delineation to improve consistency in future SBRT trials.

3.7.1. Retrospective review of benchmark case feedback proformas

My retrospective review of the feedback proformas from the PACE B benchmark contouring exercise highlighted a number of issues with regard to clinical outlining consistency between centres. The most common discrepancies were related to CTV outlining, in particular the posterior and apical sites within the prostate, and contouring of proximal seminal vesicles, which was most frequently recorded. This is consistent with the most common sites of interobserver variability reported in the literature[11,12] .

The pre-trial benchmark exercise is increasingly being used within multicentre trials to ensure protocol adherence, prior to centre approval and patient recruitment. This is important, not only for the optimization of patient safety and outcomes, but to maintain a high level of consistency which will contribute to the robustness of the trial data. This study has highlighted the added advantage of the benchmark exercise in identifying recurring issues among clinicians, which could lead to the review of contouring guidelines, and the initiation of protocol amendments or educational intervention to improve consistency. Also, the benchmark exercise is, in itself, an educational tool, since detailed feedback is provided for centres, with the opportunity for resubmission by centres not initially approved for the trial.

3.7.1.1. Limitations

This study is limited by its retrospective nature and lack of quantitative data. The results are descriptive, and therefore not always clear as to the extent of each outlining deviation, and which particular issues contributed to the trial approval status for each centre. In addition, although each case was consistently reviewed by the Chief Investigator of the trial, this consisted of a visual assessment, relying on the subjective opinion of the reviewer and, therefore, prone to bias.

3.7.2. Review of multicentre contouring

In order to quantitively evaluate the existence of CTV contouring interobserver variability, I conducted an analysis of CTV contours submitted for review within the PACE trial benchmark exercise. This has confirmed significant interobserver variability, predominantly with regards to proximal seminal vesicle (pSV) contouring. This was evidenced by demonstrating the wide range in volume (cc) of the whole CTV, prostate and pSV contours, and the use of mathematical metrics, known as conformity indices to quantitively compare investigational contours with reference contours.

The use of conformity indices is becoming increasingly popular in radiotherapy studies with a number of indices described in the literature: DICE similarity coefficient (DSC); Jaccard conformity Index (JCI); Van't Riet Index (VRI); Geographical Miss Index (GMI); Disconcorance Index (DI); and Hausdorff Distance (HD). For this study I opted to use DSC as this was available on the VODCA software and mathematically similar to JCI and VRI.

I have demonstrated a significant difference in median DSC between prostate and pSV contours. The median DSC value for the prostate contours was closer to one, signifying greater concordance with reference contours. The rate of geographical miss for prostate outlining was low, reflected by the very low median GMI, close to zero. The median disconcordance index is slightly higher indicating that overall, centres were more likely to include excess tissue in comparison to the reference prostate volume. The median GMI and DI for pSV contours are both higher in comparison to the CTV and prostate contours, which is consistent with the hypothesis that interobserver variability is more pronounced in outlining the proximal seminal vesicles. Again, the DI is higher than the GMI suggesting that centres were more likely to include more seminal vesicle within the pSV in comparison to reference contours.

3.7.2.1. Limitations

This study is limited by the small number of investigational contours included in the analysis. This was influenced by the decision to change the imaging data set used for the benchmark case during the benchmark process, which meant that only contours using the same data set could be included. The investigational contours were compared to reference contours which were predefined by myself and Dr van As, chief investigator of the PACE trial. Since target volume definition is highly subjective, the risk of observer bias will exist even with an experienced radiotherapist and therefore the optimum method for defining reference contours would be to obtain consensus contours as defined by a number of clinicans. Benchmark cases were submitted for review with combined CTV contours, and therefore for this study, I was required to create separate prostate and pSV structures, by using Boolean operators to subtract

prostate and pSV reference contours from the investigation CTV contours. As a result, any variability in the identification of the seminal vesicle insertion could not be taken into account.

3.7.2.2. Implications

Interobserver variability of target volume delineation is common in prostate radiotherapy with clinical implications in terms of tumour control and risk of toxicity. Interventions including the use of contouring protocols, MRI fusion, or the implementation of an education program on CT and MRI prostate anatomy have all been shown to improve outlining consistency[13,21]. This study has identified interobserver variability to be a particular issue in defining the proximal 1cm of the seminal vesicles. This is likely to be due to the lack of consensus in the literature regarding a recommended delineation method, and possible misinterpretation of the PACE protocol contouring guidelines. This implies the need for a concise, easily reproducible delineation method to improve consistency in future SBRT trials, in combination with the production of more detailed contouring guidelines within the PACE protocol, and consideration of other educational interventions.

There may be benefit from incorporating conformity indices (CI) into pre-trial benchmark, and prospective trial case review, as well as the peer review process within individual radiotherapy departments. These reviews often involve meticulous slice by slice visual inspection of contours, which can be time consuming and highly subjective, with no current standard to evaluate contouring agreement quantitively.

However, data provided from calculating CI is of limited value as there is currently no standardised assessment criteria to establish which absolute CI values demonstrate high or low conformity. In addition, CI values may vary between different structures. For example, as shown in this study even small changes in pSV volume will have a greater impact on CI values in comparison to prostate outlining. The clinical impact of this is unclear and therefore lower DSC or higher DI/ GMI may not be so relevant.

Establishing pass/ fail criteria for individual structures would therefore be vital before introducing to routine practice. Evaluating this over multiple structures would be time consuming and there may be potential for applying machine learning, a form of Artificial Intelligence (AI) in this setting[22]. AI is highly topical with regards to auto-segmentation, but there is currently limited data regarding its potential use in contour conformity assessment.

3.7.3. Clinician preferred vs. semiautomated delineation methodology

I have demonstrated that the consistency of proximal seminal vesicle outlining can be improved by the use of a semi-automated method for delineation. As predicted, my results confirmed significant interobserver variability when clinicians, experienced in prostate radiotherapy, were instructed to contour the proximal 1cm SV, using their own method of delineation (method A). Using my semi-automated method, I created new pSV contours based on the participants own prostate and seminal vesicle contours, which consisted of the intersection between SV and prostate + 1cm isotropic margin (method B). This resulted in a marked improvement in contour volume (cc) variability and a significant improvement in median DCS to method A, consistent with improved

concordance with the reference contour. The median GMI was low for both methods, whereas the median DI was raised at 0.41 for method A which improved to 0.12 for method B. This suggests that participants were more likely to over-contour the pSV when using their own method of delineation, which was not seen with method B.

3.7.3.1. Limitations

To complete this study, I organised and lead a contouring station at a national uro-oncology conference. This gave me the unique opportunity of being able to recruit highly experienced clinicians from a variety of UK centres within a short period of time, while ensuring consistency in terms of the setting and contouring software used. However, because of time and resource limitations, participant numbers were relatively low. There was initial difficulty gaining interest among delegates, and minimal opportunities for participants to attend within the two-day conference, in between main sessions, poster viewing and networking. The contouring session was arranged through collaboration with Raystation® who provided laptops and software for the exercise. This had the added benefit of having a representative in attendance on the first day of the conference to assist participants, a large number who had not previously used the Raystation software. The unfamiliarity of the software may have had an impact on the time and the ability of the participants to complete the exercise, and unfortunately workstation access was limited to due to the availability of only two laptops, one of which suffered recurring technical issues.

Due to the predicted time limitations, partial prostate contours were provided for participants to complete in addition to seminal vesicle contours. This eliminated the

possibility of assessing prostate contouring variability. It would also have been useful to assess participant implementation of method B to assess the simplicity and reproducibility of the method. However, due to the time constraints I had made the decision to complete pSVb structures following the event using participant prostate and seminal vesicle contours. As a result, I was not in a position to be able present my data during the final day of the conference which would have been of educational value.

3.7.3.2. Implications

I have confirmed that a relatively simple, semi-automated method for proximal seminal vesicle delineation improves clinician outlining consistency and I therefore recommend this method for use in future prostate SBRT trials.

In the PACE C trial, which opened after this studied was completed, patients with intermediate- or high- risk prostate cancer, on hormones, are randomised between conventional radiotherapy or SBRT. For patients in the unfavourable intermediate- and high-risk groups, the CTV includes 1cm pSV in the high dose volume treated to 36.25 Gy in five fractions, and 2cm pSV in a lower dose volume treated to 30 Gy. The semi-automated method for pSV definition used in my study has since been incorporated into the trial protocol contouring guidelines for which I have designed the schema as shown in Appendix 8. It would be informative to conduct a further conformity analysis of contours completed using the updated guidelines to ensure improved consistency.

The clinical impact of improving pSV outlining consistency is unclear. Relatively small volume changes in the portion of pSV as shown in this study may not be clinically relevant as compared, for example, to small discrepancies at the site of the prostatic-rectal interface. However, this will be dependent on individual patient anatomy and the risk of seminal vesicle involvement. The risk of toxicity increases when a greater proportion of seminal vesicles are included in the target volume[23-25] . The accuracy of pSV delineation and treatment therefore becomes more relevant in SBRT for higher risk prostate cancer patients, such as those included in PACE C.

3.8. Conclusions

Successful SBRT is dependent on the accuracy of clinical outlining due to the smaller margin for error as a result of precise image guidance, tighter margins and steep dose gradient. The optimisation of contouring consistency is of particular importance within a multicentre trial as this will contribute to the robustness of the data.

There was significant CTV outlining variability between centres completing the PACE B pre-trial benchmark case review, particularly in the delineation of the proximal seminal vesicles. The implementation of a semi-automated method for psv delineation has resulted in reduced interobserver variability. This method has now been incorporated into the PACE C contouring guidelines and is recommended for use in further radiotherapy/ SBRT trials.

The use of conformity indices to quantitively assess contouring consistency may be useful in the context of pre-trial benchmark case and local departmental peer review, however further work is needed to establish standard assessment criteria for individual structures.

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Chapter 4: The feasibility of CyberKnife planning for SBRT in high-risk prostate cancer and a comparison of plans using the Iris variable collimator and Incise multileaf collimator.

4.1. Introduction

In theory, SBRT could offer a particular advantage in patients with high-risk prostate cancer given the relatively high biological effective dose (BED) delivered. However, evidence is currently limited, and several unanswered questions remain, including the potential benefit of dose-escalation and elective pelvic irradiation. High-risk patients are at greater risk of seminal vesicle involvement (SVI) and therefore the inclusion of ≥2 cm SV in the clinical target volume (CTV) is often recommended[1,2]. This can create additional challenges for SBRT planning, due to the location and curvature of the SVs around the rectal wall[3,4]. In addition, there is evidence that SV motion is greater in relation to the prostate, requiring the use larger planning target volume (PTV) margins, potentially leading to increased rectal and bladder toxicity[5-8].

The CyberKnife delivers multiple non-coplanar pencil beams to achieve a high conformal dose distribution within the target. A variety of beam sizes can be created using fixed circular collimators or the Iris variable collimator (Figure 4.1) as described in section 1.2.2.1[9-10]**.** Acceptable target coverage of complex and/ or large target volumes can be more difficult to achieve, without compromising normal tissue sparing. Furthermore, a higher number of beams will be required, leading to an increase in

treatment time and required monitor units (MU). The Incise 2^{TM} multileaf collimator (MLC) (Figure 4.1) is a newer feature of the CyberKnife system which enables the use of larger, irregularly shaped fields, thereby reducing the number of beams required with a consequent improvement in plan delivery efficiency[11]. Planning studies have demonstrated a reduction in treatment time and MU, using MLC in low-/ intermediate-risk prostate cancer[12-16], however the advantage is likely to be more pronounced in high-risk cases, with more complex target volumes.

Figure 4.1: The Iris variable collimator and Incise MLC

Photographic images of the Iris variable collimator (left) and Incise multi-leaf collimator (MLC)(right). MLC image from Asmerom et al[11]

4.2. Hypotheses:

- CyberKnife planning for prostate cancer is feasible, regardless of SV extent within the CTV, although inclusion of more SV will result in increased rectal and bladder dose.
- The use of the multi-leaf collimator (MLC) in CyberKnife planning can achieve equivalent PTV coverage in comparison to the Iris variable collimator, with a reduction in overall treatment time and total monitor units.

4.3. Aims:

- To determine the proportion of CyberKnife plans achieving ≥95% PTV coverage, while meeting PACE dose constraints, at a dose of 36.25 Gy in 5 fractions prescribed to the PTV.
- To evaluate any increase in normal tissue dose, in relation to the extent of SV within the CTV and determine any correlation with PTV volume and the volume of rectal/ bladder overlap.
- To compare Incise MLC with the Iris collimator in CyberKnife planning for high-risk prostate cancer.

4.4. Methodology

4.4.1. Case selection

Eight intermediate-risk prostate cancer cases, previously treated within the PACE B trial, were selected at random. As part of the trial, all cases were deemed suitable for SBRT and had fiducial markers in situ. All patients had previously consented to the use of their images for research purposes.

4.4.2. Contouring

Each case had been previously contoured as per the PACE B protocol using planning computed tomography (CT) scan (1.5 mm slices) fused with magnetic resonance imaging (MRI). On Eclipse (Varian Medical Systems, USA) planning system, I copied the original CTV and organ-at-risk (OAR) structures for each case to create a new structure set, for use in this planning study. OAR structures were checked for completeness and contouring accuracy by me, in accordance with the PACE protocol, to include: rectum, bladder, bowel, bilateral femoral heads, penile bulb and urethra (if easily visualised).

4.4.2.1. Clinical Target Volume (CTV)

I first edited the original CTV to create a separate prostate structure and delineated the full extent of the seminal vesicles to create a new SV structure. These were then

used to create three different SV structures (Figure 4.2) using my semi-automated delineation method described in chapter 3.

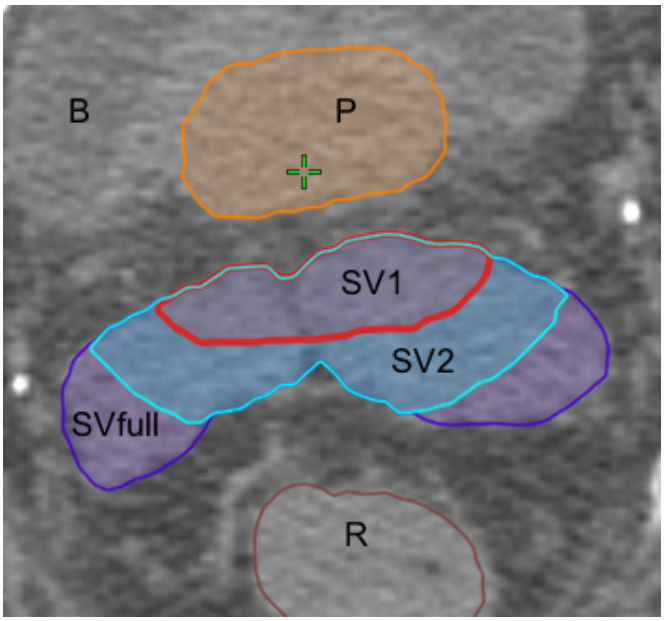
- SV1: A 1cm isotropic margin was added to the prostate structure to create a new “prostate+1cm” structure. Using the Boolean operator function on Eclipse, as previously described, I generated a SV structure consisting of the intersection between the seminal vesicle and prostate+1cm structures.
- SV2: The same method was used, but this time applying a 2 cm isotropic margin to create a “prostate+2cm” structure and generating a further SV structure consisting of the intersection between SV and prostate+2cm structures.
- SV3: This structure included the full extent of SVs as already contoured.

Three CTV structures were created: CTV1, CTV2 and CTV3; each including the prostate and the corresponding SV structure as shown in Table 4.1.

4.4.2.2. Planning Target Volume (PTV)

Three separate PTV structures (PTV1, PTV2 and PTV3) were created as summarised in Table 4.1. PTV1 was created using the same CTV – PTV margins as recommended for SBRT with CyberKnife within the PACE protocol for SBRT: 5 mm margin, reduced to 3 mm posteriorly due to proximity to rectum. Since evidence demonstrates a potential increase in SV motion relative to the prostate, I have applied a 6 mm uniform margin around the distal portion of the SVs included in CTV2 and CTV3.

Figure 4.2: The three seminal vesicle structures (SV1, SV2 and SVfull (SV3))



Axial slice from a CT planning scan demonstrating: SV1, 1 cm pSV (red); SV2, 2 cm pSV (cyan); and SVfull, full seminal vesicles (purple). P, prostate; R, rectum; B, bladder.

Table 4.1: Target volumes

CTV		PTV	
CTV1	Prostate + SV1	PTV1	CTV1 + 5 mm / 3 mm posteriorly
CTV2	Prostate + SV2	PTV2	CTV1 + 5 mm / 3 mm posteriorly and (CTV2 - CTV1) + 6 mm
CTV3	Prostate + SV3	PTV3	CTV1 + 5 mm / 3 mm posteriorly and (CTV3 – CTV1) + 6 mm

Table summarising target volumes to be used in the prostate planning study. For each case, three separate plans are created using the clinical target volumes (CTV) and planning target volumes (PTV) as described. PTV2 and PTV3 include the distal seminal vesicles (CTV2 – CTV1) and (CTV3 – CTV1) which require a 6 mm uniform margin to account for potential increased motion relative to the prostate. SV1, 1 cm proximal seminal vesicles (pSV); SV2, 2 cm pSV; SV3, full seminal vesicles.

4.4.3. CyberKnife Planning

I imported the planning CT imaging and structure set data from Eclipse to the Multiplan version 5.3 (Accuray Inc., Sunnyvale, CA, USA) system, on the CyberKnife research terminal. Prior to commencing planning I received appropriate training from Accuray and the CyberKnife physics team at RMH.

For each case, I consecutively completed up to 3 separate plans, using the Iris^{TM} collimator, for PTV1, PTV2 and PTV3, which I named IrisSV1, IrisSV2 and IrisSV3 respectively. Once I was able to achieve a clinically acceptable IrisSV1 plan, I proceeded to IrisSV2, and subsequently IrisSV3. In the event that an acceptable plan could not be achieved, I did not proceed to plan the next PTV level. I then completed one further plan with the Incise^{TM} multileaf collimator (MLC), for each case, using the highest PTV level planned with the Iris collimator (named either MLCSV1, MLCSV2 or MLCSV3), to allow direct plan comparison.

4.4.3.1. Plan set up

For each new plan the full prostate treatment path set, and appropriate collimator type (Iris or MLC) was selected. All plans were set-up for fiducial tracking. Intraprostatic fiducial markers were located, and coordinates confirmed on Multiplan, aligning the plan to centre. The testicles were outlined and set as a blocking structure. To optimise conformality, dose-limiting shell structures were set at the following distances from PTV: 3 mm (shell 1); shell 2 12 mm/10 mm posteriorly (shell 2); 30 mm/ 26 mm posteriorly (shell 3); 50 mm/ 42 mm posteriorly (shell 4).

4.4.3.2. Collimator settings

For Iris planning, 4-5 collimator sizes were selected ranging between 10 mm – 50 mm, depending on PTV size and shape. The maximum monitor unit was set at 750 MU per beam and 1,125 MU per node. For MLC planning, the “conformal-avoidance” option was selected, using all shapes (eroded, perimeter and random) provided by the system. The maximum number of nodes was set at 80, and maximum MU was set at 750 MU per segment and 1,500 MU per node.

4.4.3.3. Planning process

The sequential optimisation option was selected for planning. Maximum dose constraints were initially set to limit the solution as follows: PTV 4650 Gy; CTV 4650 Gy; shell 1 3625 Gy. Planning objectives, including shell dose limits, were inputted as successive steps through-out the optimisation process, until an optimal plan was achieved in terms of target coverage and dose constraints. After each optimisation, the plan was normalised to the prescribed dose of 36.25 Gy, to an isodose of between 77 – 82%. Dose calculation was performed in median resolution using a ray-tracing algorithm for Iris and a finite size pencil beam (FSPB) algorithm for MLC. Recalculation in high resolution was conducted only at the final stage of planning to minimise optimisation time. Peripheral dose hot spots (≥ 40% isodose) were reduced using the fine-tuning tool on Multiplan.

4.4.3.4. Dose volume constraints and objectives

The dose-volume constraints and objectives for the target volumes and OARs were the dose-volume parameters used in the PACE protocol. ≥95% of the PTV was to receive 36.25 Gy, and ≥95% of CTV to receive 40.00 Gy. The OAR dose constraints are summarised in Appendix 2.

4.4.3.5. Optimising treatment delivery efficiency.

Once an optimal plan was achieved, to optimise efficiency I gradually reduced the total MU and then selected the "Time Reduction" option on Multiplan which gradually reduces the number of beams and nodes, until the user-defined treatment time is achieved. I continued this process until the lowest treatment time was achieved, without significant compromise of target coverage or OAR dose, maintaining required dose constraints. The treatment time calculation takes into account the number of robot positions, the robot speed, number of beam angles, MU, dose rate (1000 MU/min) and number of segments in the case of MLC. Time for intra-fraction imaging and 5 minutes set-up time is also included.

4.4.4. Data analysis

4.4.4.1. Volumetric data

I recorded target volume measurements, in cubic centimetres (cc), for each case, including prostate, SV (SV1, SV2, and SV3), CTV (CTV1, CTV2 and CTV3), and PTV

(PTV1, PTV2, PTV3). The volume of overlap between each PTV, and rectum, bladder, and bowel, respectively was also recorded, since this may have an impact on the complexity of planning.

4.4.4.2. Plan data

For each plan, I recorded the prescription isodose level; maximum plan dose, PTV coverage, defined by the volume of PTV receiving 36.25 Gy (V36.25 Gy); and CTV coverage, as defined by the volume of CTV receiving 40 Gy (V40 Gy).

To confirm plan conformity and homogeneity, I recorded the new conformity index (nCI) and homogeneity index (HI) as calculated by Multiplan. The nCI indicates how precisely the target volume is overlapped by the prescription dose (calculated by nCI = PTV*PIV/ TIV, where PIV is the prescription isodose volume and *TIV* is the tumor isodose volume)[13,17,18]. I aimed to keep the nCI value ≤1.15 for all plans to maintain consistency. To assess plan efficiency, I recorded: treatment time (minutes), as estimated by Multiplan; total monitor units (MU); total number of nodes and beams used for each plan; in addition to the number of segments used for each MLC plan.

4.4.4.3. Primary endpoint

The number of acceptable plans, achieving ≥95% target volume coverage at a prescription dose of 36.25 Gy in 5 fractions, while meeting OAR dose constraints.

4.4.4.4. Secondary endpoints

- Dose to OARs – rectum, bladder, bowel and femoral heads.
- Coverage (%) and conformity (new conformity Index (nCI))
- Dose Delivery Efficiency: Treatment time, Total MU.

4.4.4.5. Plan comparison

I firstly compared data between Iris plans (IrisSV1, IrisSV2 and IrisSV3), to assess the effect on plan quality and efficiency by increasing the extent of SV within the CTV. Secondly, I compared MLC plans with the corresponding Iris plans, to assess for any improvement in quality and efficiency by the use of MLC.

4.4.5. Statistical analysis

The statistical analysis was conducted by myself, using the Prism version 9 (© 1994 - 2021 GraphPad Software, LLC) package. Volumetric and plan data will be described using descriptive statistics, including median value, with interquartile range (IQR), and range. The Shapiro-Wilk test was applied to confirm normal distribution. For normally distributed data, the paired t-test was applied to test for statistically significant differences between plan types; and the non-parametric Wilcoxon matched-pairs signed rank test used for data that was not normally distributed, set at a significance value of $p \leq 0.05$. Pearson's correlation coefficient was used to test the strength of any correlation between PTV volume and plan parameters.

4.5. Results

4.5.1. Volume analysis

Volume measurements for the eight cases included in this planning study are summarised in Table 4.2. As demonstrated in Figure 4.3, a small increase in the proportion of SV within each CTV had a marked effect on PTV volume, with a median increase of 17.8 cc (range 15.53 – 28.56) between PTV1 and PTV2, and 29.05 cc (range 21.62 – 40.63 cc) between PTV1 and PTV3.

The volume of overlap between each PTV and dose limiting structures, rectum and bladder, is summarised in Table 4.3**.** The increase in PTV volume between PTV1 and PTV2 resulted in a small, but statistically significant increase in overlap with the rectal volume, with a median increase of 0.89 cc (range 0 – 1.7 cc, p=0.01). However, the degree of further rectal overlap between PTV2 and PTV3 was minimal at 0.06 cc (range 0 - 0.2cc, p=0.02). The bladder was adequately filled, in each case, at the time of the planning, with a median bladder volume of 295.6 cc (range 172.4 – 497.0 cc). The increase in volume between PTV1 and PTV2 resulted in a median increase in bladder overlap of 1.32 cc (range 0.01 – 2.21 cc, p=0.001), but again only a very small median increase in bladder overlap between PTV2 and PTV3 of 0.07 (range 0 – 0.52 cc, p= 0.05). Overlap between PTV and bowel was minimal, occurring in only 2 cases with PTV3 with overlap of 0.04 cc and 1.2 cc in each case respectively.

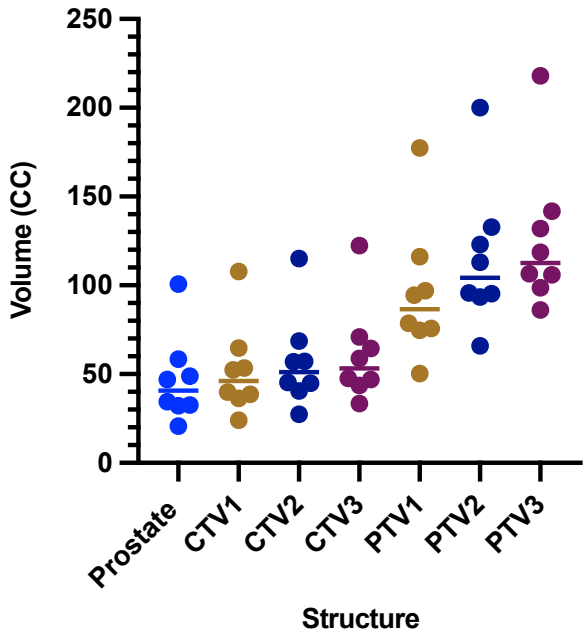
Including all 24 PTVs, there was a strong correlation between PTV volume and the volume of rectal overlap, and a moderate correlation between PTV volume and the volume of bladder overlap, as demonstrated in Figure 4.4**.**

Table 4.2: Volume measurements (cc) of target volume structures

Structure	Volume (cc)		
	Range	**Median**	**IQR**
Prostate	20.8 – 100.7	40.73	32.21 – 56.11
SV1	3.19 – 7.09	5.79	3.73 – 6.33
CTV1	23.99 – 107.8	46.13	36.92 – 61.89
PTV1	50.37 – 177.3	86.53	75.02 – 111.4
SV2	6.5 – 14.38	10.15	8.2 – 12.18
CTV2	27.30 – 115.1	51.11	41.63 – 65.74
PTV2	65.9 – 200.2	104.4	93.85 – 130.3
SV3	11.59 – 21.69	12.86	11.9 – 15.38
CTV3	33.42 – 122.40	53.19	44.54 – 69.35
PTV3	86.18 – 218.0	112.6	100.4 – 139.4

Planning structures: SV, seminal vesicle; SV1, 1cm SV; SV2 2cm SV; SV3, full SV; CTV, clinial target volume; PTV, planning target volume; IQR, interquartile range.

Figure 4.3: The effect on PTV volume

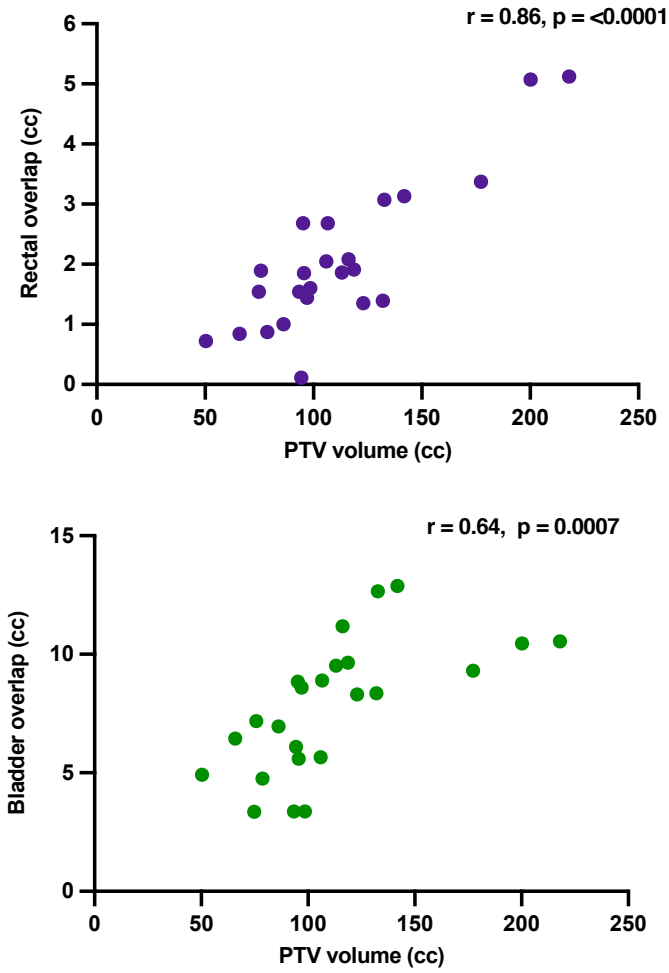


Scatter chart demonstrating the effect on PTV resulting from a small increase in CTV volume by inclusion of a greater proportion of seminal vesicle.

Table 4.3: Volume of rectum and bladder overlap with PTV1, PTV2, and PTV3

	Overlap with rectum (cc)			Overlap with bladder (cc)		
	Range	**Median**	**IQR**	**Range**	**Median**	**IQR**
PTV 1	0.11 – 3.37	1.49	0.75 -2.03	3.36 -11.18	6.64	4.79 – 9.13
PTV 2	0.84 – 5.07	1.86	1.40 – 2.97	3.37 – 12.66	8.58	5.81 – 10.23
PTV 3	1.00 -5.12	1.98	1.44-3.02	3.37 – 12.88	8.63	5.99 – 10.32

Figure 4.4: Correlation between PTV volume and overlap with rectum and bladder



Scatter charts demonstrating the correlation between PTV volume and the overlap with rectum and bladder, respectively. Purple dots: rectal overlap; Green dots: bladder overlap; r: Pearson correlation coefficient; p: significance level.

4.5.2. Iris plan analysis

The target volume coverage and dose to OARs for all Iris plans are summarised in Table 4.4.

4.5.2.1. SV1 Iris plans

All 8 (100%) completed IrisSV1 plans were deemed acceptable, at a prescription dose of 36.25 Gy in 5 fractions. The median prescription isodose was 79% (77-81%) giving a median HI value of 1.27 (range 1.23 – 1.3), and the median nCI was 1.1 (range 1.09 – 1.13) confirming adequate plan conformality. Target volume coverage of PTV V36.25 Gy ≥ 95%, and CTV V40 Gy ≥ 95% were met in all cases. All plans met the required OAR dose constraints with no minor variations, and the optimal bladder V 37 Gy (≤ 5cc) was met in 50% of cases. The total treatment time ranged between 26 and 40 minutes, with a median time of 30.5 mins. The total monitor units (MU) required for each treatment plan ranged between 29717 and 56740 (median total MU 41117). The median number of nodes used was 40 (range 24 – 72) and median number of beams 123 (range 104 – 214).

4.5.2.2. SV2 Iris plans

Six (75%) out of 8 completed IrisSV2 plans were considered acceptable. In all plans, 36.25 Gy in 5 fractions was prescribed to a median isodose of 79% (range 79 – 81%), producing a median maximum PTV dose of 45.89 Gy (range 44.75 – 45.89 Gy) and

median HI of 1.27 (range 1.23 – 1.27). The median nCI was 1.11 (range 1.08 – 1.13) confirming adequate conformality of all plans.

In one plan, the rectal constraints were not met, with a V18.1 Gy of 57%, and a with a minor deviation in PTV coverage with a V36.25 Gy of 93.6%. In addition, the femoral head V14.5 Gy was high at 19.7% and 13.8%, for left and right femoral heads respectively. Another plan achieved adequate target volume coverage but the bladder V18.1 Gy was high at 41.4%, and a femoral head V14.5 Gy of 14.2% and 13.8% for left and right, respectively. Notably both of these cases had the highest reported PTV2 volumes at 132.74 cc and 200.15 cc respectively, with the largest volume of rectal overlap (3.07 – 5.07 cc) and bladder overlap (10.46 and 12.66).

The total treatment time ranged between 35 and 53 minutes, with a median time of 43 mins. The total monitor units (MU) required for each treatment plan ranged between 45316 and 73562 (median total MU 56325). The median number of nodes used was 78 (range 50 – 96) and median number of beams 187 (range 149 – 259).

4.5.2.3. SV3 Iris plans

Six IrisSV3 plans were completed, and of these, 5 fulfilled the criteria for an acceptable plan. 36.25 Gy was prescribed to median 80% isodose (range 77 – 80%), with medium maximum dose to the PTV of 45.31 Gy (45.31 – 47.08 Gy), median HI of 1.25 (range 1.25 – 1.3), and median nCI of 1.13 (range 1.08 – 1.23). The high HI and nCI of 1.3 and 1.23, respectively, were from the one failed plan, in which PTV coverage could not be achieved with a V36.25 Gy of 88.6%, although acceptable CTV coverage. The

rectal V36 Gy and V29 Gy constraints were not met, at 1.59 cc and 22.6% respectively, although the V36 Gy was within the minor variation at < 2cc. In addition the left femoral head V 14.5 Gy was high at 50.2%. Again, this case had the highest PTV3 volume of all 6 cases, measuring 132.01 cc, although rectal and bladder overlap volumes were within 1cc of the group median.

The total treatment time ranged between 37 and 57 minutes, with a median time of 43 mins. The total monitor units (MU) required for each treatment plan ranged between 45316 and 73562 (median total MU 56441). The median number of nodes used was 63 (range 48 – 92) and median number of beams 193 (range 172 – 281).

Table 4.4: Target volume coverage and dose to organ at risk (OAR) for all Iris plans

Structure	Parameter	IrisSV1 (n = 8)	IrisSV2 (n = 8)	IrisSV3 (n = 6)
Coverage				
PTV	V 36.25 Gy (%)	97.0 Range 95.4 – 98.6	96.2 Range 93.6 – 97.7	95.7 Range 88.6 – 96.9
CTV	V 40 Gy (%)	96.4 Range 95.2 – 98.8	96.3 Range 95.4 – 97.8	97.0 Range 95.8 – 99.1
OAR dose				
Rectum	V 36 Gy (cc)	0.7 Range 0.5 – 0.9	0.8 Range 0.4 – 1.0	0.8 Range 0.6 – 1.6
	V 29 Gy (%)	11.4 Range 7.5 – 14.0	13.9 Range 7.6 – 16.1	14.4 Range 5.4 – 22.6
	V 18.1 Gy (%)	34.6 Range 22.8 – 41.5	46.1 Range 32.0 – 57.7	46.0 Range 14.5 – 64.6
Bladder	V 37 Gy (cc)	5.5 Range 3.2 - 8.3	6.5 Range 2.9 – 9.6	6.0 Range 2.7 – 7.4
	V 18.1 Gy (%)	18.4 Range 10.1 – 30.3	28.3 Range 10.4 – 41.4	32.2 Range 11.6 – 35.3
Bowel	V 30 Gy (cc)	0	0	0 Range 0 – 0.8
	V 18.1 Gy (cc)	0	0.1 Range 0 – 2.1	1.0 Range 0 – 4.1
L femoral head	V 14.5 Gy (%)	2.2 Range 0 – 4.6	2.4 Range 0 – 19.7	5.9 Range 0.1 – 50.2
R femoral head	V 14.5 Gy (%)	1.0 Range 0 – 4.1	1.5 Range 0 – 13.8	3.5 Range 0 – 15.4
Penile bulb	V 29.4 Gy (%)	0	0	0

Results recorded as median (interquartile range) and range. SV, seminal vesicle; SV1, 1cm SV; SV2, 2cm SV; SV3, full SV

4.5.3. Iris plan comparison

4.5.3.1. Dosimetry

Acceptable plans were achieved in 75% of IrisSV2 plans compared with 100% of IrisSV1 plans. Similarly, acceptable plans were achieved in 5 (83.43%) of the 6 IrisSV3 plans, equating to 62.5% of all 8 cases. However, overall, no significant difference in PTV and CTV coverage were detected between IrisSV1, IrisSV2 and IrisSV3 plans. No significant difference in conformality or homogeneity was detected, although the IrisSV3 plans had a higher median nCI and lower HI compared with the other plans.

No significant difference in rectal V36 Gy was detected, but both the median rectal V 29 Gy and V18.1 Gy were higher in the IrisSV2 plans compared to IrisSV1 plans, with a median increase of 2% (IQR 0.5 – 3.5%, p=0.02) and 12.45% (IQR 6.83 – 15.53, p=0.0013). However, there was no significant difference between IrisSV2 and IrisSV3 in either parameter. Similarly, the bladder V37 Gy was not significantly different between plans, but there was a median increase in bladder V18.1 Gy of 9.75% (IQR 7.3 – 11.55%, p=0.015) between IrisSV1 and IrisSV2 plans, with only a small and non-significant further increase between IrisSV2 and IrisSV3 plans.

4.5.3.2. Plan delivery efficiency

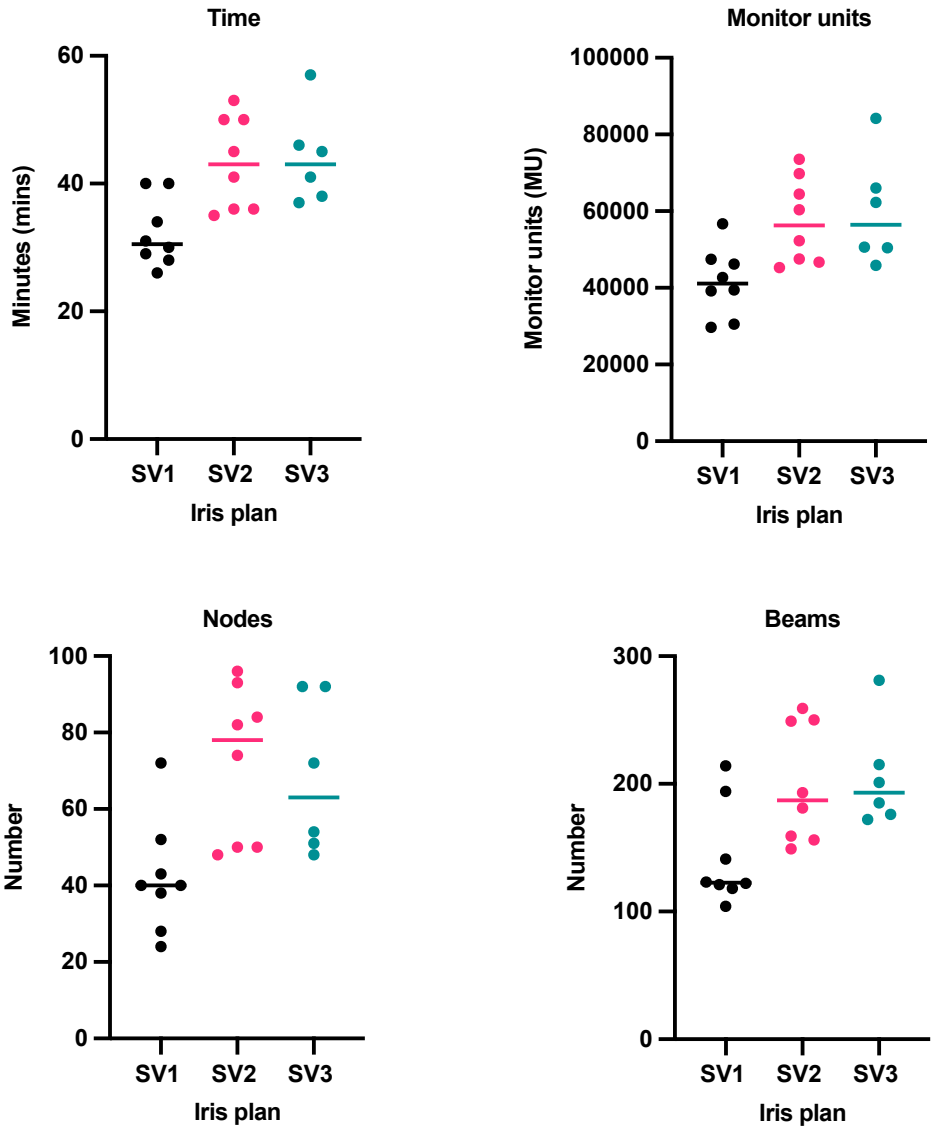
The IrisSV2 plans had a substantially longer estimated treatment time compared to IrisSV1 plans (Figure 4.5), with a median increase of 10.5 minutes (31.8%) between plans (p=0.0007). A further 3.5 minutes (9.2%) median increase was seen between IrisSV2 and IrisSV3 plans (p=0.0147). There was a median increase in MU of 46.4% (17009 MU) between IrisSV1 and IrisSV2 plans (p=0.0003), but again no significant increase between IrisSV2 and IrisSV3 plans.

The was an 89.7% median increase in the number of nodes between IrisSV1 and IrisSV2 plans (Figure 4.5). The median number of nodes used in the IrisSV1 plans was 40 (IQR 30.5 – 49.75) compared to 78 (IQR 50 – 90.75, p=0.0113). There is a fall in the median number of nodes used between IrisSV2 and IrisSV3 plans, however this was not a statistically significant difference and between each IrisSV2 and corresponding IrisSV3 plan there was a very small median increase of 0.5. There was a 38.7% (55.5 beams) median increase in the numbers of beams used between IrisSV1 and IrisSV2 plans (p=0.0022), and a 14.7% (26.5 beams) median increase in the number of beams used between IrisSV2 and IrisSV3 plans (p=0.021).

To ensure that the significant difference in efficiency parameters between IrisSV1 and IrisSV2 plans were not heavily influenced by the two cases in which acceptable IrisSV2 plans were not achieved, I conducted a further analysis including only the six cases with acceptable IrisSV1 and IrisSV2 plans. This confirmed similar results with a median time increase of 32.9% (10 minutes, IQR 6.5 – 15.75, p=0.0088), and a median MU increase of 46.4% (17009MU, IQR 10230 – 19032, p=0.0027) between plans.

There was again a large median increase (35 nodes, IQR 9.5 – 46.25) in the number of nodes used between plans, more than doubling in number in 4 of 6 cases, however this failed to reach statistical significance (p=0.056). There was a 50.7% median increase in beams between IrisSV1 and IrisSV2 plans (57 beam difference, IQR 24.75 – 85.25, p=0.016), which is even greater than the original analysis. This may be explained by the fact that the two excluded, more complex, cases already required a large number of beams to achieve an acceptable IrisSV1 plan (214 and 194 respectively), therefore, proportionally, a smaller increase between IrisSV1 and IrisSV2 plans.

Figure 4.5: Plan delivery efficiency – comparing Iris plans



Scatter charts demonstrating plan efficiency indices: time, total monitor units, number of nodes and beams used in each plan. Comparing SV1, SV2 and SV3 plans. Each dot represents values of individual plans, and the horizontal line representing the median value.

4.5.4. MLC plan analysis

Eight MLC plans were completed which included 6 MLCSV3 plans and 6 MLCSV2 plans, all prescribed 36.25 Gy in 5 fractions to a median isodose of 78% (range 77 – 80%), resulting in a medium maximum PTV dose of 46.47 Gy (range 45.31 – 47.08 Gy), and median HI of 1.28 (range 1.25 – 1.3). The median nCI was 1.12 (range 1.10 – 1.15). The dose volume data for target coverage and OAR constraints are summarised in Table 4.5.

All plans were deemed clinically acceptable, although 3 plans had minor variations. In one MLCSV3 case, the V14.5 Gy for the left femoral head was slightly outside the optimal constraint at 7.5%, but otherwise good target volume coverage and met all other OAR constraints. Of the MLCSV2 plans, one did not achieve optimal PTV coverage, although was within the minor variation range, with V36.25 Gy of 93.7% and the rectal V29 Gy was only minimally outside the 20% constraint at 20.2%. The other MLCSV2 plan achieved adequate PTV coverage, and met all OAR constraints, except for the bladder V37 Gy at 10.65 cc, which is well within the minor variation range of ≤ 20 cc.

The total treatment time ranged between 26 and 48 minutes, with a median time of 35 minutes, and MU ranged between 32587 and 50272 (median 43121). The median number of nodes used was 58 (range 46 – 66) and median number of beams 122 (range 73 – 163).

Table 4.5: Target volume coverage and dose to organ at risk (OAR) - comparing MLC and Iris plans.

		MLC (n = 8)	Iris (n = 8)	p value
Coverage				
PTV	V 36.25 Gy (%)	95.8 (95.3 – 96.2) Range 93.7 – 98.1	95.7 (94.1 – 96.3) Range 88.6 – 96.9	0.88
CTV	V 40 Gy (%)	96.4 (95.7 – 97.6) Range 95.5 – 98.2	96.7 (95.9 – 97.1) Range 95.4 – 99.1	0.78
OAR dose				
Rectum	V 36 Gy (cc)	0.6 (0.4 – 0.7) Range 0.3 – 0.9	0.8 (0.7 – 1.0) Range 0.6 – 1.6	0.02
	V 29 Gy (%)	10.6 (10.0 – 16.3) Range 5.7 – 20.2	14.7 (11.5 – 16.5) Range 5.4 – 22.6	0.27
	V 18.1 Gy (%)	34.8 (30.9 – 44.5) Range 19.0 – 49.7	48.1 (35.8 – 55.6) Range 32.0 – 57.7	0.07
Bladder	V 37 Gy (cc)	7.3 (5.9 – 9.4) Range 3.3 – 10.7	6.3 (5.8 – 9.5) Range 2.9 – 9.6	< 0.01
	V 18.1 Gy (%)	25.6 (15.0 – 34.1) Range 10.1 – 36.3	32.2 (17.5 – 35.2) Range 11.6 – 41.4	0.06
Bowel	V 30 Gy (cc)	0	0 Range 0 – 0.8	
	V 18.1 Gy (cc)	0 (0 – 0.1) Range 0 – 1.0	0 (0 – 0.5) Range 0 – 4.1	0.06
L Femoral head	V 14.5 Gy (%)	2.0 (0.8 – 4.2) Range 0.4 – 7.5	7.8 (3.4 – 18.3) Range 0.1 – 50.2	0.08
R Femoral head	V 14.5 Gy (%)	1.5 (0.2 -3.3) Range 0 – 5.0	6.0 (1.8 – 13.8) Range 0 – 15.4	0.06
Penile bulb	V 29.4 Gy (%)	0	0	

Results recorded as median (interquartile range) and range

4.5.5. MLC and Iris plan comparison

4.5.5.1. Dosimetry

Overall, MLC and Iris plans did not significantly differ in terms of target volume coverage, dose homogeneity, and conformality. The median HI was higher in the MLC plans compared to Iris (1.28 versus 1.26) demonstrating a slight reduction in plan homogeneity.

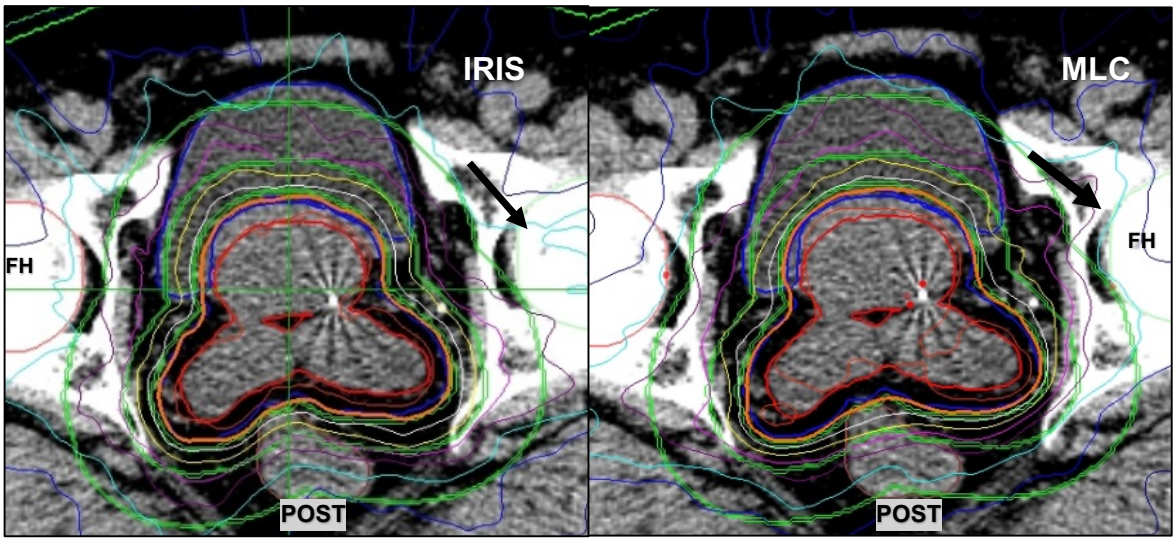
The use of the MLC allowed acceptable plan quality to be achieved in the two failed IrisSV2 cases. In one case, although no improvement in PTV coverage (MLC 93.7% compared to 93.6% in the Iris plan), rectal sparing was improved with a V18.1 Gy of 49.7%, compared to 57% with the Iris plan which was outside the mandatory constraint. The rectal V29 Gy was higher in the MLC plan at 20.2% compared to 16.1% in the Iris plan, however only minimally outside the constraint. and the femoral V 14.5 Gy was < 5% bilaterally, which I did not achieve with the Iris. In the other case, the bladder V18.1 Gy was slightly improved using the MLC to 35.8% from 41.4%, and although the bladder V37 Gy was slightly higher at 10.45 cc compared to 9.49 cc with the Iris, this is still within the minor variation allowance. Again, there was improvement in femoral head sparing with the MLC, which was not achieved with the Iris as demonstrated in Figure 4.6.

In the one case where the IrisSV3 plan was not deemed acceptable, I was able to achieve an acceptable plan using the MLC. The MLCSV3 plan achieved an improved PTV 36.25 Gy of 98.1% compared to 88.6% with the Iris. The rectal V36 Gy and V29

Gy constraints could be met at 0.67 cc and 12.8% compared with 1.59 cc and 22.6% respectively, with femoral head constraints met.

Table 4.5 demonstrates results of target volume coverage and OAR dose for all MLC plans in comparison with the corresponding Iris plans. There was not a marked difference in rectal and bladder dose between plans. There was a small but significant difference in rectal V36 Gy, with a median decrease of 0.26 cc in MLC compared with Iris plans ($p=0.0234$), as well as a median decrease of 12.1% in rectal V18.1Gy, although not reaching statistical significance. The MLC plans had a slightly higher bladder V37 Gy compared to Iris, increasing by a median of 0.99 ($p<0.01$), but the V18.1 Gy was higher with the Iris, with a median increase of 5.9% compared to MLC, which did not reach significance. There appears to be some improvement of femoral head sparing using MLC, but again this was not a significant difference.

Figure 4.6: Comparison of femoral head sparing between Iris and MLC plan



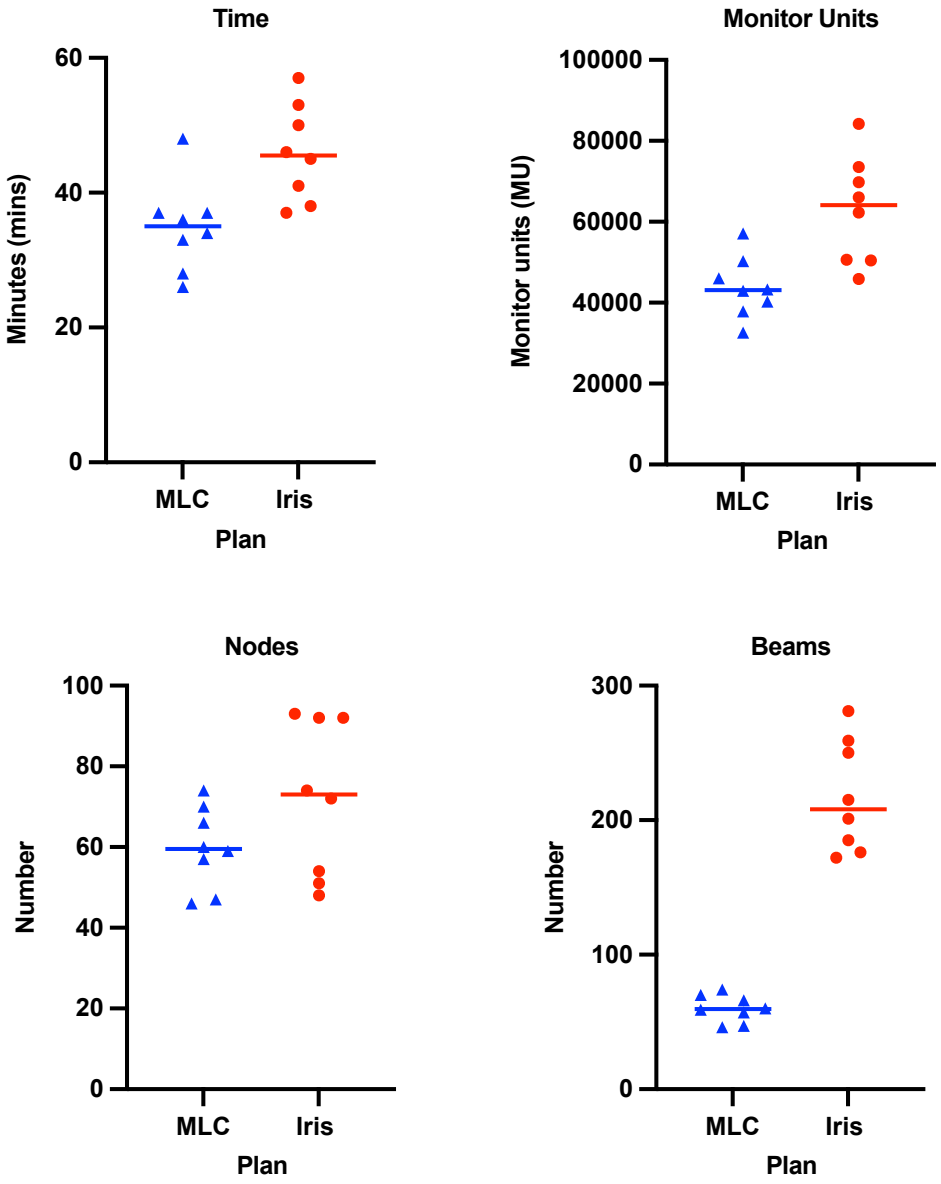
Axial slice from a CyberKnife prostate plan using the Iris variable collimator (left) and Incise multi-leaf collimator (MLC) (right). The CTV (red) includes the full seminal vesicles (SV3). The 30% isodose (cyan) is extending over the femoral heads (FH). POST, posterior.

4.5.5.2. Plan delivery efficiency

Figure 4.7 demonstrates efficiency results, comparing all MLC plans with corresponding Iris plans. The MLC plans resulted in significantly quicker treatment time compared to the Iris with a median reduction of 26.2% (10.5 mins, IQR 8 – 15 mins, p=0.0009). Similarly, there was a reduction in MU requirements for the MLC plans, with a 32.8% (18490, IQR 12599 – 30722, p=0.002). median reduction. There was a median node reduction of 7 (IQR 0.25 – 29.75, p=0.07) using MLC, and median beam reduction of 146.5 (IQR 129 – 185.8, p=<0.0001). Comparing the SV3 plans alone, the median node reduction was unchanged and median beam reduction of 141 (IQR 123.8 – 167, p=0.0002).

In conclusion, my results demonstrate that the MLC offers some gains in target coverage and dose sparing, whilst significantly reducing treatment time and monitor units.

Figure 4.7: Plan delivery efficiency comparing MLC with Iris plans



Scatter charts demonstrating plan efficiency indices: time, total monitor units, number of nodes and beams used in each plan. Comparing all multi-leaf collimator (MLC) with corresponding Iris plans . Each blue triangle represents values individual MLC plans and each red dot represents values of individual Iris plans. The horizontal line indicates the median value.

4.6. Discussion

In the majority of cases, I was able to achieve acceptable prostate CyberKnife plans using the Iris collimator, regardless of the extent of SV included within the CTV. Therefore, technically, patients with high-risk prostate cancer, with or without confirmed SV involvement, could be treated at a dose of 36.25 Gy in 5 fractions to the PTV, and 40 Gy to CTV. However, the increase in SV volume did result in a substantial increase in planning difficulty. Acceptable plans were achieved in all eight IrisSV1cases, consistent with the original PACE B treatment plans. However, only 75% of IrisSV2 and 62.5% of IrisSV3 cases were considered acceptable.

4.6.1. Iris planning

By increasing the SV portion to 2 cm, I was unable to achieve acceptable plans in two cases, due to difficulty meeting rectal and bladder constraints, and could not optimally spare the femoral heads without further compromising coverage or increasing rectal/ bladder dosage. Arguably, both plans may be deemed acceptable for treatment in the clinical setting, since the rectal and bladder V18.1 Gy were outside constraints, in separate plans, by just 7% and 1.4%, respectively, and there was only a minor variation in PTV coverage of 93.6% in one case. Including the full extent of SVs resulted in a further failed plan. In this case, I was unable to achieve adequate PTV coverage with a PTV V36.25 Gy of 88.6%, with still minor variations in rectal V36 Gy and V29 Gy constraints and no femoral head sparing.

The increase in planning difficulty may simply be due to the effect of the increasing PTV volume, since all of the failed plans had higher PTV volumes (range 132 – 200 cc) compared to the other cases. Even a small difference in CTV volume has a large impact on PTV volume as I have shown. In this series, a median increase in volume of 4.39 cc between CTV1 and CTV2 caused a median increase of 17.8 cc between PTV1 and PTV2; and a median increase of 8.03 cc between CTV 1 and CTV3, resulted in a median increase of 29.05 cc between PTV1 and PTV3.

Of note, the cases used in the study were all intermediate-risk patients treated within PACE B and were therefore treated without the addition of androgen deprivation therapy (ADT). The use of ADT may have an impact on both prostate and SV volume, and potentially the impact of volume may be less substantial in patients with high-risk disease increase in volume may have been less in patients with high-risk disease, usually treated with neo-adjuvant and concomitant ADT.

As previously discussed in chapters 1 and 2, there is known to be some association between PTV volume and toxicity, which may in part be a consequence of OAR overlap. In my study, I have demonstrated a strong correlation between PTV volume and the volume of rectal overlap ($r = 0.86$, $p = <0.0001$). There was less, but still moderate correlation between PTV volume and the volume of bladder overlap ($r = 0.64$, $p = 0.0007$). In addition to PTV volume, the SV anatomy and proximity to bladder and rectum contribute to the magnitude of OAR overlap and complexity of SBRT planning. I also demonstrated moderate correlation between SV volume and the volume of rectal overlap ($r= 0.6$, $p= 0.002$), but no significant correlation with bladder overlap. However,

this may be simply a reflection of the PTV volume, as there was also moderate correlation between SV and PTV volumes (r =0.65, p = 0.0006).

In two of the failed plans, the degree of rectal and bladder overlap was larger in comparison to the other cases. Overall, there was a very small but statistically significant increase in rectal and bladder overlap between IrisSV1 and IrisSV2 plans, which was not seen between IrisSV2 and IrisSV3 plans. Accordingly, the rectal V 29 Gy and V18.1 Gy were significantly higher in the IrisSV2 plans, with a median increase of 2% and 12.45% respectively, as well as a median increase in bladder V18.1 Gy of 9.75%. However, there was no significant difference between IrisSV2 and IrisSV3 plans in terms in rectal and bladder dose.

It is unclear if the magnitude of increase in dose to rectum and bladder would equate to a rise in toxicity. However, the study by Kim et al, detected a strong association between high grade rectal toxicity and the volume of rectum receiving high doses of radiation ≥ 35 Gy[19]. Musunuru et al demonstrated an association between high-grade rectal bleeding, and the volume of rectum receiving ≥ 38 Gy, as well as some association between treatment volume and PTV margin[20].

One method of reducing the degree of rectal overlap and hence rectal dose would be to insert a rectal spacer. In the randomised trial by Mariodos et al, in which 222 patients received IMRT, 79.2 Gy in 1.8 Gy fractions, the insertion of a Hydrogel rectal spacer resulted in a mean perirectal space of 12.6 mm post spacer application, compared to 1.6 mm at baseline, and in the control group[21]. There was a significant reduction in dose to the rectum, with a reduction in mean rectal V50 Gy, V60 Gy, V70 Gy and

V80Gy by 13.44%, 11.56%, 9.08% and 3.93%, respectively. Using an alpha/beta ratio of 3 for rectum, the rectal 80 Gy has a calculated biologically equivalent dose (BED) of 128 Gy which is slightly higher than for high-dose rectal constraint of 36 Gy used in this study. The BED for the rectal 50 Gy has a calculated BED of 80 Gy, which is 12 Gy higher than the low dose rectal constraint of 18.1 Gy used in this study. 97.3% of paptients with a spacer inserted had a 25% reduction in rectal V70 Gy compared to control, and 100% of plans met all rectal constraints compared to 92% in the control group. There was a 5% reduction in late rectal toxicity and an improvement in bowel QOL in the spacer group, however there is not data regarding any correction between toxicity and perirectal space or rectal dose.

A larger CTV-PTV margin of 6 mm was applied to the distal SVs in view of the evidence demonstrating increased SV motion relative to the prostate[5-8]. This will have had a further impact on PTV volume, and magnitude of any overlap with rectum and bladder. Reducing this margin could therefore improve SBRT plans in high-risk patients although further work is needed. The development of soft-tissue imaging such as the MR-linac may allow improved SV localisation and further evaluation to ascertain whether the use of smaller margins would be possible. Fiducials markers inserted into the SVs as used in the study by Lim Joon et al[5] would also aid localisation although this is likely to be technically challenging. The use of rectal and bladder preparation protocols may help by minimising OAR motion and are associated with improved prostate cancer outcomes following conformal radiotherapy[23].

Another approach to improving the plans in this study would be to reduce the dose delivered to the distal SVs. In patients with unfavourable intermediate- or high-risk

disease, without macroscopic evidence of SVI on diagnostic imaging, it would be reasonable to consider reducing to a dose adequate for treating microscopic disease. As described, the PACE C trial has instituted three dose levels in the planning protocol for unfavourable intermediate- and high-risk patients, in which the distal SV dose is reduced to 30 Gy in 5 fractions.

In the pre-trial planning study by Mitchell et al, using this approach, acceptable plans were achieved without compromising coverage in 4 out of 5 plans, however only 2 (40%) met all constraints without minor variation[23]. In my study I was able to achieve acceptable IrisSV3 plans in 5 out of 8 cases (62.5%), with comparable mean doses to rectum, bladder, and bowel. Although different planning techniques were employed for VMAT SBRT and no baseline information provided to make any valid comparisons, this supports the conclusion that treating the full SVs, using CyberKnife at a prescription dose of 36.25 Gy in 5 fractions is feasible.

Therefore, SBRT could be considered in high-risk patients with macroscopic SVI (T3b disease). However, it remains unclear as to whether patients with high-risk disease should additionally receive dose escalation in the form of a simultaneous integrated boost (SIB) to sites of disease within the prostate and/ or prophylactic radiotherapy/SBRT to the pelvic lymph nodes. Long-term results from randomised trials such as PIVOTALboost and SPORT trial will be highly informative[24,25].

The increase in planning difficulty between Iris plans is reflected by the increase in estimated treatment time, total MU, and number of beams required to achieve an optimal plan. The estimated treatment time significantly increased by a median of 10.5

minutes (31.8%) between IrisSV1 and IrisSV2 plans, and a further median increase of 3.5 minutes (9.2%) between IrisSV2 and IrisSV3 plans. The estimated treatment time for the IrisSV3 plans ranged between 37 and 57 minutes. The total MU significantly increased by a median of 17009 MU (46.4%) between IrisSV1 and IrisSV2 plans although this was not seen between IrisSV2 and IrisSV3 plans. This can be explained by a large 89.7% median increase in the number of nodes and 38.7% median increase in beams required for IrisSV2 plans compared to IrisSV1 plans. There was no increase in nodal usage but a further 14.7% median increase in beams between IrisSV2 and IrisSV3 plans. Therefore, although planning was feasible in the majority of cases, the increase in the extent of SV resulted in a significant deterioration in plan efficiency.

4.6.2. Benefit of MLC

In the second part of my study, I demonstrated a significant benefit from the use of MLC in comparison to the Iris collimator. Firstly, I was able to achieve some improvement in plan quality using MLC. In the three cases where I failed to meet constraints using the Iris, with the MLC I was able to achieve similar or improved coverage, but with only minor dose constraint variations compared to the Iris plans. Apart from the bladder V37 Gy, there was overall improvement in median OAR dose for all constraints, although only reaching significance for rectal V36 Gy.

However, the most prominent finding from this planning study was the marked improvement in plan efficacy as a result of using MLC. The MLC plans achieved a significantly quicker treatment time compared to the Iris plans, on average reducing by 10.5 minutes (26.2%). The duration of the MLC plans ranged between 26 and 48

minutes, compared to 37 and 57 minutes for the Iris plans. This would have clear benefits for both the patient and departmental capacity. I have also demonstrated a significant reduction in total MU and number of beams, with an average MU reduction of 32.8%, and around 70% beam reduction number, reducing by an average of 146.5 beams per plan.

This is consistent with results published planning studies, although the level of improvement in delivery efficiency provided by MLC varies greatly. The largest reduction in treatment time has been reported by McGuinness et al, with an average 45% treatment time reduction using MLC[12]. From the 5 prostate SBRT cases in the study, treatment times ranged from 19 – 26 minutes for MLC plans, compared with 32 – 47 minutes using circular collimators. The total MU and beam number were reduced by an average of 40%, and 64.7% respectively. Compared to my study, there were a number of differences including dose prescription (38 Gy in 4 fractions or 19 Gy in 2 fractions), smaller PTV margins of 2 mm, and smaller PTV volumes, which, on average, were > 50% smaller (median 42 cc compared to 113 cc in my study). It is unclear if the circular collimators in the comparison plans were fixed or Iris variable collimators, which may explain the greater difference in treatment time compared to my study. In addition, my plans were more conformal, with a median nCI of 1.12 for both techniques, compared to nCI 1.23 and 1.24 for MLC and circulator collimators respectively.

Four other studies had more in common with my study, although including mainly low- / intermediate- risk prostate cancer cases. They used the same dose prescription (36.25 Gy in 5 fractions), CTV-PTV margins (5 mm/ 3 mm posteriorly) and similar dose

constraints taken from the PACE protocol (Appendix 2) or King et al (rectum: V50% < 50%, V80% < 20%, V90% < 10% and V100% < 5%; and bladder: V50% < 40% and V100% < 10%)[26].

Kathriarachichi et al compared Iris collimator with MLC in 10 cases, with a median PTV volume of 86.9 cc (range 61.4 – 139.2)[13]. Plans were similar to mine in terms of conformity (nCI 1.11 for both plans), but higher dose homogeneity within the PTV as the prescription isodose line was kept at > 84% to limit maximum prostatic dose to 119%. No significant difference was found between rectum V36 Gy and bladder V37 Gy, but other dose parameters were not reported. MLC plans demonstrated a 36% improvement in average treatment time, with median time of 45.5 minutes and 29.3 minutes, for Iris and MLC plans, respectively. There was a 42% reduction in MU from a median of 50934 using to Iris to 29700 with MLC.

Tomida et al compared fixed collimator, variable collimator, and InCise MLC plans in 10 cases, reporting MLC plans to be 31% and 20% shorter than those of the fixed and variable collimator plans respectively[14]. The total MU of the MLC plans was about 27% lower than those of the others, and the average number of beams in the MLC plans was 28% and 32% lower than those in the fixed and variable collimator plans respectively. The only significant difference in OAR dose was the bladder V50% which was approximately 30% lower than for the circulator collimators.

Murai et al reported a lower average treatment time reduction of 19% (25 mins versus 31 mins, $p = 0.002$) in 10 cases[15]. The median PTV size was 47.5 cc (range 35–132 cm^3) and reported overlap volumes of PTV with rectum (median 1.5 cc) and bladder

(median 1.5 cc) which were similar to my study. They also demonstrated a significant improvement in rectum V50%, V80% and V90% in MLC plans and maximum dose to the rectum lowered by 0.8 Gy.

The most recent study by Masi et al included 13 cases, with PTV measuring 49 - 143cc[16]. Iris and MLC plans were equivalent in terms of coverage and conformity, with no significant difference between OAR doses, apart from small but significant reductions in bladder V18 Gy and rectum V29 Gy of 3% and 2%, respectively. They reported a significant time reduction of 15% (25.9 mins Iris and 22 mins MLC), and 9% MU reduction with MLC, which is lower than my results and those from the other published studies.

The 26% time reduction demonstrated in my study is within the range of published studies, and closest in magnitude to Tomida et al[14]. The studies by McGuiness et al and Kathriarachich et al reported greater time reductions of 36 – 45%[12,13]. The main difference in my study was the substantially larger PTV size, predominantly related the larger extent of SV inclusion in the CTV and larger margins compared to McGuinness et al. However, this does not necessarily explain the difference in treatment time reductions since I would have expected there to be a greater advantage from the use of MLC with larger target volumes. As highlighted by Masi et al[16], the median treatment time for the Iris plans in the McGuinness and Kathriarachchi studies were 40 minutes and 45 minutes, respectively, which is markedly higher than reported by Masi et al or Murai et al[15], and therefore demonstrates the potential for improved efficiency optimisation on the Iris plans. Although I report a similar Iris treatment time of 45.5 minutes, my IrisSV1 plans, which are more comparable in terms of CTV

definition and PTV volume, had a medium treatment time of 30.5 minutes even though the median PTV volume (86.53 cc) was over double reported by McGuinness et al.

4.6.3. Study limitations

The main limitation of this study is the small cohort size of 8 cases. My original aim was to include ≥10 cases, however the planning time required to complete a total of 30 plans was longer than predicted, and there was a significant time delay in commencing the study due to technical issues involving the Multiplan research station. In spite of this limitation, I have demonstrated a significant improvement in plan delivery efficiency with the use of MLC compared to Iris, without any deterioration in plan quality. However, the differences in OAR dose did not reach statistical significance which may have been influences by the low number of cases.

Although planning studies can provide useful information regarding new radiotherapy techniques, they are not always reflective of clinical practice and are prone to bias when planning approaches are compared[27,28]. The comparison of optimised plans is complex given the large number of parameters and the selection of the best clinical plan can be subjective, often with some compromise between plan quality/ OAR sparing, and plan delivery efficiency.

Ideally, to make sure the most optimal plans are compared, plans would be completed by the most experienced single planner or independent group of experienced planners[28]. As a clinician, I had limited planning experience prior to the study, but did receive adequate training in both planning methods, and had approximately the same

level of experience with either Iris or MLC. However, as MLC was not available for clinical use at the time of my study, I did not have the same level of planning support and advice from my departmental physics team in comparison to Iris planning. Also, since my study design involved more Iris planning, I gained a greater level of experience over time in comparison to MLC planning.

A further limitation of my study design which risked introducing bias was, that for each case, I completed the Iris plans first and was therefore aware of the plan outcome before commencing the MLC planning. Importantly, the length of time required for plan optimisation was higher for the Iris plans compared to MLC, although this was difficult to accurately quantify and therefore this data was not collected as part of my study. However, this highlights another potential benefit from the use of MLC, in reducing planning time. The planning time is likely to have been influenced by the planning software used (Multiplan 5.3) on the research terminal, rather than the newer and more efficient Accuray Precision™ planning system which is currently in clinical use.

In my study I have minimised bias by completing all plans myself for both techniques, and not retrospectively including original clinical treatment plans in the comparison. I attempted to keep plans as consistent as possible in terms of imposed hard constraints, shell settings, maximum nCI, and PTV coverage. The criteria for plan acceptability was clear, aided by the definitions for minor or major protocol deviations within the PACE trial protocol. However, the validity of my results may have been improved further by incorporating an independent evaluation by an experienced planner, or using an overall plan quality score, incorporating scores of multiple parameters, to allow accurate comparison.

The study by Masi et al included clinical and mathematical scoring to compare Iris and MLC plans for three tumour sites (liver, pancreas and prostate) with a wide range of PTV volumes (24 – 643 cc)[16]. Plan quality assessment involved review by two senior CyberKnife radiation oncologists who were blinded as to the collimator technique used in each plan. They scored each plan from 1 to 6 (1 = “not clinically acceptable” and 6 = ”optimum”), based on target coverage, OAR sparing, conformity, and then plan delivery efficiency, before selecting which plan would be preferable for clinical treatment. A mathematical score (global plan score) was also calculated, using the weighted sum of scores from multiple parameters.

In the clinical evaluation, the average score over 40 cases given by first observer was 5.0 and 4.5 for MLC and Iris plans, respectively ($p < 0.05$); and the second observer gave median scores of 4.5 both for Iris and MLC. For both observers the median score increased by 0.5 when delivery efficiency was included in the assessment. There was some inter-observer variability with observer agreement on the preferred plan in 16 out of 25 cases. The MLC plan was preferred by the first observer in 18 (72%) cases and in 15 (60%) cases by second observer. The average mathematical score index was also significantly higher for the MLC plans, remaining slightly but significantly higher after removing treatment time and MU scores from the calculation.

4.7. Conclusion

- SBRT planning with CyberKnife is feasible, even for high-risk prostate cancer patients, involving treatment of larger and complex-shaped target volumes.
- The increase in SV volume poses an increased challenge for planning with the Iris variable collimator, in terms of achieving adequate PTV coverage while limiting dose to surrounding normal tissues, and optimising plan delivery efficiency.
- Methods to improve plans in high-risk prostate cancer include the use of rectal spacers to reduce the volume PTV/ rectal overlap and consideration of using smaller SV margins which will require further work to accurately evaluate SV motion and deformation during SBRT, to review the possibility of using smaller margins.
- In patients without macroscopic SVI, a reduced dose of 30 Gy in 5 fractions to the distal SVs can be considered, as used in PACE C.
- The use of MLC resulted in a significant improvement in plan delivery efficiency compared to the Iris variable collimator, in all cases involving treatment of the distal SVs, with some improvement in quality, particularly in the most complex cases.
- The MLC reduced the estimated treatment time by an average of 26.2% which is within the range of published studies.
- Planning studies provide useful information; however the comparison of different planning techniques is complex due to multiple parameters, and prone to bias. Standardised planning assessment tools should therefore be recommended to improve the validity of such studies.

4.8. References

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Chapter 5: Comparison of the CyberKnife Incise multi-leaf collimator and Iris variable collimator in SBRT planning for primary renal cancer

Sections of the following chapter have been published/ presented as:

- Comparison of CyberKnife multileaf collimator and variable circular aperture collimator in renal SBRT[1].

  Morrison K, Henderson D, Khoo V, van As N.

  Poster presentation, ESTRO 37, Barcelona, Spain, April 2018.

  Abstract in Radiotherapy and Oncology 2018; 127: S499 – S500.

5.1. Introduction

The incidence of localised primary renal cancer is rising within the UK, mainly as a consequence of increased incidental radiological diagnosis[2]. Presentation is common within the elderly population, often with associated multiple comorbidities, and therefore several cases may be unsuitable for standard treatment with radical or partial nephrectomy. Management with active surveillance or thermal ablation are options for patients with smaller tumours (less than 4 cm), however local control rates following thermal ablation are inferiorto surgery and not without risk[3].

Traditionally, primary renal cancer has been thought of as radioresistant, but there is increasing evidence that this may be overcome using ablative doses of radiotherapy, achievable with SBRT[4]. A few studies have demonstrated SBRT to be relatively well tolerated, with local control rates similar to nephron-sparing treatment. However, data is of limited value, as studies are mainly retrospective with short follow-up. Data from multi-centre prospective trials will be invaluable in ascertaining the true benefit of SBRT for primary renal cancer.

SBRT planning for kidney tumours is highly complex given the close proximity to radiosenstive structures such as bowel and adjacent renal parenchyma. Larger tumours can cause an added challenge due to the increase in size of the planning target volume (PTV), with greater risk of normal tissue overlap. The CyberKnife can achieve a high degree of conformity, by delivering multiple non-coplanar beams of varying sizes as determined by the Iris variable collimator[5]. The use of the newer multi-leaf collimator (MLC) could provide additional benefit by enabling the use of larger,

irregularly shaped fields which may improve the ability to avoid surrounding structures and plan delivery efficiency[6].

5.2. Hypothesis:

Dosimetrically equivalent plans can be achieved with MLC in comparison to Iris with a reduction in estimated delivery time and total monitor units (MU).

5.3. Aims:

- To compare the proportion of MLC and Iris plans that can achieve a prescription dose of 45 Gy in 3 fractions.
- To evaluate the difference in overall treatment times and total monitor units between MLC and Iris plans.

5.4. Methodology

5.4.1. Case Selection

Cases were randomly selected from a cohort of renal cancer cases which were included in a previous planning study, completed by my predecessor. The case selection criteria, as defined for his study, was as follows:

- Diagnosis of isolated primary renal carcinoma without evidence of renal vein extension, local lymphadenopathy or metastases on imaging (histological diagnosis not required if agreed by renal MDT).
- Recommendation at renal MDT for local therapy with surgery or thermal ablation.
- Adequate diagnostic CT imaging: tumour clearly visible for accurate delineation, and ≥ 15 cm of scan data superior and inferior to the tumour, as required for CyberKnife planning.
- Maximum tumour diameter of ≤ 6 cm, and not in direct contact with small or large bowel.

5.4.2. Contouring

Contouring was previously completed by my colleague using the diagnostic CT scan, which had been uploaded to the Eclipse planning system (Varian Medical Systems, USA). The visible tumour seen on imaging was delineated as Gross Tumour Volume (GTV) and the planning target volume (PTV) was created by applying a 5 mm

expansion margin. The following organs at risk (OAR) had been contoured: bilateral kidneys (excluding GTV and renal hilum); renal hilum; small bowel; duodenum; large bowel; liver; spleen; and spinal canal.

5.4.3. Planning Technique:

I imported 15 planning data sets from Multiplan version 5.2, used in the previous planning study, to the newer version, Multiplan 5.3, which allows the option of planning with either Iris collimator or MLC. I replanned all cases myself on Multiplan 5.3. completing one Iris and one MLC plan for each case. This was done to minimise bias when comparing techniques, excluding the potential influence of using a different planners and version of Multiplan for each technique.

5.4.4. Plan set up

For each new plan the appropriate collimator type (Iris or MLC) was selected. All plans were set-up for fiducial tracking and Synchrony respiratory motion management[7]. Since no actual fiducial markers were used in this study, fiducial coordinates were set at adequately spaced points close to the GTV within the ipsilateral renal parenchyma. To optimise conformality, dose-limiting shell structures were set at the following distances from PTV: 3mm (shell 1); 12mm/10mm anteriorly (shell 2); 30mm/ 26mm anteriorly (shell 3).

5.4.4.1. Collimator settings

For Iris planning, 5-6 collimator sizes were selected ranging between 10 mm – 60 mm, depending on PTV size. The maximum monitor unit was set at 750 MU per beam and 1,125 MU per node. For MLC planning, the “conformal-avoidance” option was selected, using all shapes (eroded, perimeter and random) provided by the system. The maximum MU was set at 750 MU per segment and 1,500 MU per node.

5.4.4.2. Planning process

The planning process was similar to the process described in chapter 4. Maximum dose constraints were initially set to limit the solution as follows: PTV 5625 Gy; CTV 5625 Gy; shell 1 4500 Gy. Sequential optimisation was used, with planning objectives entered, aiming to achieve at least 95% PTV coverage at a dose of 45 Gy in 3 fractions. OAR dose constraints were derived from the UK SABR consortium consensus guidelines[8] (Table 5.1). Dose calculation was performed using ray-tracing algorithm for Iris and a finite size pencil beam (FSPB) algorithm for MLC. The process was repeated until an optimal plan was achieved. If unable to meet the constraints, the prescribed dose could be reduced in 3 Gy increments to a minimum of 36 Gy.

Table 5.1: Mandatory dose constraints

		Constraint
Kidney	Combined	Dose to ≥ 200 cc < 16 Gy
	Solitary Kidney*	V8.5 Gy <10 % (optimal), <45 % (mandatory)
Small Bowel		Dmax (0.5 cc) < 25.2 Gy D5 cc < 17.7 Gy
Large bowel		Dmax (0.5 cc) < 28.2 Gy
Duodenum or Stomach		Dmax (0.5 cc) < 22.2 Gy D5 cc <16.5 Gy D10 cc <11.4 Gy
Liver		Dose to ≥700cc < 19.2 Gy
Spinal Cord		Dmax 0.1 cc <30 Gy

Mandatory dose constraints used for renal planning study, as per UK consensus, UK SABR Consortium Guidelines 2019[8]. *adapted from 5 fraction dose constraint.

5.4.3.4. Plan comparison

MLC plans were compared with the corresponding Iris plans, to assess for any improvement in quality and efficiency by the use of MLC. In order to achieve a valid comparison I aimed to maintain relative consistency in PTV coverage and conformity between plans.

5.4.5. Statistical Analysis

The Statistical analysis was conducted by myself, using the Prism version 9 (© 1994 - 2021 GraphPad Software, LLC) package. Volumetric and plan data are described using descriptive statistics, including median value, interquartile range (IQR), and range. The Shapiro-Wilk test was applied to confirm normal distribution. For normally distributed data, the paired t-test was applied to test for statistically significant differences between plan types; and the Wilcoxon matched-pairs signed rank test used for data that was not normally distributed; set at a significance value of $p \leq 0.05$. Pearson's correlation coefficient was used to test the strength of any correlation between PTV volume and plan parameters.

5.4.5.1. Primary endpoint:

The number of acceptable plans achieving ≥95% target volume coverage at a prescription dose of 45 Gy in 3 fractions, while meeting OAR dose constraints (Table 5.1).

5.4.5.2. Secondary endpoints:

- Dose to dose-limiting OARs at 45 Gy in 3 fractions – kidney, small bowel, large bowel

- Coverage (%) and conformity (new conformity Index* (nCI))
  *takes into account the quality of target coverage and normal tissue dose

- Dose Delivery Efficiency: Treatment time, total monitor units (MU), node and beam number

5.5. Results:

5.5.1. Case characteristics

Of the 15 cases in this study, renal tumours were located on the right side in 9 cases and on the left side in 6 cases. The median tumour diameter was 3 cm (range 1.5 – 5.8 cm), and in 2 cases the tumour diameter was over 4 cm. The target volume and kidney volume measurements are summarised in Table 5.2 and individual GTV and PTV volumes are plotted in Figure 5.1. In five cases, the PTV was within 2cm of small bowel, at a median distance of 6 mm (range 2.2 – 14 mm); and 4 cases the PTV was within 2cm of the large bowel, at a median distance of 10.5 mm (range 1 – 15.6 mm).

5.5.2. Plan evaluation

5.5.2.1. Dosimetry

Acceptable plans were achieved in 14 (93.3%) cases for both Iris and MLC plans, all with ≥95% PTV coverage at a dose of 45 Gy in 3 fractions, while meeting all mandatory dose constraints. In one case the dose was reduced to 42 Gy in both Iris and MLC plans in order to meet constraints. This case had a 3.4 cm left sided renal cancer, with PTV volume of 39.1 cc, which was only 2 mm from small bowel. The PTV coverage of the Iris (95.4%) and MLC (95.1%) plan were relatively equal. Acceptable plans were not achieved at 45 Gy due to kidney and small bowel constraints not being met in both plans. In the Iris plan, 198 cc of the combined kidney volume received less than 16 Gy compared to 199 cc in the MLC, only just below the required constraint. The dose to

5cc of small bowel was 18.5 Gy in both plans which is 0.8 Gy above the required constraint.

The combined kidney volume in this case was 237 cc and therefore was not possible for the dose constraint to be met in which at least 200 cc should receive less than 16 Gy. In one case with a solitary kidney (211 cc in volume), a lower reduction in V<16 Gy was permitted since the mandatory solitary kidney constraint (V8.5 Gy < 45 %) was met, which in this case was 18.6 % and 18.3 % for the Iris and MLC plans respectively.

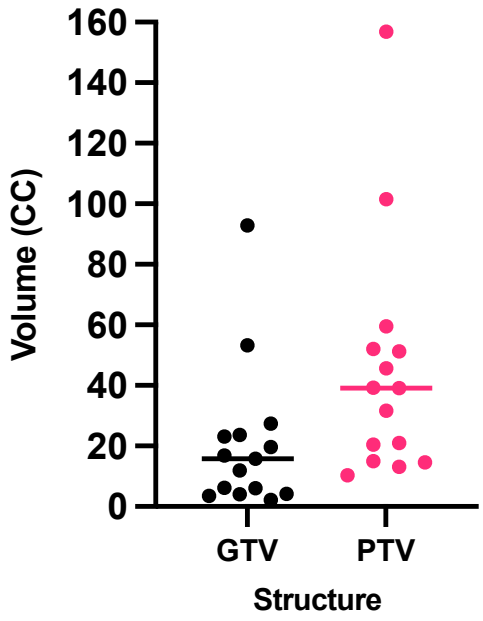
Overall, the median PTV coverage was similar at 96.7% (IQR 96 – 97.1%) for the Iris plans compared to 96.3% (IQR 95.1 – 96.3%, p=0.03) for the MLC plans. Although statistically significant, the small 0.4% difference would be unlikely to have any clinical consequence but may have some effect on other plan parameters used for comparison in this study. There was no significant difference in median prescription isodose at 81% (IQR 80 - 81%) and 80% (IQR 79 -81%) for Iris and MLC, respectively, and the median nCI for Iris and MLC was 1.11 (IQR 1.09 – 1.14) and 1.12 (IQR 1.1 – 1.14) respectively, confirming plans to be comparably conformal.

Table 5.2: Target and kidney volumes

Structure	Volume (cc)	
	Median	**Range**
GTV	15.8	2.2 – 92.9
PTV	39.10	10.3 – 156.9
Left kidney	160.6	112.8 – 273.8
Right kidney (n=14)	181.1	123.7 – 251.6
Combined kidneys	343.1	211.1 – 525.4

Summary of target volume and kidney volume measuements (cc) for 15 cases, reported as median and range. Right kidney measurements include 14 cases, as one patient with a solitary left kidney. GTV, gross tumour volume; PTV, planning target volume.

Figure 5.1: Individual gross tumour volume (GTV) and planning target volume (PTV)



Scatter chart demonstrating individual GTV and corresponding PTV measurements (cc). The horizontal bar indicates the median value.

The dose volume results for each constraint applied to the main dose limiting structures (kidneys, small bowel, large bowel) are summarised in Table 5.3. The MLC plans demonstrated a slight improvement in all parameters in comparison to the Iris plans, but no significant difference was detected apart from the small median difference in kidney volume there is a slight improvement in all parameters but no statistically significant difference apart from the small difference in volume of combined kidney parenchyma receiving <16 Gy.

Table 5.3: Dose to organs at risk, MLC compared with Iris plans

		MLC (n = 15)	**Iris (n = 15)**	**p value**
Kidney (combined)	V <16 Gy (cc)	292 (267 – 326) Range 193 – 474	286 (256 -323) Range 191 - 486	0.005
Solitary kidney*	V 8.5 Gy (%)	18.3	18.6	
Small bowel	D 0.5 cc (Gy)	15.3 (6.8 – 18.9) Range 6.1 – 23.8	17.0 (11.5 – 18.6) Range 7.4 – 23.9	0.29
	D 5 cc (Gy)	12.2 (5.9 – 16.4) Range 4.9 – 18.5	13.5 (9.8 – 15.8) Range 5.5 -18.5	0.3
Large bowel	D 0.5 cc (Gy)	20.1 (12.0 – 23.6) Range 9.8 – 26.2	16.3 (12.6 – 24.8) Range 9.3 – 28.2	0.77

Summary of dose volume measurements for kidney, small and large bowel compairing MLC and Iris plans. Reported as median value (IQR) and range. V,volume; D,dose; cc, cubic cm. *one patient

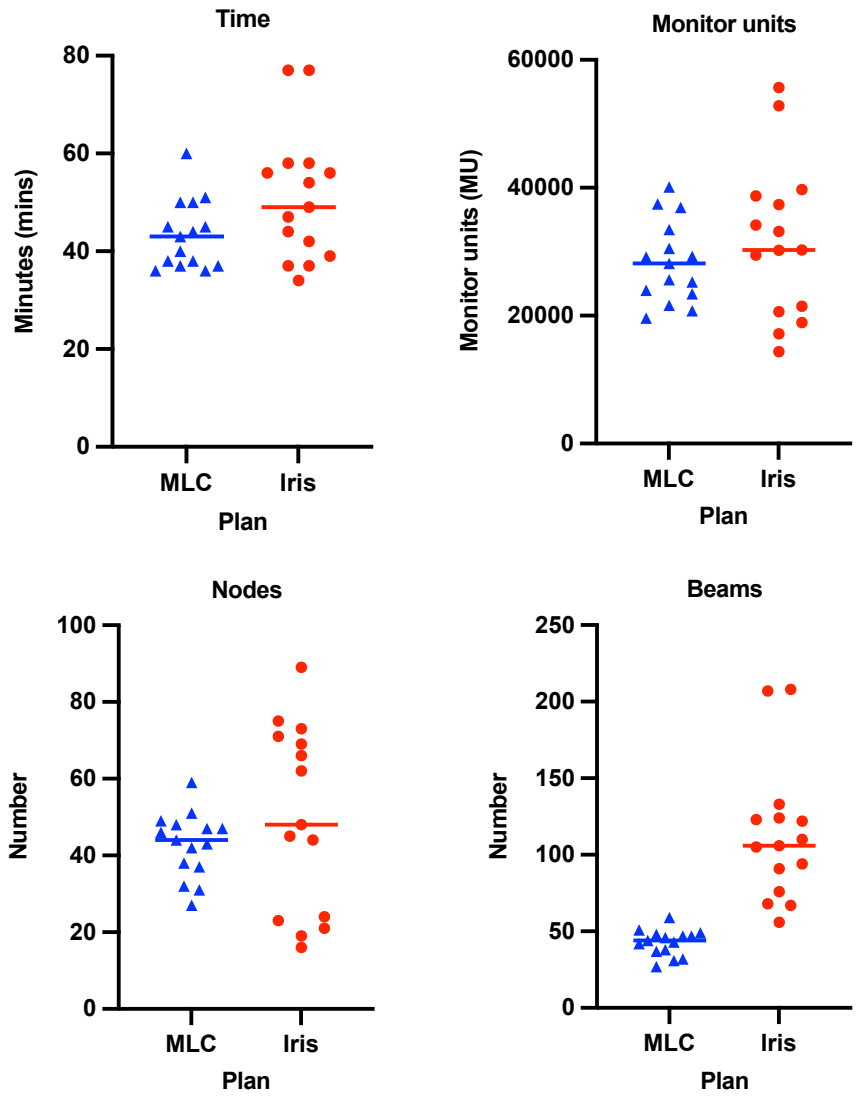
5.5.2.2. Plan delivery efficiency

The estimated treatment time (Figure 5.2) for the Iris plans ranged between 34 and 77 minutes, with median time of 49 minutes and for the MLC plans the estimated treatment time ranged between 36 and 60 minutes with a median treatment time of 43 minutes (IQR 37 – 50 mins). Therefore, there was a significant treatment time reduction of 6 minutes ($p=0.0045$) with the use of MLC. Without including the 15 minutes set-up time, this equates to a 17.6% time reduction. There was a 3.6% reduction in total MU (Figure 5.2) by using MLC compared to Iris, however this was not statistically significant. There was a 58.5% reduction in the median number of beams used from 106 (IQR 76 – 124) with the Iris and 44 (IQR 37 – 48) with the MLC.

5.5.2.3. Complex cases

Two of the 15 cases in this study had a maximum tumour diameter of ≥4 cm. In one case, with a tumour diameter of 5.5cm and PTV of 105 cc, the use of MLC resulted in a 51.6% reduction in estimated treatment time, in addition to a 46.7% MU reduction and 76.9% reduction in beam number. In addition, there was a reduction in bowel dose of 5.87 Gy, 5.48 Gy, and 9.63 Gy for the small bowel D0.5 cc, D5 cc and large bowel D0.5 cc, respectively. In the other case which had a tumour diameter of 5.8cm and PTV of 156.9 cc, the treatment time was reduced by 30.2% with a reduction in MU and beam number of 24.3% and 65.3%, respectively. However, in this case there was minimal difference in bowel doses between each plan.

Figure 5.2: Plan delivery efficiency – MLC compared to Iris plans



Scatter charts demonstrating individual plan efficiency indices: estimated treatment time; total monitor units; number of nodes and beams used in each plan. Comparing MLC and Iris plans for all cases. Each blue triangle represents values individual MLC plans and each red dot represents values of individual Iris plans. The horizontal line indicates the median value.

In 9 of the 15 cases the PTV was within 2cm of the small or large bowel, including one of the patients with tumour diameter ≥ 4cm. To determine whether the MLC provided a greater advantage in the more complex cases, a further comparison has been conducted, limited to the 10 patients with tumour diameter ≥ 4cm and/ or PTV within 2cm with small or large bowel. The dose volume results for each constraint are summarised in (Table 5.4). Although the difference in median dose to small and large bowel remains not statistically significant, there is a slightly larger reduction in median small bowel dose (D0.5 cc and D5 cc) in the MLC plans, in comparison to the original analysis.

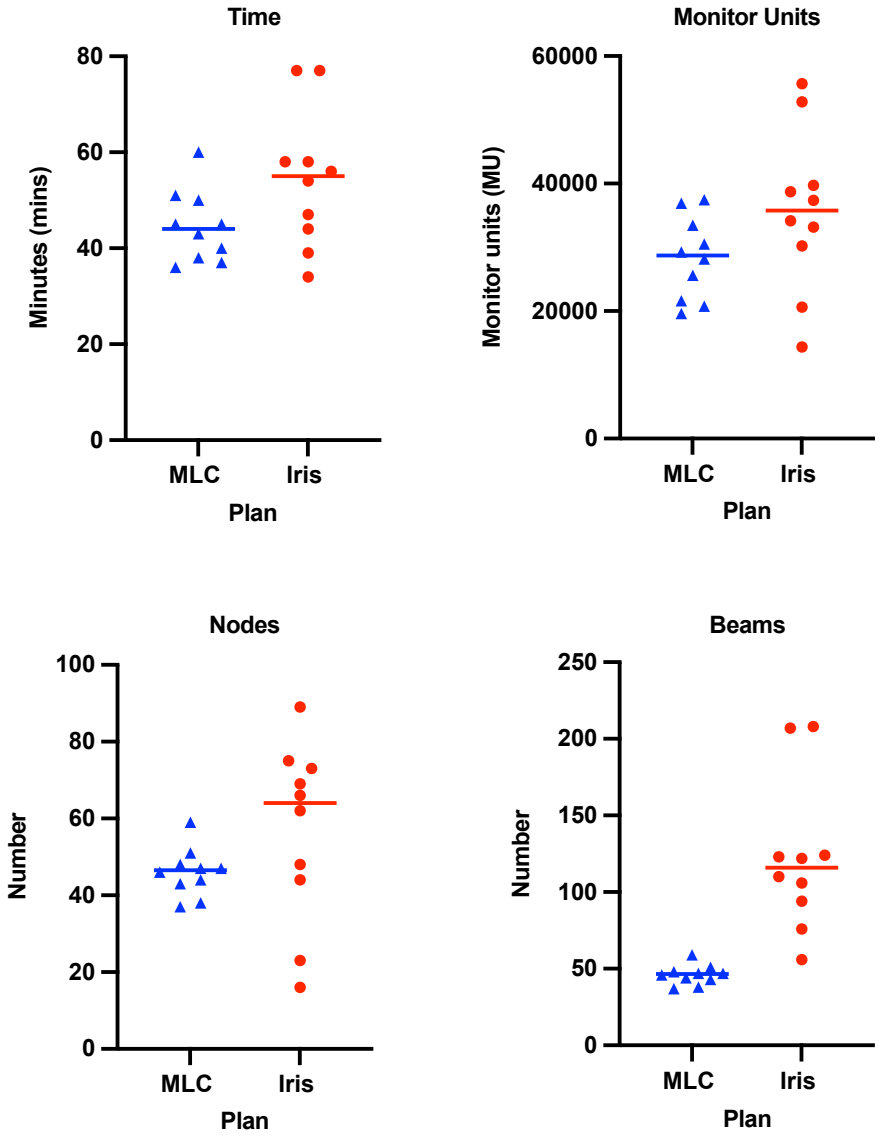
The comparison of plan delivery efficiency for the 10 complex plans is demonstrated in Figure 5.3. For the Iris plans, the median estimated treatment time was 55 minutes (IQR 42.75 – 62.75) with a range of 34 – 77 minutes, for the MLC plans, the median treatment time was 44 minutes (IQR 37.75 – 50.25) with a range of 36 - 60 mins. Therefore, on average there was a 11-minute treatment time reduction ($p=0.012$) which, without accounting for the 15 minute set-up time, equates to a 27.5% treatment time reduction. The percentage reduction in MU and beam number in the MLC plans was 22.7% ($p=0.051$) and 62.5% ($p=0.0005$), respectively.

Table 5.4: Dose to organs at risk in complex cases

		MLC (n = 10)	**Iris (n = 10)**	**p value**
Kidney (combined)	V <16 Gy (cc)	272 (226 – 305.5) Range 193 – 306	264 (223 -298) Range 191 – 337	0.014
Solitary kidney*	V8.5 Gy (%)	18.3	18.6	
Small bowel	D0.5 cc (Gy)	14.7 (6.7– 21.9) Range 6.1 – 23.8	17.5 (11.5 – 20.8) Range 7.4 – 23.9	0.10
	D5 cc (Gy)	12.5 (5.6 – 16.8) Range 4.9 – 18.5	15.3 (10.5 – 16.0) Range 5.5 -18.5	0.13
Large bowel	D0.5 cc (Gy)	22.7 (19.3 – 24.4) Range 10.7 – 26.2	21.4(16.0 – 26.3) Range 9.3 – 28.2	0.81

Summary of dose volume measurements for kidney, small and large bowel comparing MLC and Iris plans for complex cases (tumour diameter ≥ 4cm and/or PTV within 2cm of small or large bowel). Reported as median value (IQR) and range. V,volume; D,dose; cc, cubic cm.

Figure 5.3: Plan delivery efficiency for complex cases



Scatter charts demonstrating plan efficiency indices: time, total monitor units, number of nodes and beams used in each plan. Comparing MLC and Iris plans for complex cases only (PTV> 100cc and/or PTV within 2cc of small or large bowel). Each blue triangle represents values individual MLC plans and each red dot represents values of individual Iris plans. The horizontal line representing the median value.

5.5.3. Comparison with Iris plans from previous planning study

Acceptable plans, at a prescription dose of 45 Gy, were achieved in 14 (93.3%) out of 15 Iris plans. This compares to 9 (60%) of the same 15 cases from the previously mentioned study completed by my colleague on Multiplan 5.2. This highlights the importance of maintaining the same planner and planning conditions to minimise bias and allow a valid comparison.

Of the 6 cases requiring a dose reduction in the previous planning study, I was able to achieve acceptable plans at 45 Gy in 5 of those cases. The indications for dose reduction in the previous study are summarised in Table 5.5. Case 1 required a reduction to 42 Gy, and cases 2 – 5 required a reduction to 39 Gy in order to meet constraints. Case 6 required a dose reduction to 36 Gy which in my study had to be reduced to 42 Gy. As shown, all cases did not meet small bowel and/ or large bowel constraints, and in 5 cases the bowel was within 6 mm of the PTV. As previously stated, the combined kidney volume of case 6 was only 237 cc, and as a result the V<16 Gy constraint could not be met.

Comparing my Iris plans results with the corresponding plans from the previous study, there was no significant difference in terms of PTV coverage, conformity (nCI) or prescription isodose. No significant difference in kidney V<16 Gy was demonstrated. The Iris plans from the current study achieved a significant improvement in median small bowel dose for both parameters (Figure 5.4). There was a median reduction in small bowel D 0.5 cc of 4 Gy (IQR 1.8 – 8.1 Gy, $p = 0.034$) in the current plans

compared to the previous plans, and a median reduction in D5 cc of 2.4 Gy (IQR 1.2 – 4.8 Gy, p=0.035). A significant difference in median large bowel dose was not detected.

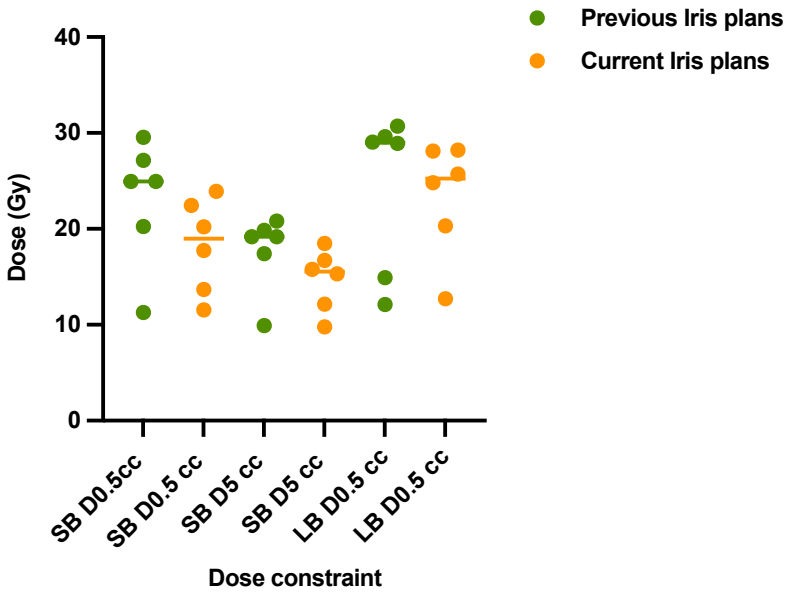
These results confirm that both Iris and MLC have the capability to treat even complex renal tumours. However, the MLC still has an advantage in terms of plan delivery efficiency. It is possible that an even greater benefit may found compared to Iris, in the treatment of larger tumours.

Table 5.5: Indications for dose reduction in previous planning study

Case	Kidneys (combined)		Small Bowel (SB)		Large Bowel (LB)	OAR ≤ 2cm from PTV
	Total volume (cc)	Vol < 16 Gy (cc) *<200 cc*	D0.5 cc (Gy) *>25.2 Gy*	D5 cc (Gy) *> 17.7 Gy*	D0.5cc (Gy) *> 28.2 Gy*	
1	256	236.12	11.27	9.92	**29.04**	**LB 1 mm**
2	211*	182.72*	**27.15**	17.43	**28.91**	**SB 6 mm**
3	393	336.1	20.25	**19.18**	**30.7**	**LB 5.7 mm**
4	525	466.99	24.96	**19.84**	12.12	
5	383	331.45	24.96	**19.17**	14.92	**SB 4.2 mm**
6	237	**195.89**	**29.55**	**20.82**	**29.61**	**SB 2.2 mm**

Summary of dose constraint deviations for 6 Iris plans from the previous planning study, not meeting required dose constraints at a prescription dose of 45 Gy in 3 fractions. The mandatory dose constraints are given in italics and dose constraint deviations in bold. Vol, volume; cc, cubic centimetres; SB; small bowel; LB, large bowel; OAR, organs at risk.

Figure 5.4: Bowel dose comparing with Iris plans from previous planning study



Scatter chart demonstrating small and large bowel doses from individual Iris plans, comparing results from current study with previous planning study. Horizontal line indicates median value. SB, small bowel; LB, large bowel; cc, cubic centimetres; Gy, Gray.

5.6. Discussion

These results confirm that CyberKnife planning for primary renal cancer is feasible at a dose of 45 Gy in 3 fractions, using either the Iris or MLC. At this dose, acceptable Iris or MLC plans were not achieved in only one case, requiring a dose reduction to 42 Gy to meet constraints. Arguably, since the kidney and small bowel dose constraint deviations were almost negligible, this may be deemed clinically acceptable but was considered a failed plan in the context of this planning study.

Overall, there was a very small improvement in median dose to kidneys, small and large bowel using MLC compared to Iris plans. However, apart from the kidney dose constraint there was not a significant difference and, therefore, superiority in terms of bowel sparing cannot be claimed for the MLC in this series.

The main finding was the significant improvement in plan delivery efficiency with the MLC compared to Iris planning. The use of MLC resulted in a 17.6% reduction in treatment time compared to Iris planning, with a marked 58.5% beam reduction, although this did not equate to a significant reduction in total MU. A reduction in treatment time from the use of MLC was an expected finding, although the magnitude of difference was small in comparison to my results from the prostate planning comparison study in chapter 4. and data from published studies. This may be explained by the number of small renal cancers in this study, with median maximum tumour diameter of 3 cm (range 1.5 – 5.8 cm), since theoretically, the properties of the MLC are likely to provide the greatest advantage over the Iris collimator when targeting large and irregularly shaped volumes.

In the two cases with larger tumours (> 4cm), the MLC allowed a more substantial treatment time reduction of approximately 25 – 50%. In addition, there was evidence of relative bowel sparing compared to the Iris plan in one of the cases. Combined with the other more complex planning cases, considered as those with a PTV within 2cm of small or large bowel, there was found to be a median treatment time reduction of 27.5% which was associated with 22.7% reduction in MU and 62.5% beam reduction. This confirms that the MLC was more beneficial in terms of plan delivery efficiency when used to plan more complex cases, either with large target volumes or in close proximity to dose limiting structures. Results also indicated that there may have been some improvement in OAR avoidance however this could not be confirmed, possibly due to the small number of cases.

The cases in this study were randomly selected from a previous planning study cohort in which the maximum tumour diameter was limited to 6 cm. Including only primary renal tumours over 4 cm in diameter (T1b) may have enabled a more compelling evaluation of the benefit of MLC in this setting, and potentially have provided the opportunity to determine the maximum tumour size which could be feasibly treated.

Patients with T1b disease, unfit for surgery, have less treatment options available to them. Primary renal cancers of this size are unsuitable for an active surveillance approach and high rates of local recurrence with thermal ablation compared to nephrectomy[9]. Therefore, it is potentially these patients who seek to benefit most from SBRT. A pooled analysis of patients with T1b tumours demonstrated favourable rates of local relapse in comparison to other nephron-sparing treatment, and cancer specific survival of >90% at 4 years[10]. In addition, treatment was well tolerated with no ≥G3

toxicity, although a 33% deterioration in chronic renal impairment was reported with 3.2% requiring dialysis. Correa et al retrospectively demonstrated the feasibility of treating even larger tumours with a median diameter of 9.5 cm, however this was in the metastatic setting, and patients were treated with a lower dose of 25 – 40 Gy in 5 fractions[11]. Although minimal follow-up imaging was available for review, evidence of local control was reported in 6 out of 7 patients.

Results from the FASTRACK II trial are likely to be extremely useful in differentiating the effectiveness of SBRT in patients with small tumours of ≤4 cm and those with larger tumours, >4cm. In this trial single-fraction SBRT at a dose of 26 Gy is delivered to the patients with tumour ≤4cm, and 42 Gy in 3 fractions is delivered to patients with tumours > 4 cm[12]. This dose fractionation was used the previous prospective trial by Pham et al, with low rates of early toxicity reported[13].

There does not appear to be a clear consensus on the optimal SBRT dose for treating primary renal cancer. There is a strong rationale to dose escalate since the relative radioresistant nature of renal cancer may be overcome by higher dose per fraction[3]. In the metanalysis by Correa et al, local failures were all reported in those receiving lower doses, which had to be reduced in some cases to meet dose constraints[14]. In the pooled International Radiosurgery Oncology Consortium analysis, which included 223 patients from 9 centres, the dose fractionation varied considerably ranging between 14 – 26 Gy for single-fraction treatment and 24 Gy – 70 Gy in 2 – 10 fractions for multi-fraction treatment[15].

This variation in dose can partly be attributed to data indicating a wide spectrum of radiosensitivity in renal cancer[4,16,17]. The FASTRACK II doses come from radiobiological studies estimating the α/β values of the two most common renal cell cancer lines to be 2.6 Gy and 6.9 Gy, respectively[17]. Using the α/β value of 6.9 Gy, the biological effective dose (BED) is calculated at 123 Gy and 127 Gy for the 26 Gy in 1 fraction and the 42 Gy in 3 fractions, respectively. Alternatively, using α/β value of 2.6 Gy gives a BED of 142 Gy for 26Gy in 1 fraction and 268 Gy for 42 Gy in 3 fractions. In an older retrospective study of 50 patients by Wersall et all, the most frequently used dose fractionation schedules were 32 Gy in 4 fractions, 40 Gy in 4 fractions and 45 Gy in 3 fractions, assuming a higher α/β value of 10 Gy, concluding that a higher dose fractionation would lead to unacceptable toxicity.

McBride et al have recommended a minimum dose of 48 Gy in 3 fractions after demonstrating no dose limiting toxicities in a dose escalation study delivering 3-fraction dose levels of 21 Gy, 27 Gy, 33 Gy, 39 Gy and 48 Gy[18]. By 36.7 months median follow-up 2 local failures were reported, both in the lower dose arms. However, at 2 years there was noted to be a significant decline in estimated glomerular filtration rate (eGFR) from 55 mg/dL to 37 mg/d. Ponsky et al dose escalated from 24 Gy to 48 Gy in 4 fractions[19]. The maximum tolerated dose was not reached, although one patient developed a G4 duodenal ulcer within 3 months of treatment. Unlike our cohort, the duodenum was not contoured as an individual structure, but the maximum bowel dose (constraint ≤ 1 cc bowel to receive 24 Gy) in this case was 54 Gy in 4 fractions. Follow-up was short at 13.7 months, but at 6 months, all 15 patients with follow-up imaging had stable disease. A second phase of the trial, from which results are yet to

be published, had a starting dose of 48 Gy in 3 fractions aiming to escalate to 54 Gy in 3 fractions and if acceptable toxicity proposed to escalate to 60 Gy in 3 fractions.

Potentially there is less justification for high dose SBRT to primary renal tumours in patients with metastatic disease, although, historically, there is evidence of improved outcomes following nephrectomy in this setting[20,21]. The benefit of this is less convincing now in the era of targeted therapy, in particular with the increasing use of immune checkpoint inhibitors which have been shown to have a survival advantage[22-24]. However, a number of studies have demonstrated that SBRT may stimulate an immune response which has the potential to initiate disease response in distant sites of nonirradiated disease, known as the abscopal effect [4,25], and a potential synergistic effect with systemic treatment[26]. This has led to increased research to evaluate the effect of combining SBRT and immune checkpoint inhibitors in patients with oligometastatic disease with some evidence to suggest that this approach is well tolerated[27]. Therefore, the concept of delivering SBRT to the primary renal tumour in this setting is highly compelling.

No published studies have been identified evaluating the benefit of using MLC in SBRT for primary renal cancer. Masi et al conducted a comparison of Iris and MLC involving 28 liver, 15 pancreas and 13 prostate cases with PTV sizes varying between 24 – 643 cc[28]. They demonstrated the highest advantage in delivery efficiency to be for the liver cases with a 24% treatment time reduction and 18.6% MU reduction. In terms of liver and bowel sparing, the MLC was most beneficial in the 7 large liver and pancreas cases, on average measuring over 8cm in diameter. In addition, the average treatment time dropped from 36.1 min to 26.9 min using MLC.

McGuinness et al demonstrated that it was feasible to plan 5 cases for pelvic fractionated radiotherapy (45 Gy in 25 fractions) using MLC for CyberKnife[29]. The target volumes ranged between 425 - 760 cc with diameters of 13.2 – 18 cm. Acceptable coverage and OAR dose was achieved in comparison to conventional linac IMRT plans. However, treatment large target volumes did have some effect on MLC plan quality and delivery efficiency in comparison to smaller targets, since whole pelvis diameters were large than the maximum MLC field size of 10 x 12 cm.

5.6.1. Study Limitations

Aside from the lack of cases with larger tumours, one of the main limitations of this study include the small number of cases, which were restricted owing to the planning time required. Although it would have been more time efficient to compare MLC plans with the Iris plans from the previous planning study conducted by my colleague, collimator, I have demonstrated that this would have introduced a substantial amount of bias and potentially have led to the conclusion that the MLC produced far superior plans in terms of normal tissue sparing, which is not supported by my results.

As previously discussed in chapter 4, although planning studies provide useful information and allow comparison of new techniques, they are of limited value as they do not necessarily mirror clinical practice. In addition, plan comparison is highly complex and therefore the use of a scoring method like the method implemented by Masi, et al, may have improved the validity of my results[28].

5.7. Conclusion

SBRT planning with CyberKnife for primary renal cancer was feasible at a dose of 45 Gy in 3 fractions using either Iris™ variable collimator (Iris) or Incise™ multi-leaf collimator (MLC). Plans were equivalent in terms of organ at risk sparing, however, as hypothesised, there was a significant improvement in estimated treatment time using the MLC. The magnitude of improvement in plan delivery efficiency was more marked in cases with tumours >4cm or PTV within 2 cm of the small or large bowel. Therefore, in clinical practice the use of MLC may allow patients with larger renal cancers to be efficiently treated with SBRT, and potentially enable further dose escalation by improving normal tissue sparing.

5.8. References

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Chapter 6: Conclusion

6.1. Summary and future research

This thesis is an evaluation of methods to improve the quality of SBRT with Cyberknife in early prostate cancer by investigating strategies to reduce toxicity and optimising contouring and planning techniques. Furthermore, I have assessed the applicability of SBRT planning in high-risk prostate cancer and primary renal cancer.

6.1.1. Five-year outcomes of SBRT with CyberKnife in localised prostate cancer - UK experience.

In chapter 2 I aimed to determine the long-term efficacy and tolerability of prostate stereotactic body radiotherapy (SBRT), with CyberKnife at a dose of 36.25 Gy in 5 fractions, in a single-centre UK cohort of 62 patients. I have demonstrated a high rate of freedom from biochemical progression (FFBP) of 94% at 5 years follow-up, equivalent or better than results from other studies, internationally. The majority of patients fitted the eligibility criteria for PACE B with low- and favourable intermediate-risk disease, not receiving androgen deprivation therapy. In this group the 5-year FFBP rate is 96%, which is very encouraging, pending long-term results from PACE B. In addition a low median PSA nadir (nPSA) of 0.17 ng/ml, with median time to nadir of 5 years, suggest favourable prognosis with reference to brachytherapy studies demonstrating an association between a lower nPSA of ≤0.2 ng/ml and long-term efficacy[1,2].

Acceptable rates of acute toxicity have been confirmed demonstrating RTOG grade ≥2 (G2) genitourinary (GU) and gastrointestinal (GI) toxicity to have occurred in 37.1% and 27.4% of patients, respectively, peaking in the first 2 weeks after commencing treatment, and settling by 8 – 12 weeks follow up. Acute toxicity rates are consistent with results from the CHHIP trial, but higher in comparison to results from PACE B and some of the large prospective SBRT studies, which may be partially related to differences in toxicity reporting[3,4]. Late GI ≥G2 toxicity is consistent with published data at 8.1%, but an unexpectedly high rate of late ≥G2 genitourinary toxicity has been demonstrated, occurring in 22.9% of patients, including two patients requiring intervention for urethral strictures. However, the majority of patients experienced symptoms typical of late urinary flare which settled with conservative management within 6- 12 months and are consistent with the pattern of toxicity reported in a number of brachytherapy and other SBRT studies. In addition, these patients represent the first UK cohort and therefore results may reflect the level of experience in SBRT at that time.

I have analysed the effect of volume and plan dosimetry variables on the rate of toxicity and found patients with larger prostates volumes (>50 cc), and hence larger planning target volumes (PTV), to have higher rates of acute and late toxicity. In terms of acute toxicity, a much higher incidence of urinary symptoms occurred in patients with smaller bladder volumes (< 150 cc) and consequently there is significant association with the volume of bladder receiving 18.1 Gy. No significant association between rectal dosimetry and GI toxicity has been demonstrated. The main finding is the significantly higher rate of late urinary toxicity in patients with large prostates (>50 cc) receiving SBRT over 5 consecutive days rather than on alternate days. Compared to patients

receiving alternate-day fractionation, this group had around a 30% higher rate of toxicity (p=0.019). Although there was also higher rates of late GU toxicity in patients with smaller prostates receiving daily fractionation, the difference is not statistically significant.

My recommendation is that patients with larger prostates > 50 cc should be carefully managed to reduce the risk of acute and late urinary toxicity. IPSS scores are routinely used to assess patients prior to radiotherapy but my results do not show a correlation between prostate volume and baseline IPSS score. Therefore, patients with large prostates should be considered for prophylactic alpha-adrenoreceptor antagonists prior to commencing treatment, and for up to 2 years post treatment, regardless of baseline IPSS score. In order to reduce the risk of late urinary toxicity, these patients should be considered for treatment scheduled on alternate days over 10 – 11 days.

My data supports the use of strict pre-treatment bladder filling protocols, aiming for a bladder volume of ≥150 cc and the implementation of pre-radiotherapy lower urinary tract symptom (LUTS) clinics to optimise bladder function. Since the patients in this study were treated, a combined radiographer- and urology nurse-led pre-radiotherapy LUTs clinic has been developed at RMH. It would now be useful to conduct an audit of bladder filling and acute urinary toxicity to assess any affect this has had compared to the results of this study. Since bladder volume is highly variable with evidence of a reduction in volume during the course SBRT, the use of bladder ultrasound to confirm bladder volume prior to planning and before each treatment should be considered.

The results of this study add to the evidence supporting the use of SBRT in low- and intermediate-risk prostate cancer, but ultimately the long -term results from the PACE B trial will be vital to adequately compare efficacy and toxicity of SBRT with conventional radiotherapy. In addition, the question of whether SBRT is safe and effective in patients with high-risk prostate cancer has not been addressed and given the lack of published data in this population, data from PACE C is greatly anticipated.

6.1.2. Quality assurance in SBRT planning for localised prostate cancer using data from multiple centres within the PACE B trial.

In chapter 3 I conducted an analysis of interobserver contouring variability within the pre-trial quality assurance benchmark exercise for PACE B trial entry, confirming significant variability, primarily, in the delineation of the proximal seminal vesicles (SV).

There is substantial variability in the volume of the CTV structures, particularly of the pSVs ranging between 2.21 – 20.59 cc with a mean volume of 9.72 cc which was larger than the reference pSV structure of 8.7 cc. The use of conformity indices is extremely useful in quantitively comparing investigational contours with reference contours. The median DICE similarity co-efficient, which gives an overall indication of how well the investigational contour conforms to the reference contour, is lower for the pSV contours at 0.72 compared to the prostate contours at 0.9, demonstrating less agreement between centres for pSV outlining. The median disconcordance index value for pSV contouring is higher than the geographical miss index, indicating that centres were more likely to include excessive SV compared to the reference contour, rather than under-contour which is consistent with the volume analysis.

Interobserver variability of pSV outlining may have implications for the interpretation of results in large clinical trials such as PACE B. The presence of geographical miss may affect tumour response, while over-contouring, as seen more commonly in this study, may unnecessarily increase the rate of rectal or bladder toxicity. Given the high degree of precision involved in SBRT, the effectiveness and tolerability of the treatment is highly dependent on the accuracy of clinical outlining. My results therefore demonstrate that a more consistent method for pSV delineation is warranted. This has been particularly relevant in the development of the PACE C protocol since the inclusion of higher risk patients involves irradiating a larger portion of the SVs, with a potential increase in toxicity[5,6].

In the third study, described in chapter 3, I aimed to determine if a reduction in interobserver variability could be achieved using a simple semi-automated method of 1cm pSV delineation. Contours completed by 19 experienced clinical oncologists, at a national uro-oncology conference, were used to compare 1cm pSV contours defined using the individual clinician-defined method (method A) with contours defined using the investigational semi-automated method (method B). The contours defined using method A are significantly larger in volume, with a difference in mean volume of > 5 cc. The median DICE conformity index value is significantly higher using method B which, compared to method A, also has a significantly lower disconcordance index value.

My results confirm that reduced interobserver variability is created by the use of the semi-automated method for 1cm pSV delineation, and clinicans are less likely to include excessive SV within the CTV compared to using their own delineation method.

I therefore recommend this method for use in future prostate SBRT trials which has already been incorporated into the trial protocol for PACE C in which 1cm pSV is included all patients and 2cm pSV included for unfavourable intermediate- and high-risk patients. Secondly, I advocate the use of conformity indices in the context of a clinical trial quality assurance programme or departmental peer review to aid effective contour comparison.

6.1.3. The feasibility of CyberKnife planning for SBRT in high-risk prostate cancer and a comparison of plans using the Iris variable collimator and Incise multileaf collimator

As discussed in chapter 1, including ≥2 cm SV in the CTV for high-risk prostate cancer patients can create additional challenges for SBRT planning, due to the location and curvature of the SVs around the rectal wall[5,7]. Larger margins to account for increased SV motion, relative to the prostate, will have a further impact on the size of the planning target volume (PTV) which, as demonstrated in chapter 1, can potentially lead to increased rectal and bladder toxicity. The impact on SBRT planning in 8 prostate cases has been assessed in the first part of chapter 4 in which I demonstrate that, regardless of SV extent, planning with CyberKnife is feasible in the majority of cases, at a prescription dose of 36.25 Gy in 5 fractions, However, there was a definite increase in plan complexity, with acceptable plans achieved in just 5 cases when the full SVs were included in the target volume.

The effect of PTV size on planning difficulty is evident in that the three failed plans had larger PTVs compared to the other cases, ranging between 132 – 200 cc. In addition,

I have demonstrated a strong correlation between PTV volume and the degree of rectal overlap, resulting in significantly higher rectal doses and difficulty meeting planning constraints. Implanting a rectal gel spacer to increase the distance between prostate and rectum is one method which has been shown to improve rectal dose[8]. As discussed, the clinical advantage of this approach is unconvincing in all patients, but in selected cases, such as those in this study with a large target volume and greater degree of rectal overlap, this approach may be of particular value. Further work is needed to distinguish the group of patients that seek to benefit most from the use of rectal spacers.

Although I conclude that SBRT with CyberKnife is technically feasible in patients with high-risk prostate cancer, several questions remain. The potential effect of androgen deprivation therapy (ADT) on prostate and SV volume cannot be taken into account, and it is unclear the effect ADT may have on SV motion and deformation which may influence margin size[9]. The use of a larger margin to account for distal SV motion has a further impact on PTV size and, therefore, utilising the improved soft tissue imaging of the magnetic resonance (MR) linear accelerator, would be useful in providing additional information about intrafraction SV motion and deformation in order to re-evaluate the minimum margin size required.

A further option to minimise rectal dose is to reduce the dose delivered to the distal SVs as used in the CHHIP and PACE C trials. This would be a rational approach in high-risk patients without evidence of SV involvement on diagnostic imaging, assuming that the dose delivered is adequate for the treatment of microscopic disease. However, this may not be sufficient in patients with macroscopic SV involvement, and

it therefore remains vital to demonstrate the optimum technique for SBRT delivery in these cases. This is relevant whatever the outcomes are from trials evaluating pelvic SBRT or use of a simultaneous integrated boost (SIB) to sites of intraprostatic disease.

One of the limitations of CyberKnife treatment is the length of time required to deliver multiple beams from a large number of points around the patient, in addition to the time taken for intrafraction imaging and motion compensation. As a result, SBRT for high-risk patients is likely to be even longer since in my study there was a significant increase in treatment time, total monitor unit and beam requirements by increasing the pSV extent from 1cm to 2cm. The development of the Incise multi-leaf collimator (MLC), with the ability to create large and irregularly shaped fields, has provided the opportunity to improve plan delivery efficiency by requiring a lower number of with wider diameter compared to the Iris variable collimator (Iris), as described in chapters 1, 4 and 5.

In the second part of chapter 4 I demonstrated a significant benefit from the use of MLC in comparison to the Iris collimator. In terms of plan delivery efficiency, the use of MLC resulted in a 26% average treatment time reduction as a consequence of reducing beam number by around 70%. In addition, the use of MLC noticeably reduced the planning time required and enabled me to achieve higher quality plans, with improved normal tissue sparing, in those cases where acceptable plans could not be achieved with the Iris.

6.1.4. Comparison of the CyberKnife Incise multi-leaf collimator and Iris variable collimator in SBRT planning for primary renal cancer

Given the potential benefit of MLC, particularly in more complex planning cases, chapter 5 evaluated its application in SBRT for primary renal cancer which creates it own challenges for radiotherapy planning due to its location close to bowel and normal renal parenchyma. In patients unsuitable for a surgical approach, there is increasing interest in renal SBRT which could allow delivery of an ablative dose of radiotherapy and potentially overcome the perceived radio-resistance of this disease. At a dose of 42 - 45 Gy in 3 fractions, I have demonstrated that planning with CyberKnife is feasible regardless of the choice of collimator, but that the MLC significantly improves plan delivery efficiency with a 17.6% reduction in treatment time.

The magnitude of median time reduction and the insignificant decrease in bowel dose is less than predicted which may be explained by the relatively small size of the renal tumours including in this study. The greatest advantage from the MLC in terms of both efficiency and normal tissue sparing is seen in cases with larger tumours >4 cm in maximum diameter, or those with small or large bowel within 2cm of the PTV. Further research specifically evaluating the delivery of SBRT in larger renal tumours is therefore needed and results from trials such as FASTRACK II are likely to be highly informative[10]. SBRT for large primary renal tumours may also be relevant in the metastatic setting given the evidence of an immune response and possible synergistic effect with immunotherapy[11-13]. This is therefore an immensely exciting area for future SBRT research.

6.2. Final conclusion

In conclusion, there are two overarching themes running through this thesis. Firstly, I have clearly demonstrated that, for CyberKnife SBRT, size really does matter in terms of toxicity, planning complexity and treatment delivery time. Therefore, it is important to identify those patients with larger target volumes at the outset and implement methods to optimise treatment delivery and minimise the risk of toxicity. In the context of prostate cancer this may include the use of prophylactic alpha-blockers, strict bladder filling protocol, rectal spacers and alternate-day fractionation. In both prostate and renal cancer, I have shown consistent advantages for the use of the MLC have and demonstrated an increased benefit in patients with large target volumes.

Secondly, in each chapter I have highlighted the importance of quality assurance in all aspects of SBRT planning and delivery. In chapter 2 I demonstrated the importance of comparing treatment outcomes with other studies in the field but drew attention to the fact that valid comparison could be improved with the use of standardised toxicity scoring criteria and follow-up schedules. In chapter 3 I confirmed the benefit of implementing a robust trial quality assurance programme and developed an easily reproducible method for seminal vesicle outlining. Given the importance of target volume size and the extremely precise nature of SBRT, it is vital to ensure accuracy of clinical contouring at a departmental level, through regular peer review. In chapters 4 and 5 I stressed the limitations and complexities of comparative planning studies and considered methods of minimising bias, potentially with the use of a standardised assessment tools. All of these factors must be taken into account to maximise the validity and impact of future research in the field of SBRT.

6.3. References

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Appendix 1: Summary of prostate SBRT trials

Study	Number of patients	Median follow-up (months)	Risk group (L / I / H)	Technique	CTV – PTV margin	Dose and fractionation	Schedule	ADT (%)	bDFS	Toxicity
Randomised Trials										
PACE B[1] 2019	874 SBRT 433 CFMHF 441	12 weeks	L and I	CK or linac fiducials	5mm/ 3mm post	36.25 Gy / 5 # to PTV, 40 Gy / 5 # to CTV	Daily/ alt days	No		Acute (RTOG) G2+ GU 23%, GI 10% (CTCAE) G2+ GU 30.8%, GI 16%
Prospective Trials										
Meier[2] 2018 Multicentre, prospective	309	61	L and I	CK fiducials		36.25 Gy / 5 # to PTV, 40 Gy / 5 # to CTV	NR	No	5 yrs 97.1% L 97.3%; I 97.1%	Acute (CTCAE v3) Gd 2 GU 26%; GI 8% Late Gd2 GU 12% GI 2%; Gd 3 GU 2%
Helou[3] 2017 3 trials	259	38 33 (40 Gy) 54 (35 Gy)	L and I (35 Gy low risk)	Linac/ IMRT fiducials	5mm (4mm initial trial)	40Gy/ 5# (68.3%) 35Gy/ 5# (31.7%)	11-29 days	Yes 4.6%	NR	RTOG late Gd2 GU 32.6%; GI 12%; Gd 3 GU 1.9% GI 0.8%; Gd4 GI 1.1% Higher in 40Gy group
Loblaw[4] 2017 2 trials	114	Study 1 8.9 yrs Study 2 8.5 yrs						1 pt	5 yrs 97.3% 8yrs 94.9%	
Bolzicco[5] 2013 Prospective	100	36 months (6-76)	L 41 I 42 H 17	CK fiducials	5mm /3mm post.	35Gy / 5#	Daily	29%	bPFS 94.4% Median PSA nadir year 3 0.45ng/ml	RTOG Acute Gd2 GU: 12%, GI: 18% RTOG late Gd2 GU 3%, GI 1%; Gd3 GU: 1%
Henderson[6] 2016	81	2.5yrs	L, I, H (6%)	CK fiducials	5mm /3mm post.	36.25Gy / 5 #to PTV 40Gy / 5 # to CTV	Daily/ alt days	12%	NR	RTOG Acute Gd2+ GU 30%; GI 22%; Late Gd2+ GU 13%; GI 11%; Gd 3 GU 2% GI 1%
Dixit[7] 2017	45	NR	L 11, I 28 H 6	CK fiducials	5mm /3mm post.	36.25Gy in 5 fractions	Alt days	16%		CTCAEv3 Acute Gd2 GU 11.1% GI2.2%; No grade 3 or 4 Late toxicity NR
McBride[8] 2012	45	44.5	L	CK fiducials	5mm /3mm post.	36.25 - 37.5 Gy 5 fractions	7 days	No	3 yrs 97.7%	Acute (CTCAEv4) Gd 2 GU: 19%, G2 GI: 7%; Gd 3+: 0

										Late (CTCAEv4) G2 GU: 17%; G3: 2%; G2 GI: 7%, G3: 5%
Fuller[9] 2014	79	Minimum 5 years	L and I	CK fiducials	0 - 5mm	38Gy / 4 fractions Heterogenous planning	NR	NR		
Boyer[10] 2017	60	27.6	L (20) I (40)	IMRT Calypso/ fiducials CBCT/ Exactrac	5mm / 3mm post.	37 Gy / 5 #	Alt days	No	NR	CTCAEv4 Acute Gd2 GU: 25%, GI: 5% Late Gd2 GU: 6.7%, GI: 8.3%; Gd3+ GI: 1.7%
Kotecha[11] 2016	24	25 months	I 46 %, H 54%	Heterogenous planning technique		36.25 Gy / 5 # sto Low Dose PTV 50 Gy / 5 # to High Dose PTV	Alternate days	Yes 67 %	NR	CTCAEv4 acute gd 2 GU: frequency 38%, retention 16%; GI nil Late gd2 GU: cystitis 4%, frequency 4%; proctitis 8%; no gd3 toxicity
Kim[12] 2014 and Hannan[13] 2016 (Timmerman)	91	54 months	L and I	Tomotherapy or linac Fiducials or Calypso. rectal balloon,	2 - 3mm	Phase 1: 45 Gy - 50 Gy / 5 # Phase II: 50 Gy / 5 #		16.5%	5 yr 98.6% 45 Gy 90.9% 47.5Gy100% 47.5 Gy and 50 Gy	CTCAEv3 Acute Gd2 GU 22% GI 21%; Gd3 GI 1% Late Gd2 GU 21% GI 13%; Gd 3; GU 4% GI 4%; Gd4 ; GU 1% GI 2%
D'Agostino[14] 2016	90	28 months	L (53) I (37)	VMAT CBCT Fiducials		35 Gy / 5 #	Alt days	12 pts		CTCAEv4 Acute Gd2 GU: 32.2%; GI: 5.5% CTCAE Late Gd 2 GU: 2.2%; GI 0
Rucinska[15] 2016	68	24 months	Low and intermediate	IMRT/ Fiducials/ CBCT	CTV: prostate +1cm SV and 3mm / 2mm post margin. PTV: CTV+ 2mm	33.5 Gy / 5 #	Twice weekly	76.5%	No PSA failure	RTOG Acute gd2 GU: 35.3%, Gi: 10.3%; gd3 GU 1.5%. Late gd 2 GU: 11.8%, GI 4.4%. No late gd3 toxicity
King[16] 2012	67	32.4	L	CK fiducials	5mm /3mm post.	36.25Gy 5 fractions	Daily / alt days	No	4 year bPFS 94%	Late CTCAEv3 Gd2 GU: 5%, Gd3: 4%; Gd2 GI: 2%, Gd3+:0
Retrospective studies										
King[17] 2013 Pooled analysis	1100	36	L (58%) I (31%) H (11%)	CK fiducials	5mm/ 3mm post. or 2mm/ 0mm post	Median 36.25 Gy / 5 # (range 35 – 40 Gy)	Daily (>95%)	14	5 year bDFS: L 95%; I 84%; H 81%	NR
Katz and Kang[18] 2016	515	84	L (324) I (153) H (38)	CK fiducials	5mm / 3mm post.	35 Gy - 36.25Gy /5 #	Daily	14	8 yrs L 93.6%; I 84.3% H 65%	Late GU Gd 3 1.7%
Katz[19] 2017	230	108	L			35 Gy– 36.25 Gy / 5 #		NR	10 year bDFS 93.7%	Late (RTOG): GU Gd2:9%; Gd3 3%; GI Gd 2 4%, no Gd3/4

Katz[20] 2013	304	60	L (211), I (81) H (12)		5mm / 3mm post. (8mm on side of disease in high risk)	35 - 36.25 Gy / 5 #	Daily	19	5 year bPFS L 97%; I 90.7%; H 74.1%	Acute (RTOG) GU Gd2+ 14 (2 35 Gy); GI 11 (2 35 Gy) Late (RTOG) Gd2+ GU 4% (35 Gy), 9% (36.25 Gy); Gd3 2% (36.25 G)y; GI Gd2+ 2% (35 Gy), 5% (36.25 Gy)
Rana[21] 2015	102	4.3 years	L (36.3%) I (54.9%) H (7.8%)	CK fiducials	5mm /3mm post.	36.25 Gy 5 fractions	Daily	8.9%	3 yr FFBF 100%	RTOG G2 GU 9.9%, GI G2 3%; No G3/4
Koskela[22] 2017	218	23	L (22%) I (27%) H (51%)	CK fiducials	3-5mm / 3mm post.	35 - 36.25Gy / 5 #	Alt days	65	95.4% L 100%; I 96.6%; H 92.8%	CTCAEv3 No acute G3 toxicity. G2 NR. 1.4% required catheter Late Gd 3 GU1.8% GI 0.9%
Kataria[23] 2017	145	67.2	L (65) I (80)	CK fiducials	5mm (3mm post)	35 - 37.5 Gy 5 fractions	Alt days	No	5 yrs L 98.5%; I 95.5%	
Chen[24] 2013	100	27.6	L (37) I (55) H (8)			35 – 36.25 Gy 5 fractions	Alt days	11	99% at 2 yrs	CTCAEv3 Acute Gd2 GU: 35%, GI: 5% CTCAEv3 Late Gd2 GU: 30%, GI 1%; Gd3 GU: 1%
Oilai[25] 2016	263 142 SBRT; 121 IMRT	51 43 (SBRT) 34 (SBRT)	L / I / H	CK fiducials	5mm / 3mm post.	35Gy - 37.5Gy 5 fractions		SBRT 28.2% IMRT 71.9%	5 yr FFBF 89.7% SBRT, 90.3% IMRT	RTOG persistent Gd 2 GU 14%; GI 3%; Gd 3 NR
Oilai[26] 2013	70	31	L (51%) I (31%) H (17%)			35Gy - 37.5Gy 5 fractions	Daily 17%	33%	3 yr 94.5%; L 100%; I 95%; H 77.1%	RTOG Acute Gd2 GU 19% GI 4%; Gd3 GU4%; Late Gd2 GU29% GI 4%; Gd3 GU 3%
Freeman and King[27] 2011	41-	60	L	CK fiducials	5mm /3mm post.	35 or 36.25Gy 5 fractions	Daily (38)	No	5 yr bPFS 93%	Late RTOG Gd3 GU: 2%; Gd3+ GI: 0
Friedland[28] 2009	112	24	L /I /H	CK fiducials	5mm /3mm post.	35 to 36Gy / 5#	Daily	19% (	3 PSA failures	Gd3 rectal toxicity in 1 patient (not specified if acute or late)
Kang[29] 2011	44	13	L/ I / H	CK fiducials	4mm / 2mm post.	32-36Gy / 4 #	Daily	NR	5 yrs 93.6%	CTCAEv3 Acute Gd2 GU: 14%, Gd3+:0; GI: 9%, Gd3+:0 CTCAEv3 Late Gd2 GU: 7%, Gd3+:0; GI: 11%, Gd3+:0

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Appendix 2: PACE protocol dose constraints

OAR	Dose constraint
Rectum	V18.1 Gy <50% (i.e. 50% rectum <18.1 Gy) V29 Gy <20 % V36 Gy <1cc (Minor variation: V36Gy ≥ 1cc, but < 2cc)
Bladder	V18.1 Gy <40% V37 Gy <10cc (optimal V37 Gy <5 cc) (Minor variation: V37Gy ≥ 10cc, but < 20cc)
Prostatic urethra (if visualised)	V42Gy <50% (optimal, not mandatory)
Femoral head	V14.5 Gy <5% (optimal)
Penile Bulb	V29.5 Gy <50%
Bowel	V18.1 Gy <5cc V30 Gy <1cc

Dose constraints taken from the PACE protocol, including acceptable minor variations.

Appendix 3: Radiation Therapy Oncology Group (RTOG) Toxicity Grading

Instructions:
1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused death of the patient.
4 An accurate baseline prior to start of therapy is necessary.

Toxicity	0	1	2	3	4
Diarrhoea	None	Increase of 2-3 stools per day over pre-radiotherapy baseline	Increase of 4-6 stools per day or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day or incontinence or severe cramping	Increase of ≥10 stools/day or grossly bloody diarrhoea or need for parenteral support
Proctitis	None	Increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including haemorrhoids),not requiring medication	Increased stool frequency, bleeding, mucus discharge or rectal discomfort requiring medication; anal fissure	Increased stool frequency/diarrhoea, requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge necessitating pads	Perforation, bleeding, necrosis or other life-threatening complication requiring surgical intervention (eg colostomy)
Cystitis (see instructions below)	None	Mild	Moderate	Severe	Life-threatening
Haematuria	None	Micro only	Gross/no clots	Gross with clots	Requires transfusion
Urethral stricture	None	-	-	Urethral stricture	-

Bladder changes – cystitis/frequency

Grade 0: No symptoms
Grade 1: Frequency of urination nocturia twice pretreatment habit/dysuria, urgency not requiring medication.
Grade 2: Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm
requiring local anaesthetic.

Grade 3: Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvic pain or bladder spasm requiring regular, frequent narcotic/gross haematuria with/without clot passage.
Grade 4: Haematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis.
Grade 5: Death directly due to radiation morbidity.

Appendix 4: International Prostate Symptom Score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	**Your score**
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	

	None	1 time	2 times	3 times	4 times	5 times or more	**Your score**
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

Total IPSS score	

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

Appendix 5: International Index of Erectile Function (IIEF-5)

	1	2	3	4	5
How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
4 During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
5 When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always

Appendix 6: Summary of data from prostate SBRT plan dosimetry

		Acute GU toxicity					Late GU toxicity				
	Overall	**G0**	**G1**	**G2**	**G3**	**G2/3**	**G0**	**G1**	**G2**	**G3**	**G2/3**
PTV Volume (cc)	108.6	87.12	111.1	120.4	109.6	120.4	105.1	113.5	124.5	131.8	130.5
Bladder											
Volume (cc)	262.2	294	270.5	205.3	98.41	171	259.9	235.3	262	301.7	262.4
D max (Gy)	43.4	43.25	43.07	43.7	43.0	43.6	43.4	44.2	42.72	44.08	43.18
V 37 Gy (cc)	5.75	4.31	6.38	5.98	4.05	5.30	5.42	8.17	3.92	7.44	4.46
V18.1 Gy (%)	24.15	19.50	24.95	27.10	40.10	28.00	26.9	24.00	23.1	19.90	21.10
Urethra	n=28	n=17	n=4	n=4	n=3	n=7	n=17	n=4	n=4	n=3	n=7
Dmax (Gy)	44.60	45.03	44.78	44.34	43.82	44.34	44.94	44.57	44.40	44.93	44.57
V 44 Gy (%)	6.10	7.40	8.65	3.70	0.00	3.70	6.50	3.10	7.15	19.70	8.60
		Acute GI toxicity					**Late GI toxicity**				
	Overall	**G0**	**G1**	**G2**	**G3**	**G2/3**	**G0**	**G1**	**G2**	**G3**	**G2/3**
PTV Volume (cc)	108.6	105.3	108.4	128.7	31.0	125.3	108.6	106.6	110.6	149.25	124.5
Rectum											
Volume (cc)	62.65	70.73	62.50	66.00	58.7	62.59	60.7	77.75	49.05	92.5	58.7
D max (Gy)	39.9	41.4	33.70	40.9	40.9	41.4	40.6	39.9	41.35	41.8	41.3
V 36 Gy (cc)	1.3	1.17	1.3	1.35	1.8	1.5	1.3	1.25	1.6	2.0	1.7
V 29 Gy (cc)	11.8	11	11.5	13.8	16.3	13.9	12.1	11.35	11.85	10.1	10.1
V18.1 Gy (%)	33.25	28.2	33.7	34.45	45.3	35.0	40.6	29.95	33.8	23.5	32.6
Bowel											
V30 Gy (cc)	0	0	0	0	0	0	0			0	0
V 18.1 (cc)	0	0	0	0	0	0	0			0	0

Median results given for Planning target volume (PTV) ,bladder and urethra in all patients, and categorised according to worst reported RTOG acute and late genitourinary (GU) score. n, number of patients with a contoured urethral structure at the time of planning.

Appendix 7: Proximal seminal vesicles outlining exercise guide, British Urology Group (BUG) Annual Meeting September 2018

Participant: **1 - 28**

Thank you for participating in this outlining exercise which will take approximately 10 minutes to complete.

The aim of the exercise is to assess variability in proximal seminal vesicle (pSV) outlining between participants, and evaluate an alternative method which may improve consistency.

Case: Patient with intermediate-risk prostate cancer for radical radiotherapy. The clinical target volume (CTV) is to include the whole prostate and the proximal 1cm seminal vesicles.

Please complete the following tasks:

Task 1: **Prostate**. Complete the remaining superior slices of the prostate outline.

Task 2: **Seminal vesicles**. Outline the full seminal vesicles.

Task 3: **pSV_exercise A**. Copy and manually edit the seminal vesicles to include only the proximal 1cm.

Task 4: **pSV_exercise B**. This should be done using the **ROI algebra** function on RayStation as shown:

Create a 1cm symmetrical margin around the prostate (prostate + 1cm). Outline should consist of the intersection between prostate + 1cm and the seminal vesicle outline.

Exercise now complete. Please press **SAVE.**

Appendix 8: Clinical target volume definition schema from PACE C protocol

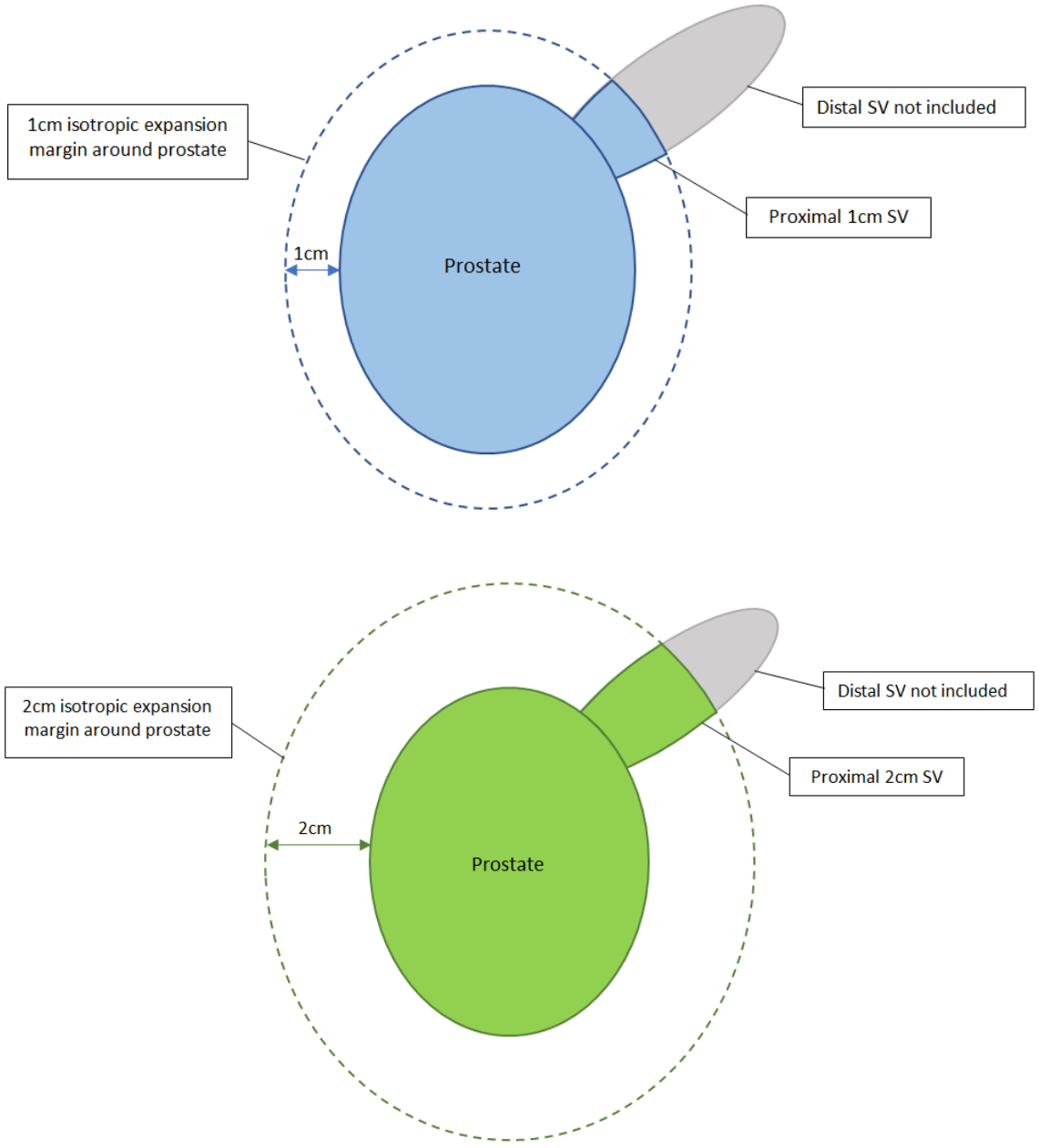

Figure 1. (a) Proximal 1 cm (for CTVpsv) and (b) Proximal 2 cm (for CTVsv) of Seminal Vesicles

First contour prostate and create 1 cm and 2 cm rings by isotropic expansion of the prostate (Figure 2).