Investigation of the RayPilot Tracking System for use in dose escalated Prostate SBRT

A thesis submitted to the University of Manchester for the degree of Doctor of Clinical Science in the Faculty of Biology Medicine & Health

2021

Michael P Trainer

Edinburgh Cancer Centre

Contents

Preface:

Word count (total)……43207

Word count (excluding references and figures)…….33414

I. Glossary of terms

Abbreviation	Definition
2D	Two-dimensional
3D	Three-dimensional
AAA	Anisotropic Analytical Algorithm
ACCORD	Academic and clinical central office for research and development
ANOVA	Analysis of variance
AP	Anterior, Posterior
ASTRO	American society for radiation oncology
CASP	Critical appraisal skills programme
CBCT	Cone-beam computed tomography
cm	Centimetres
CTV	Clinical target volume
DIL	Dominant intraprostatic lesion
DVH	Dose volume histogram
EM	Electromagnetic
ESTRO	European society for radiotherapy and oncology
EQD2	Equivalent dose in 2Gy fractions
GTV	Gross tumour volume
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
KIM	Kilovoltage intrafraction monitoring
kV	kilovoltage
MATLAB	Matrix laboratory
mpMRI	Multi-parametric magnetic resonance imaging

I. Glossary of terms

MR	Magnetic resonance
MRI	Magnetic resonance imaging
MV	megavoltage
NTCP	Normal tissue complication probability
OAR	Organ at risk
PD	Prescribed dose
PRV	Planning risk volume
PSA	Prostate-specific antigen
PTV	Planning Target Volume
RL	Right, Left
SBRT	Stereotactic body radiation therapy
SI	Superior, inferior
SIRLAP	Superior, inferior, right, left, anterior, posterior
TCP	Tumour control probability
VMAT	Volumetric modulated arc therapy

II. List of Figures and tables

III. Abstract

Aim: To investigate the use of the RayPilot tracking system to help treat prostate SBRT with a dose escalated boost of 45Gy in 5#.

Method and materials: Seven patients in the PRINToUT trial received prostate SBRT (36.25Gy in 5#) treated using 3 VMAT arcs delivered on Truebeam linacs and planned using the Eclipse TPS (v13.6). Pre-treatment imaging was with kV orthogonal and CBCT and tumour tracking using the RayPilot system. RayPilot uses an electromagnetic transmitter inserted into the prostate. The position of the transmitter was analysed retrospectively using the RayPilot system readout and the transmitter position on CBCT images. A planning study, adding a dose escalated boost (45Gy in 5#) to the prostate SBRT plans was carried out, with additional plans simulating degrees of patient displacement from the clinical imaging data. All new plans were assessed against the PRINToUT protocol.

Results: From the CBCT images, the mean displacement of the RayPilot transmitter comparing the CT and the CBCT scans was -0.04cm(x), 0.07cm(y) & 0.16cm(z). The RayPilot system recorded all treatments except #3, 4 & 5 for patient 4 due to technical issues with the mean displacement of the transmitter within 0.03cm. In the planning study the PTV, CTV and PTV(boost) dose coverage was acceptable with dose escalation but only two patients in the study met all of the rectum dose constraints. Simulating the CBCT positional data, PTV coverage was not met on four patients and for the RayPilot data the plan dosimetry was not significantly affected by the displacements.

Conclusion: The RayPilot tracking system could be used in the treatment of prostate SBRT with a dose escalated boost. Further studies would be required before this could be used as a primary imaging method for patient positioning.

IV. Lay abstract

Prostate radiotherapy treatments are typically delivered over 20-39 treatment days, with a “fraction” of the overall radiation dose given on each day. There is growing evidence suggesting benefits of reducing the number of treatment days and delivering more radiation dose each day. This is known as “SBRT”. Prostate radiotherapy treatments are extremely targeted, delivering a high dose to the prostate with the dose reducing sharply outside this volume. If the prostate is not positioned correctly during a fraction, a reduction in the intended dose can occur which can impact the efficacy of the treatment. However, the position of the prostate is checked and adjusted before each treatment through X-ray imaging of radio-opaque markers implanted in the prostate. Tracking systems provide additional positional information while the radiation is delivered.

Seven prostate patients had SBRT treatments utilising a tracking system called RayPilot, which uses an electromagnetic transmitter implanted in the prostate to give real-time positional information during treatment. A more complex version of SBRT aims to treat the whole prostate but further target the gross tumour with a larger radiation dose. The imaging and tracking data in this study were analysed to assess if RayPilot could be used for tumour tracking in this more complex treatment delivery. Positional data acquired during each patient’s treatment delivery was used to simulate the delivered radiation if this more complex technique had been used. The simulated dose to the prostate and the tumour was found to be within acceptable clinical parameters for all patients. The study concluded that it was feasible to use the RayPilot tracking system to treat SBRT with a higher dose to the tumour but identified further work to be carried out.

V. Declaration

The work contained in this thesis is the author's own original research. It has been written by the author and has not been previously submitted for examination for the award of a degree.

VI. Copyright Statement

VII. Acknowledgements

This research project would not have been possible without the support, patience and advice from Mike Kirby, Linda Carruthers and Bill Nailon in their role as supervisors. Also, the support from the larger multidisciplinary team at the Edinburgh Cancer centre, including Susan Adamson and Duncan McLaren, was invaluable in delivering this research project.

VIII. Brief statement for examiners

This research project was completed as a module within the Higher Specialist Scientific Training (HSST) programme. This is a five-year work-based scheme aimed to develop Clinical Scientists with the skills and knowledge they require to act as Consultants and results in the award of Doctor of Clinical Science (DClinSci).

The course included three main themes of study:

- Leadership and Management
- Scientific and clinical
- Research and innovation

The Doctoral award, is completed through a combination of taught academic modules and a research project completed in the trainee's department. The academic modules included a range of topics and were assessed through written assignments, presentations and other methods to evidence the required level of specialist knowledge had been achieved in each subject. Completed modules, assessment method and word count are included in Appendix 1 to support this thesis submission.

Although distinct from this research project, the specialist skills and knowledge gained from the taught modules were applied directly to aspects of this thesis and research. The leadership and management modules provided theoretical and practical exposure to a range of tools that can help improve efficiency, time management, communication, project management and reflective practices. The scientific modules provided a deeper understanding of specific radiotherapy topics including dosimetry, plan optimisation and imaging. These were particularly relevant to this project and were developed further to meet the challenge of delivering this thesis.

1 Introduction

1.1 Background

One of the key learning objectives identified through HSST participation was to develop the skills required to deliver and lead research in a clinical radiotherapy department. This research project included some novel application of a clinical system, utilising real clinical data and influencing the direction of a clinical service whilst fulfilling the remit of academic research.

The ability to deliver precise radiation doses to a target during radiotherapy using techniques such as volumetric arc therapy (VMAT) can be advantageous, as it allows the prescription dose to be delivered to the tumour whilst sharp dose gradients help to minimise the dose to organs at risk and normal tissue (1). This more targeted radiotherapy can be problematic for treating mobile tumours, and even with advanced image-guided radiotherapy (IGRT) techniques to position the patient correctly before their fraction, target displacement can occur during the beam delivery – known as intrafraction motion (2). This can lead to a reduction in the dose delivered to the target (3), and can be mitigated by the use of appropriate target margins (4).

Hypofractionation delivers a higher dose per fraction to the target whilst reducing the number of fractions, sometimes known as stereotactic body radiotherapy (SBRT) (5). This can have radiobiological advantages (6), improve departmental efficiencies and be more convenient for patients by reducing the number of visits. Reducing the number of patient visits has been identified as an advantage in reducing the risk to patients and staff during the COVID-19 pandemic (7). However, with a larger contribution to the overall dose from each fraction, the delivery of each fraction can be more complex and resource intensive than a standard

fraction. Target displacements through intrafraction motion during SBRT can have a greater impact on the delivered dose than standard fractionations (8). The reduced number of fractions means that positional displacements from an individual fraction may have a greater impact on the overall dose. The impact of random positional errors for a single fraction, can be blurred out over a longer fractionation, but can have a similar impact to a systematic error when the fractionation is reduced. Target tracking is a technique where the position of the target is monitored throughout treatment. This data can be used to inform motion management strategies which include beam gating (9) or real-time adaption of the plan during treatment delivery (10).

This research project investigated the use of a system called RayPilot (11), which uses an electromagnetic transmitter inserted into the prostate and tracks its position in real-time during treatment. The device is inserted through the patient's perineum in theatre by a radiologist. The transmitter is connected through a cable to a sensor plate with 16 antennae, which is placed on the treatment couch during the treatment (Fig 1). The antennae can detect the positional coordinates of the transmitter in real-time. An algorithm within the software uses the positional coordinates to calculate a displacement vector against a reference position. If the displacement exceeds a designated tolerance, then an alert is given in software allowing the treatment staff to manually halt the treatment delivery.

This system had been procured to be used within research studies at the Edinburgh Cancer Centre. Its use in the delivery of prostate SBRT within the PRINoUT clinical trial (12) provided the opportunity to investigate the system's novel aspects using high quality clinical data collected within a trial.

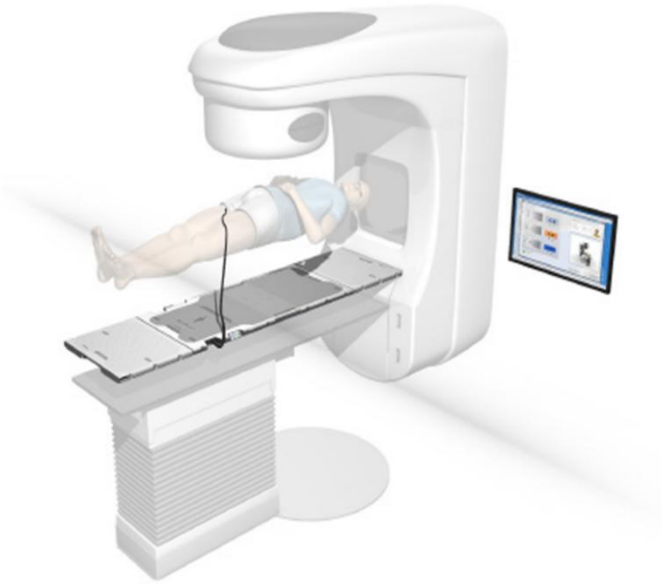


Fig 1: Diagram of the orientation and set up of a patient using the RayPilot positional tracking system during a radiotherapy treatment

To support research of the RayPilot system, a review on current radiotherapy tumour tracking methodologies and clinical practice for dose escalated prostate SBRT was carried out. This informed the direction of the project and helped form research questions. Imaging and tracking data collected from the patients in the study was analysed to assess the performance of the tracking device and this data was used in a planning study to investigate its use in treating prostate SBRT with a dose escalated boost. The results are presented in the format of three scientific papers.

The study was carried out between September 2018 and January 2021 at the Edinburgh Cancer Centre. Between March 2020 and June 2020, no work on this project was carried out, in line a mandate from NHS Lothian that development work would be paused due to the response of the COVID-19 pandemic. Research work was resumed in July 2020.

1.2 Rationale for journal format

As the project developed, it became apparent that the volume of empirical results would be sufficient to be grouped into three distinct work packages.

- Paper A: *Investigation of the accuracy and stability of RayPilot for prostate motion management during SBRT: Initial experiences*
- Paper B: *Analysis of the intrafractional motion of the prostate during SBRT using an EM Transmitter*
- Paper C: *Investigating a planning solution and the dosimetric impact of intrafraction motion for dose escalated prostate SBRT using the RayPilot Tracking system*

Whilst these work packages were linked, it was apparent that the results from each could generate sufficient content for independent scientific publications. This aligned well to the journal format style of thesis in which each academic paper contributes to the flow of the overall thesis. In this case, the results generated by the work packages contained in papers A & B contributed to the methodology in the work package reported in paper C. The data reported in paper A and paper B were submitted and accepted as posters at ESTRO 2020 (13) (Appendix 3) and ASTRO 2020 (14) (Appendix 4) respectively. The inclusion in the thesis of these studies in the respective journal formats for these organisations seemed appropriate. One of the key learning objectives identified through HSST participation was to develop the skills necessary to deliver and lead research in a clinical radiotherapy department. Writing the thesis in this style provided exposure to the rigour of writing scientific papers and offered a framework to further develop and apply these skills in the future.

1.3 Referencing system

To maintain consistency with each intended target journal, the individual papers were presented as a complete piece of work with distinct references and figure numbers, separate from the rest of the thesis. This was denoted by the prefix of the respective letter A, B or C of

the paper in the thesis. The references at the end of the thesis and figure numbers include every other section, excluding the three empirical results papers.

1.4 Research questions and output

Three research questions were formulated for this study following a review of current literature and clinical practice:

- *What is the accuracy and stability of RayPilot for prostate motion management during SBRT?*
- *How does RayPilot compare against other motion management systems for SBRT?*
- *Can RayPilot be used for dose escalated prostate SBRT?*

The research study has produced the following research output at time of writing:

- ***Poster presentation at ESTRO 2020 (November 28th – December 1st 2020)***
- ***Poster presentation at ASTRO 2020 (October 25th – October 28th 2020)***
- ***Poster presentation at ScoRFF 2020 (12 March 2020)***
- ***Paper A: Scientific paper included in thesis***
- ***Paper B: Scientific paper included in thesis***
- ***Paper C: Scientific paper included in thesis***

The following are proposed future research outputs:

- *Abstract submission based on work package reported in Paper C to be submitted to ESTRO 2021*

2. A review of available research

- *Submission of work packages within Papers A, B and C to an appropriate scientific journal for peer review and publication*

1.5 Summary of contributions

This research project contained in this thesis was the work of the named author, however there were additional contributions from others involved in the project. This section aims to highlight the aspects of the research project carried out by the author and acknowledge where appropriate, additional contributors.

During the development of the PRINToUT trial, there was a significant involvement from the author as the lead physicist for commissioning the trial and subsequent prostate SABR treatment technique and taking overall responsibility for the treatment planning aspect of the trial. Individual components carried out included the development and testing of a planning solution, producing the quality system documentation such as work instructions, providing staff training, attending MDT's, devising the treatment workflow, commissioning the treatment planning technique and writing the commissioning report. A lead role was also taken during a review of the trial 6 months after the first patient, including implementing some changes to the planning workflow and the approach to the on-treatment image review.

As the member of the physics team responsible for the RayPilot system, this involved performing acceptance and commissioning measurements on the system, troubleshooting during clinical use when required and liaising with the manufacturers for upgrades, services and replacement systems. There were two occasions during the research project where some of the hardware of the system was replaced, and a full acceptance and commissioning was carried out.

The Literature review, including journal searches and final write up was carried out by the author, however guidance and input into this process was received through regular meetings with the project supervisors (Mike Kirby, Linda Carruthers & Bill Nailon). This gave an opportunity to get valuable feedback on review techniques and writing style that had a significant influence on the final review.

The practical measurements in paper A of the thesis were measured and collated by the author. This included isolating the co-ordinates manually of each measurement point from the patient CT and CBCT images used in the study. This approach was determined following guidance from the project supervisors. The final version of paper A was written by the author, however the other named authors contributed through draft reviews, with comments or suggestions being integrated into the final version.

For the research outlined in Paper B, the practical measurements were carried out by the author. Some input into aspects of particular patient treatments was given by one of the treatment radiographers, Susan Adamson, who was included as one of the authors. This included information on practical issues for individual treatment fractions. This provided added context for these measurements, especially where positional outliers had to be removed from the overall measurements. The paper was written in full by the author of this thesis, however the other named authors contributed throughout the project and offered comments and advice on the write up that influenced the final version.

2. A review of available research

The planning study contained in Paper C was carried out solely by the author, under guidance from the project supervisors. This included developing and testing the planning solution for prostate SBRT with an integrated boost. The implementation of the displacements from clinical data was carried out manually on each patient and the dose statistics for each scenario was collated for final analysis. The practical aspects of this were all carried out by the author, however there was input from the project supervisors on the approach to the planning study and analysis. The final write up was written by the thesis author, with several reviews and input from the project supervisors who were also named as authors.

The critical appraisal paper was written solely by the author. The project supervisors provided additional input into this paper, including comments and advice on writing style and content.

1.6 Declarations

The oncology department at the Edinburgh Cancer Centre has an ongoing research collaboration agreement with Micropos, the manufacturer of the RayPilot positional management system.

2. A review of available research

2.1 Aim

A review was undertaken to inform the research question and design of a study investigating the use of a tracking system called RayPilot (11) in prostate SBRT with a boost to the focal lesion. The review focused on studies with comparable tracking systems, comparisons of established imaging devices and on current practice for clinical and theoretical solutions for prostate SBRT delivery, with and without dose escalation to the focal lesion.

2.2 Introduction

A research study was devised to assess the viability of the RayPilot system for tracking intra-fractional motion of the prostate during SBRT radiotherapy and whether it could be used in dose escalated SBRT to a focal lesion. A literature review was conducted on current available technology for motion management in prostate radiotherapy and current practice for SBRT to the prostate with an escalated boost. An initial review was carried out between September 2018 and January 2019, and updated between July and December 2020 to capture emerging evidence.

2.3 Search methodology

Searches were carried out on PubMed (15) and Google Scholar (16) aiming for a comprehensive overview of available literature on motion management in prostate SBRT and for clinical solutions to focal lesion boosts. Varying the date ranges of each search allowed for recent publications to be highlighted without excluding important older articles. Based on the scope of the project, papers with studies on implementation, benchmarking

and imaging system comparisons were preferred. Some papers of interest became apparent through the reference section of some journals. This is a process known as “snowballing” and can provide additional context but can dilute the focus of the search. To mitigate this any keywords or systems found through snowballing were also fed into further systematic searches on PubMed.

Table 1*: Example of a selection of keywords searched on PubMed along with the number of papers that each search found. These figures are correct from the 12/01/19.*

Primary search word	Additional search words	Date range within	Number of papers
Calypso	Radiotherapy + Tracking	1 year	14
	Radiotherapy + Tracking	5 years	102
	Radiotherapy + Tracking	all	205
	Prostate	1 year	21
	Prostate	5 years	143
	Prostate	all	272
	Prostate + SBRT	1 year	11
	Prostate + SBRT	5 years	53
	Prostate + SBRT	all	72
Tracking	Radiotherapy	1 year	835
	Radiotherapy	5 years	4425
	Radiotherapy	all	7033
	Prostate + Radiotherapy	1 year	355
	Prostate + Radiotherapy	5 years	1823
	Prostate + Radiotherapy	all	2963
Cyberknife	Radiotherapy + Tracking	1 year	79
	Radiotherapy + Tracking	5 years	462
	Radiotherapy + Tracking	all	724
	Prostate	1 year	69
	Prostate	5 years	437
	Prostate	all	706
	Prostate + SBRT	1 year	48
	Prostate + SBRT	5 years	281
	Prostate + SBRT	all	385
Radiotherapy	Tracking + review	1 year	656
	Tracking + review	5 years	3305
	Tracking + review	all	5018
	Tracking + implementation	1 year	235
	Tracking + implementation	5 years	1231
	Tracking + implementation	all	2046
	Calypso + implementation	1 year	11
	Calypso + implementation	5 years	73
	Calypso + implementation	all	132
Raypilot	Radiotherapy	1 year	1
	Radiotherapy	5 years	4
	Radiotherapy	all	4

***Table 2**: Example structure of search methodology and number of results carried out on PubMed July 2020*

Main keyword(s)	Secondary keyword (s)	Additional keyword(s)	Time range (within)	Number of results
Prostate	Focal lesion		all	332
			1 year	49
			5 years	151
Prostate Radiotherapy	Focal Lesion		All	59
			1 year	11
			5 years	34
		Boost	all	2
			1 year	2
			5 years	2
		imaging	All	9
			1 year	9
			5 years	9
		tracking	all	0
			1 year	0
			5 years	0
		SBRT	All	3
			1 year	1
			5 years	2
		Cyberknife	All	0
			1 year	0
			5 years	0
	Boost	Cyberknife	All	17
			1 year	1
			5 years	10
		SBRT	All	44
			1 year	8
			5 years	30

A large number of relevant publications were available, therefore the review focussed on preferred topics. For the novel RayPilot system, searches produced relatively few papers but research using similar more established tracking solutions were included.

Due to the extensive literature base found in the search it was both necessary and practical to omit much of this from the review, following the techniques proposed by Pinchbeck et al. (17) summarised in table 3 and utilising the critical appraisal skills programme checklist (18).

***Table 3**: Summary of rationale for inclusion / exclusion of papers within review*

Question	Points of interest for inclusion
What was the main purpose of the study?	• Tracking devices for Prostate Radiotherapy • Preference for devices with similar set-up to RayPilot, such as Calypso • Do they provide quantitative data on accuracy and precision • Was there comparison against kV imaging and CBCT • Was dose escalated prostate SBRT delivered • Was Dose escalated prostate SBRT carried out with imaging • Was this a planning study?
What type of study design was used?	• Was the study designed well and applicable to our own research aims • Was it a retrospective or prospective study and does this affect the quality of the results • How many patients or data points were included
Is the study internally relevant?	• What were the aims of the study • Was there any bias introduced in the study that would affect the results • Have they made any assumptions and does this affect the results • Were the results statistically relevant and was this discussed • What has been the impact of the study
Can the study be applied externally?	• Does their methodology provide sufficient detail • Do they provide clear conclusions • Can their results be applied to other populations such as our own study • Were the results clinically relevant to our patient population and was this discussed in the paper • Could the results be applied to SBRT treatments and dose escalated focal lesions
Other factors	• Preference for higher impact journals • Has SBRT been used for treatment • Were the limitations of the study clearly laid out and discussed • Was there discussion on future studies • Who are the authors • Is there any conflict of interest

2.4 Review

A selection of key articles, are reviewed below and summarised in table 4 with information on the author, date, journal, study aim, treatment regime and technical aspects of the study design and methodology. The quality of the research within each article was assessed and scored following the methodology described in Downs & Black (19), with each article's scoring included in the table. This method uses a checklist containing 27 questions to be applied to each paper, with a maximum possible score of 28 for randomised studies and 25 for nonrandomised studies. Hooper et al. (20) used the Downs and Black methodology (19) during a systematic review carried out on age related macular degeneration. They define

three quality ranges based on the scoring; excellent (26-28), good (20-25), fair (15-19) and weak (≤14).

The Downs and Black (19) scoring system preferences large randomised clinical trials, which would indicate that these studies would be a higher quality of research. This would be reflected in both the level of analysis and quality assurance required to set up a clinical trial and the importance placed on large scale randomised clinical trials for influencing clinical practice. A number of the studies within this review were small pilot studies or in-house cohort studies and as such did not score as highly using this method. However, this was only a measure of data quality and not an indication of the relevance to this research study.

The remainder of this chapter provides a critical review of the key messages from these papers and any implications for the proposed research. The papers have been grouped according to the issue topic considered or the specific solutions tool studied.

***Table 4**: Summary of the journals reviewed including author, topic, aims and the technical details of the study*

Author, Date and Journal	**Topic of interest**	**Downs & Black score**	**Aim of study**	**Details of the study**
Mah et al. (2002) (21) International Journal for Radiation Oncology Biology Physics	Prostate Motion	18	Measuring Intra-fractional prostate motion using MRI	**Patients: 42** **Site: Prostate** **Radiotherapy delivery: n/a** **Fractionation: imaged after planning scan only** Patients in the study received an MR scan directly after their planning scan using a flat couch and to be consistent with their treatment position and with consistency in rectum and bladder filling. They also looked at rectal filling and any correlation with prostate motion with each scan categorised into “empty”, “faeces” or “gas”.
Mutanga et al. (2011) (22) International Journal for Radiation Oncology Biology Physics	Prostate Motion	17	Looking at the day to day reproducibility of intra-fraction motion	**Patients: 108** **Site: Prostate** **Radiotherapy delivery: 7 Field IMRT** **Fractionation: 78Gy/39# Vs 64.6Gy/19#** All treatments were delivered as IMRT with a combination of MV and kV 2-D planar imaging used for online positional verification, with a tolerance of 0.2cm above which the couch would be used to correct the patient position. The effect of motion from treatment times were also assessed against a set of 10 patients who had been treated with a dose regime requiring only 3 static fields rather than the 7 IMRT fields in the main study. This

				meant that the mean treatment time would be decreased from 11 mins to 5 mins.
Braide et al. (2018) (25) Radiotherapy and Oncology	Ray Pilot	14	Feasibility of using the Ray Pilot Device for prostate radiotherapy	**Patients: 10** **Site: Prostate** **Radiotherapy delivery: 7 Field IMRT** **Fractionation: 78Gy/39#** The RayPilot transponder was inserted into Prostate IMRT patients and the position of the device was monitored during each fraction whilst using kV orthogonal imaging and gold seeds as the primary imaging modality and the departmental protocol. They were looking at the differences in position of the two imaging modalities and the feasibility of RayPilot's use through clinical experience.
Biston et al. (2019) (27) Radiotherapy and Oncology	Ray Pilot	14	To compare the RayPilot monitoring system with the Ultrasound imaging using a trans perineal probe	**Patients: 10** **Site: Prostate** **Radiotherapy delivery: n/a** **Fractionation: n/a** A Phantom study was carried out to investigate differences between the positional accuracy of the RayPilot system and an ultrasound probe. This included varying the displacement vector and rotations of each system and comparing the recorded values. The Intra fraction motion of 10 patients were also analysed, looking at discrepancies between the two systems. They recorded the percentage time of treatment where the discrepancy between the systems was 1-5mm, and this data was analysed.
Bell et al. (2017) (30) Journal of Medical Radiation Sciences	Calypso	15	Initial Experiences of using Calypso for Intra-fraction motion management of Prostate VMAT	**Patients: 3** **Site: Prostate** **Radiotherapy delivery: VMAT** **Fractionation: 80Gy/40#** They inserted the Calypso beacons whilst continuing to use the implanted marker seeds as the primary matching mode. The position of the beacons and any inferred shifts were compared against the seed markers for positional analysis.
Hamilton et al. (2017) (31) Journal of Applied Clinical Medical Physics	Calypso	18	To compare the positional accuracy of the Calypso system and existing imaging	**Patients: CRIS Phantom (50 different treatment orientations)** **Site: Prostate** **Radiotherapy delivery: n/a** **Fractionation: n/a** A phantom was imaged using the Calypso system, kV planar imaging and CBCT. They used a CRIS Pelvis phantom with spacers and a stand to implement different angular positions for the phantom. Imaging software was used to determine a correction including for rotations and the differences in these corrections were assessed statistically using Lin's concordance correlation coefficients with 95% confidence intervals with the interpretation of the scores based on recommendations from a report by McBride.
Lovelock et al. (2015) (33) International Journal for Radiation Oncology Biology Physics	Calypso	19	To look at the impact on target coverage on prostate SBRT from continuous prostate monitoring	Patients: 89 Site: Prostate Radiotherapy delivery: SBRT Fractionation: 32.5Gy/5# & 40Gy/5# The monitoring system was used to analyse the position of the patient's prostate. The study was carried out over five years from 2009-2014. Due to the tight target margins for these patients, a threshold of 0.2cm for the real-time imaging was used. This meant that if a displacement greater than this amount was determined from the Calypso system, then the treatment was halted and a couch shift was instigated before treatment was resumed. Orthogonal imaging was carried out prior to treatment to assess both the patient position and to check if there had been any migration of the transponders. The dosimetric impact to the target from utilising the tracking system was also assessed and analysed through treatment planning data.

Vanhanen et al. (2018) (28) European Journal of Medical Physics	RayPilot & Calypso	15	To evaluate the accuracy and stability of RayPilot and Calypso for Prostate positional tracking	**Patients: 48 (22 RayPilot, 26 Calypso)** **Site: Prostate** **Radiotherapy delivery:** **Raypilot (not stated),** **Calypso VMAT / SBRT** **Fractionation:** **RayPilot; 60Gy/20# (12 patients) 78Gy/39# (10 patients)** **Calypso; 60Gy/20# (14 patients), 36.25Gy/5# or 35Gy/5# (12patients)** The data from the RayPilot arm of the study was gathered retrospectively from another study on rectal retractors. The Calypso patient's data was gathered prospectively. The positional differences between the tracking system and 2-D kV planar imaging with fiducial markers were analysed statistically using Bland-Altman analysis methods. The stability of the transponders, transmitters and fiducial markers were also analysed by calculating the difference in the centroid position of the fiducial markers with the central position of the transponder / transmitter and comparing this difference to that observed in the treatment planning scan.
Holmes et al. (2018) (36) Journal of radiosurgery and SBRT	Cyberknife	16	To investigate the reduction of errors in prostate tracking using the cyberknife system with an improved fiducial implantation	**Patients: 54** **Site: Prostate** **Radiotherapy delivery: SBRT** **Fractionation: 36.25Gy / 5# (to an 80% isodose)** The fiducial marker insertion protocol was altered after 26 patients from the manufacturer's generic method to a modified protocol, involving implantation in a single coronal plane for simplification and to try and retain a minimum distance of 2cm between the markers whilst also trying to reduce migration.
Choi et al. (2018) (38) Journal of Korean medical science	Cyberknife	17	To Analyse the clinical outcome of prostate SBRT treated using the Cyberknife system against the magnitude of intra-fraction motion	**Patients: 71** **Site: Prostate** **Radiotherapy delivery: SBRT** **Fractionation: 37.5Gy/5# (PTV V_{100}>95%)** The study included all local patients who had Prostate SBRT between 2010 and 2017 using the Cyberknife system, with a median follow up period of 47 months. Each patient's inter-fraction motion was corrected using kV planar imaging and the intra-fraction motion was observed using the same imaging system, with the inserted markers being considered a surrogate for the prostate position.
Kruijf et al. (2013) (39) International Journal for Radiation Oncology Biology Physics	RealEye	16	To carry out an evaluation of the Real Eye system with the performance and safety of the device tested	**Patients: 20** **Site: Prostate** **Radiotherapy delivery: SBRT** **Fractionation: Dose not given. 35# / 37#** This study was carried out across two different sites in Belgium and the Netherlands. The patients would also have gold seeds implanted, which was the current standard of care at each site to be used to test the tracer against. The aim of the study was to look at both the performance of the device as a localiser and the safety of its use. The tracer position was assessed during 5 treatment fractions for each patient, spread throughout their long course of radiotherapy.
Shchory et al. (2010) (42) International Journal for Radiation Oncology Biology Physics	RealEye	15	To measure the accuracy of the RealEye system	**Patients: n/a** **Site: anthropomorphic breathing phantom** **Radiotherapy delivery: n/a** **Fractionation: n/a** In this study they tested the positional accuracy of the tracer system within a phantom that simulated breathing to assess its efficacy for patient positioning and recording motion. This position of the device was benchmarked against a Microscribe co-ordinate measuring machine (CMM) which has an accuracy of 0.038cm. The breathing phantom with the tracer placed inside produced a breathing motion with an amplitude of up to 4cm, which can be viewed as a rigorous test of

				the range of motion expected clinically. As the tracking system detectors are located on the gantry head, the tests were carried out over a range of gantry angles and with the treatment beam on to simulate an actual treatment. It was also felt that the anthropomorphic phantom provided realistic scatter conditions to those of a patient.
Ng et al. (2012) (40) International Journal for Radiation Oncology Biology Physics	KIM	14	To report initial experiences of implementing the KIM system for monitoring the prostate during VMAT delivery	**Patients: 10** **Site: Prostate** **Radiotherapy delivery: VMAT** **Fractionation: 80Gy/40#** The study was carried out retrospectively on patients who had gold seed markers implanted, which were used to determine if the prostate had been displaced during the treatment and what the magnitude and direction of this was. This was an observational study only and as such no interventions were carried out based on the results. Overall 268 from a possible 400 fractions were monitored. The discrepancy between the KIM system of and the triangulation of kV/MV images was used to verify the system and the results of the validation were compared against two other established methods of tumour tracking.
Keall et al. (2016) (46) International Journal for Radiation Oncology Biology Physics	KIM	16	To analyse the motion accuracy of using the KIM tracking system for gating	**Patients: 6** **Site: Prostate** **Radiotherapy delivery: VMAT** **Fractionation: 80Gy/40#** This study was carried out with 197 out of 200 fractions using the KIM system. Gating was utilised, with the beam being terminated if any motion of more than 0.3cm in any direction occurred for more than 5 seconds. The positional accuracy of the KIM system was then compared against kV/MV imaging that was acquired simultaneously.
Das et al. (2014) (48) American Journal of Clinical Oncology	ultrasound, X-ray imaging with fiducial markers, CBCT, Calypso and Cine MRI	14	To provide a comprehensive literature review for selected image guided radiotherapy solutions for prostate treatments.	**Patients: n/a** **Site: Prostate** **Radiotherapy delivery: Comparison of IGRT methods** **Fractionation: n/a** They reviewed all relevant published journals over the past 20 years with a focus on articles comparing different IGRT methods, with their findings summarised in tables within the article. The main advantages and disadvantages of each system, their associated costs and any comparison of the modalities that had been carried out were discussed.
Aluwini et al. (2013) (52) Radiation Oncology	Focal lesion	17	Presenting initial clinical results and toxicity for SBRT Prostate with focal boost	**Patients: 50** **Site: Prostate** **Radiotherapy delivery: Cyberknife SBRT** **Fractionation: 38Gy (44Gy boost) /4#** Over 4 years, patients with low or intermediate risk disease were treated using SBRT with a boost to the focal lesion if visible on an MRI. This study looked at the PSA response, Quality of life and toxicity with a median follow up of 23 months. The CTV to PTV expansion was 0.3cm isotropically, and the planning was carried out using Multiplan (Accuray Version 2.1.5).
Feng et al. (2015) (53) Acta Oncologica	Focal Lesion	14	To test methodology for outlining Focal lesion on MR scans and fusing to CT planning scans	**Patients: 14** **Site: Prostate** **Radiotherapy delivery: SBRT with SIB (planning study only)** **Fractionation: 36.25Gy (47.5Gy boost) /5#** A study looking at a cohort of patients who had previously received long course radiotherapy (either 20# or 37#), with a novel image analysis technique used to map the focal lesion outlined on an MR scan onto the planning CT scan. These contours were used in a planning study for the suitable patients (n=7),

				producing treatment plans with dose escalation to the focal lesion.
McDonald et al. (2019) (55) Advances in Radiation Oncology	Focal Lesion	17	To report the early results of a clinical trial for prostate SBRT delivering SIB	**Patients: 26** **Site: Prostate** **Radiotherapy delivery: SBRT with SIB** **Fractionation: 36.25Gy (40Gy boost) /5#** A clinical trial was conducted looking at the feasibility of delivering SBRT to the prostate with an MR defined SIB. The main purpose of the study was to show feasibility of the treatment technique and report on the urinary retention of the patients, with the trial being deemed successful if this occurred in less than 15% of patients.
Draulans et al. (2019) (61) Radiotherapy and Oncology	SBRT focal lesion boost	13	Review paper looking retrospectively at treatment strategies	**Patients: n/a** **Site: Prostate** **Radiotherapy delivery: SBRT** **Fractionation: >5Gy /#** A literature review was carried out within PubMed, using keywords such as “stereotactic radiation therapy”, with searches up to October 2018 included. The focus was on hypofractionated studies but also for studies where the focal lesion had received a simultaneous integrated boost. To be included into this review, the studies required at least 40 patients to have been involved and hypofractionated treatments with fractions of 5Gy or more. 415 titles were reviewed, with 36 papers fully read and 26 included in the review.
Murray et al. (2014) (57) International Journal of Radiation Oncology	SBRT focal lesion boost	17	Planning study for treating SBRT prostate with boost	**Patients: 10** **Site: Prostate** **Radiotherapy delivery: SBRT** **Fractionation: 42.5Gy 7# , Boost 115% (increased by 5% increments)** A retrospective study was carried out on 10 prostate patients, creating 4 SBRT plans for each patient: 1) with no boost, 2) Boost to focal lesion, seminal vesicles not treated, 3) Boost to focal lesion, seminal lesion treated with intermediate dose 4) Boost to focal lesion, seminal vesicles receive higher dose. VMAT plans were created on the Monaco TPS v.3.3. The plan analysis was carried out using the LQ-Piosson Marsden Model for the TCP, and the Lyman-Kutcher-Burman Model for the NTCP.
Draulans et al. (2020) (65) Radiotherapy and Oncology	Prostate SBRT integrated boost	24	Primary endpoint analysis for Hypo-FLAME trial	**Patients: 100** **Site: Prostate** **Radiotherapy delivery: Prostate SBRT VMAT** **Fractionation: 35Gy/5# boost up to 50Gy over 5 weeks** A phase 2 clinical trial called hypo-FLAME was carried out across four centres in the Netherlands and Belgium between April 2016 and December 2018. The trial prescribed 35Gy to the whole prostate whilst adding an integrated boost up to 50Gy. Their early endpoints assessed acute GU and GI toxicity (within 90 days) using an established scoring method (CTCAE v4.0). The lesion was contoured using multi-parametric MR images, around which a 0.4cm margin was added to include the macroscopic disease. One of the centres treated using a rectal balloon, the other centres assessed rectum volume on CBCT and intervened if necessary.
Goldman et al. (2019) (49) Royal Australasian college of surgeons	mpMRI	24	To determine the accuracy of mpMRI for detecting prostate lesions through a retrospective study	**Patients: 64** **Site: Prostate** **Radiotherapy delivery: N/A** **Fractionation: N/A** A retrospective study was carried out looking at 64 patients who had received a radical prostatectomy and mpMRI between April 2013 and April 2016 at a regional cancer centre. A comparison was carried out between

				the reported mpMRI data and the biopsy with regards predicting the cancer location and Gleason score, with a Spearman's rho test used to analyse the correlation.
Johnson et al. (2019) (50) European Urology	mpMRI	24	To investigate the rate of detection of the prostate focal lesion using mpMRI	**Patients: 588** **Site: Prostate** **Radiotherapy delivery: N/A** **Fractionation: N/A** A large retrospective study was carried out on prostate cancer patients who had receive a mpMRI and a prostatectomy between June 2010 and February 2018. The correlation of prediction of location and severity of disease between each method was investigated using multivariate analysis.
Bijina et al. (2020) (59) Asian Pacific Journal of Cancer Prevention	Prostate SBRT integrated boost	12	A planning study aiming to compare the dosimetry of different delivery techniques for prostate SBRT with an integrated boost	**Patients: 13** **Site: Prostate** **Radiotherapy delivery: Prostate SBRT: Linac, Cyberknife & Helical Tomotherapy** **Fractionation: 37.5Gy/5# (45Gy boost)** A planning study was carried out, looking at the dosimetric differences between three systems capable of treating prostate SBRT with an integrated to the lesion. A separate plan for each of the treatment methods was created on their respective treatment planning systems (Eclipse v13.6, VoLO v5.1.4 & Multiplan v5.1.4). The plans were assessed using criteria such as DVH, PTV mean/max/min dose and conformity index. The results were statistically analysed using a one-way ANOVA test. The significance level was devised through Tukeys post hoc test.
Kim et al. (2020) (63) Scientific reports – Nature	Cyberknife / integrated boost	18	A dosimetric planning study on Prostate SBRT with an integrated boost treated using Cyberknife	**Patients: 15** **Site: Prostate** **Radiotherapy delivery: Prostate SBRT Cyberknife** **Fractionation: 35Gy/5#, 35Gy (40Gy boost)/5#, 35Gy (45Gy boost)/5#** 15 patients with prostate cancer who had their lesion contoured were included in a planning study. Three separate SBRT plans were created for each patient. One treated the prostate with no boost, the second treated the whole prostate and included a 40Gy boost and the third treated the whole prostate and included a 45Gy boost.

2.4.1 Prostate Motion

Discrepancies between the position of a patient on a planning CT image and their treatment position can potentially impact the dosimetry of their radiotherapy treatment. Intrafraction movement occurs during a radiotherapy fraction and interfraction movement from one fraction to the next.

Mah et al. investigated intrafraction prostate motion using cine-MRI (21). The cine-MRI acquires a series of images over nine minutes producing a moving image. The mean prostate displacements were small, with the largest being 0.02cm (A/P) and only 3% of

motions exceeding 1.0cm. They concluded that prostate intrafraction motion can be measured using this method. They also noted that interfraction motion would have more of an impact on the dosimetry of a patient plan as this is generally larger than intrafraction motion. However, modern IGRT techniques in radiotherapy can reduce the impact of interfraction motion, and so the remaining positional uncertainty caused by intrafraction motion, although smaller, would have more impact in practice. Rectum filling was analysed using a non-parametric Wilcoxon test, and they found statistically significant differences where gas was present.

Although Mah et al. reported dosimetric impact of prostate motion on IMRT treatments they did not discuss SBRT where motion can have a greater impact. Each patient only had one scan, therefore intra-fractional motion variations throughout treatment were not considered. They concluded that rectum filling can influence prostate motion, but didn't specify the optimal rectal state to minimise prostate motion (19).

Mutanga et al. studied intrafraction motion retrospectively using 2-D kV and MV treatment images (22). In approximately 40% of fractions a systematic displacement of more than 0.2cm was noted. Even after the position was adjusted using the correction software, the marker position exceeded 0.2cm in 10% of fractions. However, it was not clear in the paper if this difference was due to limitations with the seed matching or intra-fraction motion.

Mutanga et al. did not discuss the stability of the gold seeds used as a surrogate for the prostate position(22). If these migrated this could falsely indicate a shift of target position. This is a potential disadvantage of a retrospective study, as verifying this information will be dependent on the information gathered at the time. The addition of 3D CBCT images would have assisted this as the position of the seeds could be referenced against the 3D anatomy of the patient as well as their co-ordinates in the imaging space. The dosimetric impact of the motion wasn't discussed, which would have helped put the risk of intra-fraction and inter-

fraction motion in a clinical context for the target and OARs. Mutanga et al. (22) demonstrates that prostate motion can occur at a magnitude greater than the PRINToUT study imaging tolerance of 0.2cm.

2.4.2 RayPilot

The RayPilot system has been developed by Micropos Medical (23) as a real-time tracking system for the prostate(24) . It consists of a table-top array of antennae, and a small transmitter inserted transperineally into the prostate. When the transmitter signal is detected by the antennae its 3D position is known. The transmitter is attached to a thin wire that protrudes from the patient and remains in situ until after all fractions are delivered.

Braide et al. (25) reviewed their initial experiences using Raypilot for Prostate radiotherapy. They reported that patients tolerated the device for treatment, although all 10 patients in the study reported discomfort during the insertion and 8 patients reported some impact on their daily routine during the time the device was implanted. Manufacturer recommendations on the transmitter angle (within 30 degrees of the horizontal plane) was not achieved in three of the ten patients. The position of the transmitter relative to the seeds was assessed using Matlab (25) and transmitter displacements exceeding 0.2cm were classified as unstable. The results showed only four of the ten patients had their transmitter defined as stable, with a maximum displacement of 0.5cm. They concluded that the device could be used for this treatment, but more evidence was required for it to be used as a primary imaging device and further studies on device stability would be useful.

Data gathered from staff groups within the paper by Braide et al. (25) was collected retrospectively, using a more flexible written approach. A more standardised approach mixing written data and questionnaires may have provided clearer results. They analysed the relative position of the transmitter and seeds using Matlab software (26). The use of 3D

imaging, which could have provided additional information on the transmitters relative position wasn't discussed. The treatment schedule was carried out over 8 weeks. Although not an SBRT fractionation it demonstrates the device can be tolerated over a longer period and therefore could be feasible for SBRT.

Some advantages of RayPilot over Calypso were also discussed, such as removal of the transmitter after treatment allowing follow up MR imaging (25). However, there was clear evidence in the paper for the instability of the transmitters, and therefore the requirement of additional imaging throughout treatment is advised for future studies before this is established. RayPilot is designed for real-time prostate tracking, however the study by Braide et al. (25) was limited to the relative position of the device during pre-treatment imaging. Real-time imaging data, analysed alongside planar imaging to determine the stability of the transmitter position of the prostate would have been useful and could be carried out in further studies.

A study investigating the differences between two real time tracking systems was performed by Biston et al. (27). The difference in positional accuracy of the RayPilot system and an ultrasound probe were compared using a phantom. Known displacements in a range of vectors and rotations for each system were measured using both systems with any differences between the two recorded. They also analysed data from 10 patients on treatment and highlighting the percentage time of treatment where the monitoring systems had a discrepancy, with increments ranging from 0.1-0.5cm. Their phantom study showed deviations of less than 0.05cm between the two systems when displacements were introduced. The patient study showed similar results, with the absolute mean difference between the displacements of each system being <0.055cm excluding one patient (<0.177cm).

They concluded that both systems were suitable for continuous monitoring of a prostate during radiotherapy. The advantages of the removable transmitter used in the RayPilot

system over similar systems such as Calypso were highlighted. The advantages of ultrasound imaging as an alternative monitoring system, such as being non-invasive, inexpensive and non-irradiating, were also highlighted for the reader.

The literature review in Biston et al. (27) found a wide base of studies where a comparison of two monitoring systems for prostate radiotherapy were compared. However, none of the studies they reviewed had compared two monitoring systems simultaneously, due to the potential interference from the respective systems. This was a novel aspect of this study, and allowed a direct comparison between two systems on the same clinical data.

Vanhanen et al. (28) compared two electromagnetic tracking systems, RayPilot and Calypso, benchmarked against 2-D kV imaging and looked at the stability of the markers. Bland Altman analysis compared the differences in positional correction between the electromagnetic and the kV tracking system. The mean difference between kV orthogonals and Calypso was -0.02cm (AP), 0.01cm (SI) & -0.01cm (LR) - consistent with published literature. The mean difference between kV orthogonals and RayPilot was 0.03cm (AP), -0.22cm (SI) & 0.00cm (LR), with the SI data ranging from -0.61cm to 0.86cm. The fiducial markers and Calypso transponders were assessed as stable, and the RayPilot transmitter deemed not stable. The RayPilot results were noted to be consistent with the findings in Braide et al. (25).

Vanhanen et al. (28) showed Calypso to be interchangeable with the kV orthogonal positioning system and deemed stable, and RayPilot to be unstable and not appropriate as a primary imager without further research. Although the RayPilot data was gathered retrospectively, they were looking quantitively at positional coordinates and therefore their methodology was appropriate. The impact on positional accuracy of RayPilot due to migration was shown and migration corrected measurements produced. As the RayPilot

patients were treated over 20 or 39 fractions, their transmitters were inserted for longer than an SBRT treatment. The Calypso study included 12 patients receiving SBRT, so if migration worsened over time this may not have been captured in the results. This was not discussed, but would have provided a more direct comparison between the two systems.

The comparison was limited to three planes, omitting rotational differences between the systems (28). The bias towards SI migration of the transmitters was highlighted with no discussion on why this was seen. The method by which the transmitter is inserted, or the connecting wire protruding from the patient throughout treatment may have influenced this but this would have to be investigated. For SBRT, due to the shorter treatment times it would be interesting to assess if the migration is still noted, or whether it could be mitigated. There was no discussion on the dosimetric impact of the positional differences and little information around the RayPilot treatment delivery method. The comparison between the couch shifts of the kV orthogonal images and RayPilot or Calypso used Bland-Altman analysis. Their assessment of the migration, utilising the centroid of the fiducial markers as a reference, was a useful method for comparing the seeds to the single transmitter position. It is not known how relevant this position in the seed matching software.

2.4.3 Calypso

The Calypso motion management system (29) uses three electromagnetic transponders, implanted in the prostate, using their centroid position and tracked by a receiver located in the treatment unit (30). Bell et al. (30)reported their initial experiences, successfully utilising Calypso for 116 out of 120 fractions. Due to the significant artefact observed on the MR scans with the Calypso beacons present, MR imaging was acquired before implantation. Prostate rotations were outside their 10 degrees tolerance in 28 fractions. When this was observed, they advised CBCT imaging to verify the prostate position, but they did not report the number of these cases requiring adjustment.

Bell et al. (30)noted a number of patients with rotations exceeding their locally defined tolerance using Calypso. They highlighted a number of intrafraction movements occurring after on-treatment set-up imaging. This would not have been identified and corrected without real-time motion management. Discussion on the clinical or dosimetric impact of the findings would have been useful however the paper would be helpful to a department looking to implement this device for the first time. There was very little critical content on the device but several aspects of the study would be of interest for research on tracking devices, such as their analysis method of prostate rotation.

Calypso's accuracy was assessed by Hamilton et al. against CBCT and 2-D kV imaging using an anthropomorphic phantom(31). They noted a number of studies on positional differences between Calypso and orthogonal planar images, but few included rotational positioning. The differences in the imaging corrections were assessed statistically using Lin's concordance correlation coefficients (32) with 95% confidence intervals following recommendations for looking at differences in microbiology laboratory tests.

Hamilton et al. (31) researched phantom positional corrections, designed as a quality assurance study rather than clinical verification of Calypso. They used seed matching software, whereas in their clinical practice manual matching was performed. This may infer their results would have differed clinically, however the use of matching software removes any user bias so the results would be consistent and applicable for other centres. They recommended more than 50 samples, which may have influenced the number of phantom positions chosen by Hamilton et al. (31). The use of recommendations from a study on laboratory tests in microbiology is a good example of translating scientific and statistical methodology to other modalities and the importance of looking at research methods outside of one's own core subject.

Lovelock et al. studied the benefits of target tracking compared to pre-treatment imaging for prostate SBRT patients (33). The beam was halted due to the target motion in more than a third of the fractions, which would not have been highlighted without tracking. The median time between set-up imaging and the end of treatment was 6 minutes 40 seconds, and despite positional interventions the mean impact on treatment time by adding tracking was only 30-40 seconds. 15 delivered fields with a displacement of 0.4cm or more were identified by Calypso. The dosimetric impact was calculated, and they found 10% of patients with a minimum PTV dose lower than 90% of the prescribed dose, with the lowest being 77%.

The benefits of motion management for prostate SBRT patients were stated in Lovelock et al. (33) and would be a useful reference for studies involving this technique. Their research on the dosimetric impact of motion management was a strength of this study and by using DVH data, this is presented in a format familiar to clinical staff for appraisal. Their findings could be used as evidence in a business case for motion management in SBRT. The importance of OAR dosimetry when reviewing motion management was highlighted and could be adopted in further research.

2.4.4 Cyberknife

The Cyberknife system uses dynamic image guidance (34) and consists of a linear accelerator mounted on a robotic arm and a kV imaging system. Radio-opaque markers are implanted into the target to track its position. The system automatically corrects for target motion in real-time, adjusting the arm position as the motion occurs and has been successfully used to treat prostate radiotherapy including SBRT (35).

Holmes et al. investigated marker implantation protocols for Prostate SBRT (36). The “relative pose problem” (37) is where translations of the x, y and z axes in the planning and

treatment spaces can be mapped. For this to be mathematically possible requires three fiducials. If the markers are too close together, the software cannot distinguish between them. Their existing protocol for implanting markers caused errors for 23% of their prostate patients. They devised an alternative implanting protocol and compared its positional accuracy against the original. Their results showed no instances of rotation errors. The dosimetric impact was simulated by rotating the planned doses and assessing the target coverage and rectum dose. They concluded that a rotation of 3 degrees can lead to a 9% decrease in PTV dose and a dose increase of 4% to rectum dose.

The dosimetric assessment in Holmes et al. (36) assumed a single systematic rotation on all fractions, which may not be representative of an actual treatment. This analysis was carried out on a series of pre-determined rotations and may not be clinically representative. As a QA exercise however, it showed the potential impact from rotations. The study timeline meant patients analysed using the original insertion protocol were the first treated with this technique at their centre. The second cohort using the new insertion protocol were treated after this. This could introduce bias as the centre would have built up experience in the technique during the first cohort, however the positional issues appeared to be software dependant and caused by seed proximity, therefore it is an objective test of insertion technique. For RayPilot, due to their being only one transponder, the “relative pose problem” discussed in this paper would not apply.

A retrospective study by Choi et al. on clinical outcomes of prostate SBRT patients treated with Cyberknife was carried out by using treatment logs to determine target motion (38). 21.1% of patients exceeded 0.36cm of motion in the A/P direction and less than 4% with more than 0.36cm motion in other directions. No patient’s prostate motion was greater than 0.72cm in any direction. The study noted a correlation between OAR toxicity and magnitude of motion existed. A statistically significant difference in the toxicity of patients with more than 0.26cm motion in the A/P direction was shown. Also shown was a statistically

significant difference in rectum toxicity due to radial motion above 0.33cm. There was no evidence that motion had an impact on treatment outcomes.

Choi et al. concluded the prostate motion in their study did not exceed their PTV margins and did not have a statistically significant impact on treatment outcomes(38). However, they acknowledge other studies show intra-fraction motion significantly impacting Prostate SBRT delivery. Interestingly, they showed a difference in toxicity due to A/P motion observed of less than 0.36cm. This would be of interest to other centres and could be investigated in further studies and reviewing if interventional imaging limits are appropriate.

2.4.5 RealEye

The RealEye system was assessed by Kruijf et al. for safety and performance as a tracking system for prostate radiotherapy (39). RealEye utilises a radioactive tracer (iridium wire), implanted into the patient. Sensors mounted on the gantry track the position of the tracer and its position in 3D is calculated. The positional stability of the implant was analysed retrospectively using the relative position before and after a CBCT. They found only one patient with significant increase in symptoms during the treatment. The paper concluded that the implantation of the system was both feasible and safe.

Kruijf et al. used CBCT imaging for positional verification of their implant giving 3-D information about the position of the device(39). The mean difference in position between the tracer readout and its CBCT position was 0.134cm. This was comparable to the prostate motion noted during CBCT acquisition and so may not be due to differences in the imaging systems. Some consideration for the impact on intra-fraction motion during acquisition of the CBCT should be taken in other studies. They also show that the RealEye system does not provide information about rotations, or deformation of the prostate.

This study was a solid test of the system, and the utilisation of more than one site was a good way of reducing user bias from a single centre study. However, the number of patients analysed was small and therefore it could not be seen as robust evidence to use this tracking system without any additional imaging.

2.4.6 Kilovoltage intrafraction monitoring (KIM)

Initial clinical results utilising a 2D kV imaging system called kilovoltage intrafraction monitoring (KIM) were reported by Ng et al. (40)which they implemented for prostate IMRT(40). KIM uses 2D planar kV images of seeds at a series of gantry angles during the treatment. It found that the 3D motion of the prostate was outside of 0.3cm 4.7% of the time, however there was one instance highlighted where the displacement was 1.5cm. The accuracy of the KIM system was calculated to be within 0.046cm and compared favourably with both Calypso (0.054cm) (41)and RealEye (0.089cm)(42). Advantages include compatibility with MR imaging post treatment and ability to detect rotational discrepancies. The study is limited to retrospective impact of positional discrepancy, without real-time feedback of the position of the target. This was highlighted briefly in the discussion and has been noted in other studies.

Ng et al. discuss the advantage that KIM would be possible on most modern linacs with a kV mounted imager (40). One limitation identified was the scatter contribution from the MV treatment beam whilst acquiring the images. This was mitigated in the study by increasing their detector SSD to 180cm reducing the scatter contribution, but not eliminating it. The author presents additional solutions including improvements in the analysis software. However, setting up this system with in-house software would require access to advanced computer scientist skills, which can be difficult to resource in NHS departments, although commercial solutions are now available(43). Their comparison looked exclusively at

geometric accuracy and therefore studies comparing accuracy within clinical patients would be advantageous for further reading.

Ng et al. showed the KIM system could be implemented safely for use with prostate treatments, however did not discuss SBRT(40). The difference between the accuracy of the systems is small (0.008cm Vs Calypso) and not clinically significant, so other measurables should be used to conclude superior.

Ng et al. (40) report the additional concomitant dose to the patient using the KIM system over a whole treatment course (40 fractions) to be 61mSv. The Calypso system involves no radiation dose to the patient, and has comparable accuracy which would be an advantage of this system. The RayPilot system also involves no radiation dose to the patient for the tracking, however would require additional IGRT systems such as orthogonal kV planar imaging to correctly position the patient for the treatment. The balance between the risk from concomitant dose and the need for accuracy of patient position during treatment should be considered by a department when assessing the appropriate tracking system to use (44) (45). For SBRT treatments where the number of fractions is reduced, the impact of positional inaccuracy during treatment increases whereas the concomitant dose should be reduced when compared to a conventional fractionation. This study provided clear criterion to compare different tracking modalities, which could be integrated into future research.

Keall et al. reported on the accuracy of KIM in a prospective clinical trial, using the gating system to switch off the beam if the prostate motion exceeded 0.3cm for five seconds (46). This intervention strategy was based on Colvill et al. (47) and would maintain the plan dosimetry whilst reducing unnecessary beam interventions (47). The KIM system was benchmarked against kV/MV triangulation during treatment, considered to be the gold standard. Differences in the system were found to be less than 0.1cm for all fractions. Of the

197 fractions, the gating system halted the beam in 14.5% of these, with the largest observed motion 1.17cm.

Keall et al. produced favourable results, showing that the implementation of the KIM system with gating can eliminate prostate displacements (over 0.5cm) during treatment delivery (46). The introduction of a time and distance threshold was interesting and would be more representative of the delivered dose. The RayPilot system requires manual intervention and including a time to the imaging tolerance would be difficult to practically implement. This approach proved useful in this study and further evidence if it would be appropriate for SBRT would be useful.

2.4.7 Review paper

Das et al. (48) reviewed imaging modalities for prostate radiotherapy, with a focus on ultrasound, kV imaging, CBCT, Calypso and Cine-MRI discussing the main advantages and disadvantages of each system, their associated costs and any direct comparison of the modalities. The system costs varied significantly, with the installation of the MRI cine system being $1-3 million, the CBCT $500,000 and the Calypso system $350,000. The accuracy of the systems and impact was discussed, with ultrasound requiring the largest PTV margins and Calypso the smallest. The requirement of ionising radiation and additional dose to the patient, such as with the CBCT and the X-ray imaging, was noted as a limitation for some systems. Calypso was the only system capable of identifying intra-fraction motion.

Das et al. quotes the cost per treatment for each imaging modality, estimated from Medicare rates in the USA (48). This would not be representative of the cost to a UK NHS service. The cost for a CBCT system was estimated to be $500,000. With modern commercial Radiotherapy Linacs often including an integrated CBCT system, it would seem that this figure may be a bit high but the exact source material was not given. It would be useful to

estimate the cost of imaging techniques within PRINToUT and the cost effectiveness of RayPilot.

The layout of this paper and in particular the summary tables were useful for the reader as it was clear what was being assessed, with short summary conclusions for each parameter. Although they have summarised a range of measurables for each system, they stated that a lack of published data on clinical outcomes meant there was not strong clinical evidence for one system's superiority over another. Current studies looking into this, specifically Calypso Vs fiducial markers were discussed and would be of interest for future reviews. The importance of managing prostate rotation was consistently noted throughout Das et al. Vanhanen et al. stated that RayPilot can detect rotations (24) but other RayPilot reviews did not discuss this.

2.4.8 mpMRI

Multi-parametric MRI (mpMRI) has emerged as a useful imaging tool for the detection of the focal lesion in a prostate for cancer diagnosis. Goldman et al. (49) carried out a retrospective study looking at the efficacy of mpMRI to predict a patient's Gleason score as well as the index lesion location. They found that the lesion from the mpMRI matched the biopsy for 89.1% of the patients. The Gleason scores assessed using mpMRI correlated with the biopsy for 75% of the patients. They concluded that these results were favourable but that further work would be required before mpMRI could be utilised to identify patients where biopsy is required.

Within Goldman et al. two radiologists were used to interpret the mpMRI images to delineate the prostate lesion (49). While this would minimise single user bias, there was no peer review of the volumes carried out between the radiologists with each only delineating their

allocated cohort. This may have added value to the study if this had been arranged, even for a small number of patients, to verify a consistent approach was used.

A retrospective study by Johnson et al. looked at the rate of focal lesion detection in prostate cancer using mpMRI (50). The study looked at a large number of patients who had received mpMRI and a prostatectomy, Lesions were delineated by one of three experienced radiologists accompanied by a research fellow. They found that the mpMRI detected 45% of lesions and 64% of clinically significant lesions. Further analysis into the lesions that were not identified, showed that these were in the most part the smaller lesions and the detection rate in the study increased with the size of the lesion. The smallest lesion (0.1-0.5cm) had a detection rate of 10%, whereas the larger lesions (>2.0cm) had a detection rate of 78%.

Johnson et al. excluded patients who had mpMRI taken at other institutions (50). Although this reduced the numbers of patients in the study, it helped reduce bias caused by differences in scanner set up or protocols between centres. However, the fact that this was a single centre study would also introduce bias into the study. Differences between scanners or departmental protocols could have an impact on these results, and therefore should be viewed within this context. Evidence from multi-centre studies would be helpful for clinical implementation.

There was selection bias in both Johnson et al. (50) and Goldman et al. (49) as they only included patients who had a prostatectomy. If another accurate method of confirming lesion position and disease stage that was non-invasive was available, this study could be repeated with a wider demographic of patients.

2.4.9 Prostate SBRT with boost: Cyberknife

A study by Aluwini et al. using Cyberknife (51) to treat low and intermediate risk prostate cancer patients with SBRT and focal boost published early results (52). This provided follow up data (median: 23 months) for patients in the study, with toxicity scoring following the EORTC-RTOG methodology. Their results showed that this treatment regime was feasible and reported the toxicity at an acceptable level. The advantages of SBRT versus brachytherapy were discussed, where the invasive aspects of brachytherapy and need for a hospital stay were deemed less convenient than the SBRT option. They recommend that larger clinical trials would be required to evidence this method of treatment as more effective than established techniques. They presented acute GI toxicity of grade 2 in 12% of patients and grade 3 in 2% stating that their toxicity was low compared to established literature. The PSA nadir for patients with 2 years follow up was 0.6 ng/ml and a PSA bounce was noted in 14% of patients. . It was acknowledged that the follow up period for this study was not long enough to confirm any strong clinical conclusions.

There was only minimal detail in Aluwini et al. of the Cyberknife treatment delivery, utilising four gold seeds implanted in the prostate (52). This tracking method aided their introduction of SBRT and allowed confidence in their reduced margins. No additional imaging or verification of the position of the focal lesion during treatment was discussed. This would imply that the position of the seeds was used as a surrogate for the relative position of the focal lesion during treatment. A similar approach could be adopted with the RayPilot transmitter during treatment, however some 3-D verification of the position of the lesion would be advantageous. Their comparison of SBRT to Brachytherapy was interesting, stating SBRT was clinically comparable and had some practical advantages. However, this study only included patients who weren't eligible for Brachytherapy which limited the demographic and a randomised trial would be more useful evidencing clinical superiority.

2.4.10 Prostate SBRT with MR defined boost

Using MR scans to identify the focal lesion was investigated in a retrospective study of prostate patients by Feng et al. (53). Registration of the planning scan and the MR was carried out using rigid and a non-rigid registration. Their study concluded that the non-rigid method of registration estimated the position of the focal lesion correctly. A planning study for patients was carried out to produce SBRT plan with an integrated boost for each patient in this study. They were able to achieve clinically acceptable plans for each of the patients planned, with their organ at risk doses and target coverage meeting constraints from the PACE trial (54). The variability in position of the focal lesion within the prostate was noted, however this didn't impact the ability to meet the designated plan constraints.

In Feng et al. (53), the non-rigid registration method for the MR scans was felt to allow a more accurate and reproducible method for delineating the focal lesion for the treatment plan. This paper highlights the need for accurate registration techniques to support the MR imaging to accurately define focal lesions. The study showed that dose escalated SBRT plans could be created within the PACE trial constraints. The PRINToUT trial (12) aligned to the PACE protocol, so this study could provide a consistent approach to follow. The planning study in Feng et al. (53) used NTCP and TCP to compare the SBRT plan and the original clinical plan.

McDonald et al. explored the feasibility of prostate SBRT delivery and the integrated boost of an MR defined focal lesion in a pilot study (55). The prostate was delineated using CT and MRI information, with the focal lesion contouring involving the clinical oncologist and surgeon. Image guidance through CBCT and then kV planar imaging was used to confirm the position prior to treatment and to monitor its position during the delivery using triggered imaging. Two patients or 7% of the study had acute urinary symptoms but there were no grade 3 toxicities reported. They had pre-defined criteria for plan acceptability and toxicity

levels for the study to have been deemed successful, and their results were within this. They noted that the development of a rectal spacer (56) since their trial was designed has led to this being incorporated into their future studies. Further evidence supporting irradiating the whole prostate to 40Gy in 5# became available after publication, and therefore their planned follow up study may no longer be relevant. However, their regimen could be useful as a means of maintaining acceptable OAR doses and provides context for future studies.

Some limitations of the pilot study in McDonald et al. (55) included being a single centre study with low patient numbers. The treatment method was shown to be feasible, however follow up on patient toxicity was continuing after publication. At the time of their publication reports were widely available showing urinary retention is not commonly noted in SBRT irradiation, which was their primary endpoint but was not known at the time of the study design. This illustrated that this is an emerging technique and the research and evidence base can be updating quickly.

The inclusion of TCP and NTCP modelling to assess the plans was a useful means for providing clinical context to the planning studies in Fenget al. and McDonald et al. (53) (53). McDonald et al. (55) used TCP and NTCP data to inform their planning process, for example replanning to reduce the NTCP of the rectum. Not all clinical departments would have expertise or protocols to calculate TCP and NTCP values accurately or in a timely manner, however plan doses should be fully optimised based on dose values from the planning system. It would be interesting to compare this study to one using the same iterative process of reducing OAR doses whilst maintaining coverage, but using only the dose distributions and DVH information and whether using NTCP and TCP produced a different outcome. The anatomical geometry was discussed as being a potential flag for higher OAR doses, such as a focal lesion PTV abutting the rectum. This would be interesting to investigate in further planning studies.

Uncertainty in the value of the alpha/beta ratio of the prostate in McDonald et al. (55) was relevant to their results. They used an alpha/beta of 1.5 and although variation in this value would impact the results, this was the most representative. The radiobiological calculations were based on the linear quadratic model, and there are some limitations applying this method to high doses per fraction as it can overestimate cell killing and therefore the NTCP.

2.4.11 Prostate SBRT with boost: Planning studies

A planning study by Murray et al. was carried out looking at the impact that different SBRT treatment regimens would have on TCP and NTCP (57). The dose to the focal lesion was boosted in some iterations of the planning study, with the boost dose being increased incrementally until defined OAR dose limits were breached. They found that when dose escalating, the limiting structure for further dose increases was most commonly the rectum. The example plans with the least favourable rectal doses came from a dataset with two focal with lesions (one abutting the rectum) and one dataset with a relatively large boost volume. The NTCP modelling used in this study designated the rectum as a serial organ, due to the Dmax (0.5cc) dose tolerance. They found that for the dose escalated plans, this was a limiting factor as the NTCP was very sensitive to increases in the rectum doses. By replanning and focusing on reducing the rectum Dmax (0.5cc) as much as possible without compromising the PTV, they were able to significantly improve the NTCP whilst maintaining plan quality.

Increasing the boost dose incrementally in Murray et al. (57) was a useful way to highlight the achievable limits for each patient plan. For clinical implementation of an isotoxic protocol, it may be more important to follow an established protocol within a clinical trial than simply using a method of dose escalation in isolation. Dose escalating a focal lesion in prostate SBRT is not a widely established technique and there are additional factors such as uncertainty in the positional verification of the lesion that may also influence the successful

delivery of a treatment plan so these should be considered. The relationship between increased dose to OARs and increased risk of toxicity should be understood well before a study of this sort is delivered clinically. They note that the PTV margin for the lesion can be a point of uncertainty, with a range of 0-0.8cm noted from their publication reviews. They used a 0.4cm margin for the focal lesion, which is consistent with the FLAME trial (58). One of the limitations was the uncertainty regarding delineation the focal lesion. They used mpMRI, but discuss that other studies have successfully used MR spectroscopy, radiolabelled iodine or PET imaging. They also state that their rigid registration method would introduce some uncertainty in this process and this would be mitigated if deformable registration had been available.

Bijina et al. (59) carried out a planning study aiming to compare the plan dosimetry of three treatment delivery methods (Rapidarc, Cyberknife and Tomotherapy) for prostate SBRT and escalated boost. A separate plan for each method was completed for every patient in the study. These were assessed using a range of metrics including DVH and conformity indices. They concluded that the plans based on the Rapidarc delivery were superior.

They deemed Rapidarc as the superior delivery method, assessed using both DVH data and conformity indices (59). This is a useful way to assess the dose falls off optimally, and gives clear quantifiable results. Each system had a separate planning system and different dose calculation algorithms. This would have influenced the study and it would be hard to isolate differences in the results that were due to the delivery method alone. There was no discussion on the accuracy of delivering each of these treatment methods or their imaging and target tracking options. Statistical analysis was carried out to compare the different treatment methods using one-way analysis of variance. This allowed the study to conclude superiority of a technique over another using appropriate confidence intervals.

A planning study based on Cyberknife delivery of dose escalated prostate SBRT by Kim et al. (60) looked at the impact of varying the prescription dose to the boost. They reported acceptable doses for 73% of plans with a 40Gy in 5# boost and 60% of plans with a 45Gy in 5# boost and suggest a relationship exists between exceeding rectal tolerance and posterior positioning of the lesion. They concluded that their protocol and technique was safe to use for treatment.

The results and discussion of the planning study by Kim et al. (60) highlighted posteriorly positioned lesions as a limiting factor for meeting OAR constraints, with literature showing 70% of prostate lesions located here. They recommend that for posterior lesions their lower boost prescription (40Gy in 5#) should be used. This seems a sensible strategy and adds weight to having multiple dose levels available for the boost structure. However, application of this would require clear criteria on assessing the position of the lesion, and may limit direct comparisons between their patients receiving different doses. Even with this lower dose level, they would not have achieved clinically acceptable plans for 27% of the patients in their study. Dropping the dose incrementally for the boost does seem like a more standardised approach than compromising the boost volume until the OAR dose is met. As this was only a planning study, no clinical outcomes or toxicity data was available.

2.4.12 Prostate SBRT with boost: Review paper

A literature review with a focus on treatment strategies for prostate focal lesions with dose escalation was carried out by Draulans et al. (61). This highlighted some data which enforced the idea of the efficacy of dose escalation in prostate radiotherapy (62). The radiobiological advantages of dose escalation are evidenced in this review, however caution was noted with regard to toxicity when dose is escalated for the whole prostate, for example to 50Gy in 5# (63). This may be a driver for more focused boosts to the lesion only, reducing dose to organs and subsequently toxicity. The dose range within the review was 32Gy-50Gy,

with doses per fraction ranging from 6.7Gy-10Gy. Prescribed doses of 35Gy in 5# and 36.25Gy in 5# were noted as being the most common. Of the 21 reviewed trials, 16 of these were treated using Cyberknife, although they discussed that it is was now more common to include linear accelerators into recent studies.

Prostate motion was highlighted in Draulans et al. as a potential issue for focal lesion localisation (61). With rotational displacements potentially more problematic for boost volumes. The longer treatment times associated with SBRT were flagged as a potential issue for motion, with the probability of a >0.3cm displacement rising from 10% during a five-minute treatment, to 20% for a ten-minute treatment. The most common CTV to PTV margins in those studies reviewed was 0.5cm in all directions except posterior, with 0.3cm. There was no discussion about the margins for the focal lesion, although they did discuss the possibility of larger margins for seminal vesicles.

Image guidance strategies for prostate SBRT were discussed by Draulans et al. (61). As the majority of studies involved utilised Cyberknife delivery, this was the most commonly used imaging system. kV planar imaging was noted to have shown favourable results for prostate localisation over CBCT. Using kV planar triggered imaging was highlighted as being an option for treatment delivery in some studies, although the increase in treatment time could increase risk of prostate motion. Recent studies where MR-guided radiotherapy was in use was proposed as being a viable means for localising the focal lesion during treatment and also for adaptive radiotherapy. They recommended that prostate SBRT with an ablative boost to the focal lesion only be undertaken as part of a clinical trial (61).

Draulans et al. produced a flowchart used to illustrate the search methodology and the number of papers included in their systematic review (61). This included detail on number of papers reviewed, read and included in the study. There was discussion in the review regarding imaging, focusing on target position. The localisation of the focal lesion was not

discussed widely however, which would infer that the position of the focal lesion relative to the seeds would be assumed to remain stable and within the agreed margins. The potential for rotational displacements of the focal lesion position was discussed to but no detail of the impact was included.

The Draulans et al. review included some studies on MR-guided radiotherapy, which could be useful for localisation of the focal lesion (61). This treatment method is still emerging, and it would be interesting to examine the imaging data during treatment to isolate the position of the focal lesion and its displacements. Rectal spacers were noted to reduce the dose to the rectum by increasing the distance between the high dose region and the rectal wall and to help immobilise the prostate (64). For focal lesions, this may provide a potential dosimetric advantage for more posterior lesions.

2.4.13 HYPO-Flame trial

In a follow up publication, Draulans et al. analysed the early endpoints of the Hypo-Flame trial (65). This multi-centre trial was designed to treat prostate SBRT with an integrated boost. The defined endpoints of the trial were the acute GI and GU toxicity. They found that after 90 days, 34% of patients had experienced Grade 2 GU toxicity and 5% of the patients experienced grade 2 GI toxicity. No patients in the trial experienced grade 3 toxicity. These results were reported to be acceptable compared to other studies and the trial protocol evidenced as safe to deliver.

This study reported across four centres and two countries, with this spread of departments and health systems advantageous to reduce bias (65). The Hypo-fractionated treatment was delivered with one fraction per week. This was intended to give an EQD2 dose of 85Gy. This was calculated using the linear quadratic model, which is known to have limitations for

higher doses per fraction, so direct comparisons of the results against longer courses of radiotherapy may not be appropriate. The sample size of 100 patients was chosen as it allowed an appropriate power for the statistical tests, which is a useful way of ensuring statistical relevance of a study. Within the planning solution, the priority was given to meeting the OAR doses over coverage of the focal lesion, but there was no discussion about how this approach impacted target coverage. As the study included early toxicity as a primary endpoint, there was no discussion on tumour control. There is a larger phase 3 trial FLAME that was running alongside this study that has an arm with dose escalation that will focus on outcome data. The data on boost target compromise in this trial and how this correlates with clinical outcomes would be interesting.

2.5 Further research

This literature review was focused on prostate SBRT and dose escalated boosts. Tracking methodologies from other anatomical sites such as thorax, where the target motion can be more complex, could provide another layer of insight. This could be discussed in further reviews or studies of RayPilot positional geometry. As the subject covered was broad with a large number of publications available, there were areas of interest that could not be discussed in detail. The themes that would best supplement the research were investigated in depth, but a large amount of literature on other tracking methodologies such as Dynamic Multi-leaf Collimator tracking (66), 6 degrees of freedom couches (67), ultrasound (68) MRI (69) and EPID (70) were reviewed, which also informed the study and may be useful in further research.

2.6 Conclusions

This scoping review successfully completed and used to identify research questions and inform design of investigations as summarised in Table 5.

Although there is a large body of research papers on prostate motion management and tumour tracking, no system is clearly evidenced as superior. Indeed, there is little evidence from comparative studies that included clinical follow up and would be useful for radiotherapy centres looking to purchase and implement a system for prostate motion management. This review considered dosimetric implications of tracking systems to be particularly useful, with the advantage that results given in this format would be familiar to clinicians and other planning staff used to interpreting dose information in this way.

The efficacy of prostate SBRT with a dose escalated boost to the focal lesion has been evidenced through a number of scientific papers and trials. Although direct verification of the focal lesion position was not discussed widely, this may be down to the limitation of the IGRT systems to delineate this anatomy. There was wide evidence of studies being carried out where established IGRT methods were used alone, such as 2D planar kV with the seeds used as a surrogate for both the prostate position and the position of the focal lesion. This would align with the approach in the PRINToUT trial (12), and therefore give confidence this would be an appropriate methodology for a planning study. As recommended by the review paper Draulans et al. (61), with very little established 5-year follow up data for dose escalated prostate SBRT, this should be implemented only as part of a clinical trial. A planning study following the PACE trial protocol but with dose escalation was carried out successfully and could be considered as a model to follow (54). TCP and NTCP modelling was discussed in both Feng et al. (53) and Murray et al. (57). This is seen as a useful method for plan regimen comparisons and in Murray et al. they used this data to feed back into the planning process to change the priorities of the plan. Whilst this is an interesting approach, there are acknowledged limitations of applying this modelling technique for hypofractionation. This would have to be investigated further before any inclusion in a study.

The niche aspects of Raypilot provide opportunities for novel approaches to previous studies. What was clear from the literature is that for prostate motion management there is

no system clearly evidenced as superior, indeed it was noted that there is little evidence comparing systems that included clinical follow up.

Table 5: Summary of research questions for local study and key aspects for investigation that have been highlighted by this review

Research Questions	**Key aspects**
What is the accuracy and stability of RayPilot for prostate motion management during SBRT?	• Positional stability to include degradation over time. • Positional accuracy to include all directions and rotations • Intrafractional positional stability • Benchmarking against kV imaging and CBCT • Dosimetric impact of the device for SBRT. This should include dosimetry to the target and OARs • Could RayPilot be used as a primary imaging device
How does Raypilot compare against other motion management systems for prostate SBRT?	• Quantitative comparison against Calypso, Cyberknife and other existing methods within the literature • Should include data on accuracy, precision and stability and look at the limitations of each system • Dosimetric analysis for the impact on SBRT treatments for each modality • Clearly defined parameters such as cost, treatment time implications, additional imaging and patient comfort could be discussed
Can Raypilot be used for dose escalated prostate SBRT?	• Is the quality of the pre-treatment imaging high enough for verification of focal lesion position • What imaging devices would be suitable for focal lesion delineation? • Would rotations have an impact and could this be managed • What is the positional stability of the transmitter relative to the focal lesion? • What margins would be appropriate • What other motion management systems have been used for this purpose and how does their performance compare to RayPilot • Can clinically acceptable dose escalated Prostate SBRT plans be created for patients within the PRINToUT study?

3. Paper A: Target Journal – Radiotherapy & Oncology

Investigation of the accuracy and stability of RayPilot for prostate motion management during SBRT: Initial experiences

Authors: Michael Trainer[1], William H Nailon[1,3], Linda J Carruthers[1], Mike Kirby[2]

[1]Department of Oncology Physics, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK

[2]Directorate of Radiotherapy, Liverpool University, Liverpool, UK

[3]School of Engineering, The University of Edinburgh, Edinburgh, UK

1. Paper A

3.1 Abstract

Purpose/Objective: Real-time positional verification is an important consideration in the safe delivery of SBRT. The purpose of this study was to assess the viability of the RayPilot system for intra-fractional motion tracking during prostate SBRT by benchmarking this system against current imaging protocols.

Materials/ methods: The RayPilot system consists of a table-top array containing antennae connected to a transmitter which is inserted in the prostate. Seven patients had SBRT prostate treatments (36·25 Gy/5#) within the PRINToUT trial. On-treatment positional verification was through kV orthogonal pairs matched to fiducial markers, with additional pre- and post-treatment CBCTs. In parallel, the RayPilot system was used to monitor the transmitter position during treatment with the beam halted manually for displacements of more than 0.2cm. The co-ordinates of the markers and the transmitter in the planning CT and pre and post-treatment CBCT images were recorded offline.

Results: The mean displacement (+/- standard deviation) of the RayPilot transmitter for all seven patients and all five fractions comparing the CT and each of the pre and post CBCT scans was -0.04cm (+/-0.1cm) (LR) , 0.07cm (+/-. 0.2cm) (AP) & 0.16cm (+/- 0.5cm) (SI). The mean displacement in the same images of the three fiducial markers for all seven patients and all fractions was -0.03 (+/- 0.1cm) (LR), -0.03 (+/- 0.14cm) (AP) & -0.03 (+/- 0.14cm) (SI).

Comparing the pre and post CBCT images, the mean displacement (+/- standard deviation) of the transmitter for all patients and fractions was -0.02cm (+/- 0.11cm) (LR), -0.00cm (+/- 0.15cm) (AP) & -0.02cm (+/- 0.18cm) (SI). The mean displacement for all three fiducial markers comparing the pre and post CBCT images for all patients was 0.02cm (+/- 0.09cm) (LR), -0.03cm (+/- 0.13cm) (AP) & 0.04cm (+/- 0.11cm) (SI).

Conclusion: Initial results show that the RayPilot system can be used for tumour tracking during Prostate SBRT. The positional stability of the device against the local imaging protocol was variable. Further work is required to verify the RayPilot device as a stand-alone modality for SBRT.

3.2 Introduction

Prostate cancer is the most common male cancer diagnosis, with 48,600 cases being reported in the UK in 2017 (A1). Radiotherapy is an important part of the treatment regime for prostate cancer and is used in almost a third of patients (A1). Established radiotherapy schedules, involving a long course of treatment (20-39 fractions) are routinely used in the UK with a typical dose per fraction of 2-3Gy (A2). Due to the lower alpha/beta ratio of prostate cancer there may be radiobiological advantages to a more hypofractionated treatment schedule (A3). There has been growing interest in the use of ultra-hypofractionated treatment schedules, also known as prostate SBRT, where a dose per fraction of >5Gy is delivered to the target in a reduced number of fractions (A4). Some recent trials comparing the efficacy of prostate SBRT against established techniques have published promising early results and long term data is eagerly anticipated (A5)(A6).

Interfraction motion refers to positional changes of a patient between fractions and can often be mitigated through image guidance techniques (A7)(A8). Intrafraction motion occurs during the treatment delivery and can be harder to detect and correct for. Positional changes of a patient during prostate SBRT treatments may have a greater impact on the treatment than for longer fractionations. This is because each single fraction contributes to a larger percentage of the dose contribution. If some of the target is outside the field for a single fraction, this volume would have a reduced dose contribution for this fraction. This would equate to 20% of the overall treatment for a five-fraction regime. If the displacement was

systematic, this could impact the dosimetry of the whole treatment. Studies have shown that displacements can lead to a reduction of dose to the target (A9)(A10).

Tracking devices can be used to reduce the impact of intrafraction motion in prostate SBRT delivery, by giving real-time information about the position of the target during treatment delivery and systems to correct positional changes (A11). When investigating the stability and accuracy of a novel system such as the RayPilot electromagnetic (EM) transmitter system for target tracking during prostate SBRT, it is important to put this in the context of established systems such as Calypso (A12) or Cyberknife (A13). Calypso (A12) uses four transponders placed within the prostate to track the position of the target during treatment allowing beam gating to occur when displacements are outside a defined tolerance. The Cyberknife system (A13) uses in-room orthogonal 2D kV imaging to track the position of fiducial markers placed in the target in real-time and adjust the position of the beam delivery based on displacements. The radiotherapy treatment is delivered through a linear accelerator mounted on a robotic arm. When the target position changes the system will automatically change the position of the robotic arm to correct for this.

The aim of this study was to document the initial experiences of using the RayPilot electromagnetic (EM) transmitter system for target tracking during prostate SBRT with respect to the commonly available IGRT methods of 2D kV orthogonal imaging and 3D kV CBCT volumetric imaging.

3.3 Materials and methods

The RayPilot system includes an EM Transmitter and couch top array which are connected together by an electrical cable (A14). The couch top array contains 16 antennae which can be used to calculate the position in space of the transmitter with respect to the treatment machine isocentre. The transmitter is inserted into the prostate transperineally to allow the

localisation of the target during treatment. The transmitter remains in-situ after insertion for the whole treatment course after which time it is removed.

This study included seven patients who were enrolled in the PRINToUT study (A15), a study investigating the relationship between the volatile organic compounds released in breath during prostate SBRT and tumour and normal tissue response to radiotherapy. The age range for the study was 53-81, with a mean age of 70.7. Five patients had a Gleason score of 6 and two score of 7. Pre-treatment and prior to the CT planning scan, each patient had a multi-parametric MR scan which includes a T2 weighted, diffusion-weighted and dynamic contrast MRI's. Three fiducial seeds inserted into the prostate followed by ultrasound guided insertion of the EM transmitter. Radiotherapy planning CT scans were registered with the MR images using both rigid registration methods. The MR and the CT were both used to delineate the target volumes for the treatment. The PRINToUT radiotherapy protocol, including organ at risk doses was aligned with the PACE trial (A5). Each patient was prescribed 36.25Gy in 5# (Appendix 2) and the treatment plan was designed to cover the PTV with 95% of the prescribed dose and the CTV with 100%. This was a minor deviation from the PACE protocol which boosted the CTV to 40Gy. For the PTV, the CTV was expanded by 0.5cm in all directions except in the posterior direction, where a 0.3cm margin was applied.

Treatments were planned using the Eclipse treatment planning system (v13.6) (A12) calculated using the AAA algorithm (v10.0.28) and delivered with three full rotation 6MV VMAT arcs on a Truebeam linear accelerator. The imaging protocol was set up to allow the use of the RayPilot tracking system as a supplementary imaging method for on-treatment geometric verification. The Primary imaging method for positioning was the 2-D orthogonal X-ray imaging system, acquired before treatment and between each arc. An imaging tolerance of 0.2cm was used before any positional correction was instigated. Once the patient is positioned, a CBCT image was taken directly before the beam delivery to provide

3D anatomical information and allow assessment of the shape and position of the OARs and verify the position of the RayPilot transmitter. An additional post fraction CBCT was acquired directly after the last arc. The RayPilot system was used to track the position of the target once the patient was positioned. If a displacement of 0.2cm or greater in any direction was noted during treatment delivery, the beam was halted manually and a kV orthogonal pair was used to verify the target position and correct if necessary. An example of the workflow showing the order of the imaging and treatment arcs used during the study is included in Fig A1.

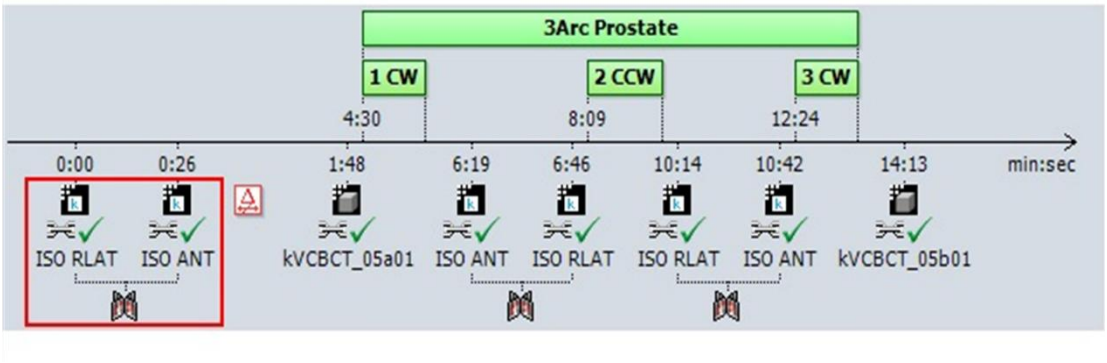


Fig A1*: Example of a typical imaging workflow at each fraction in this study. Orthogonal kV pairs (ISO Images) were taken before treatment and between each arc. CBCT images were taken before and after treatment delivery.*

The imaging data was analysed retrospectively by a single observer, using the Aria OIS offline review module (A12) looking specifically at the position of the RayPilot transmitter and each of the 3 fiducial markers. The coordinates of each point of interest were recorded using the planning CT image and each of the pre and post-fraction CBCT images in the sagittal, transverse and coronal imaging planes. The position of the tip of the RayPilot transmitter was used as a surrogate for the position of the transmitter, Fig A2(a). The coordinates of the fiducial markers were recorded by estimating the centre of the seed on the image. The spatial resolution from the images was 0.09cm in the LR (x) and AP (y) planes and 0.1cm SI (z).

1. Paper A

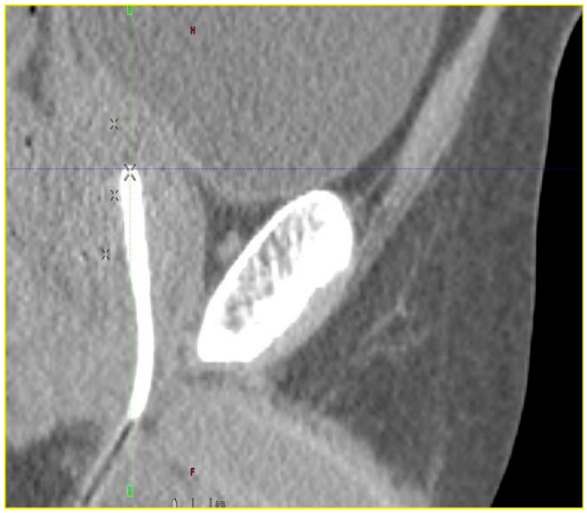


Fig A2(a) CT Image

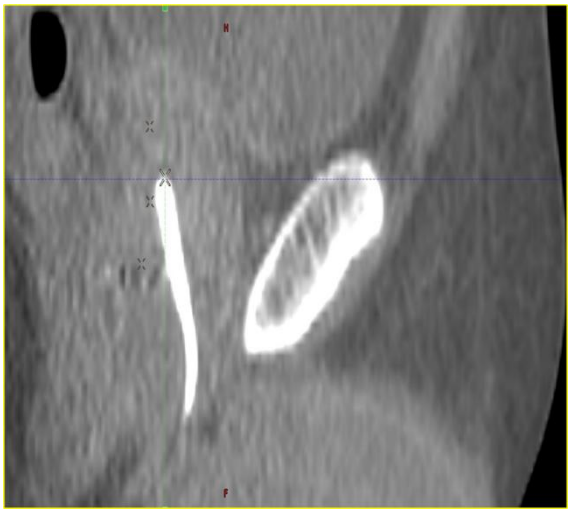


Fig A2(b) CBCT Image

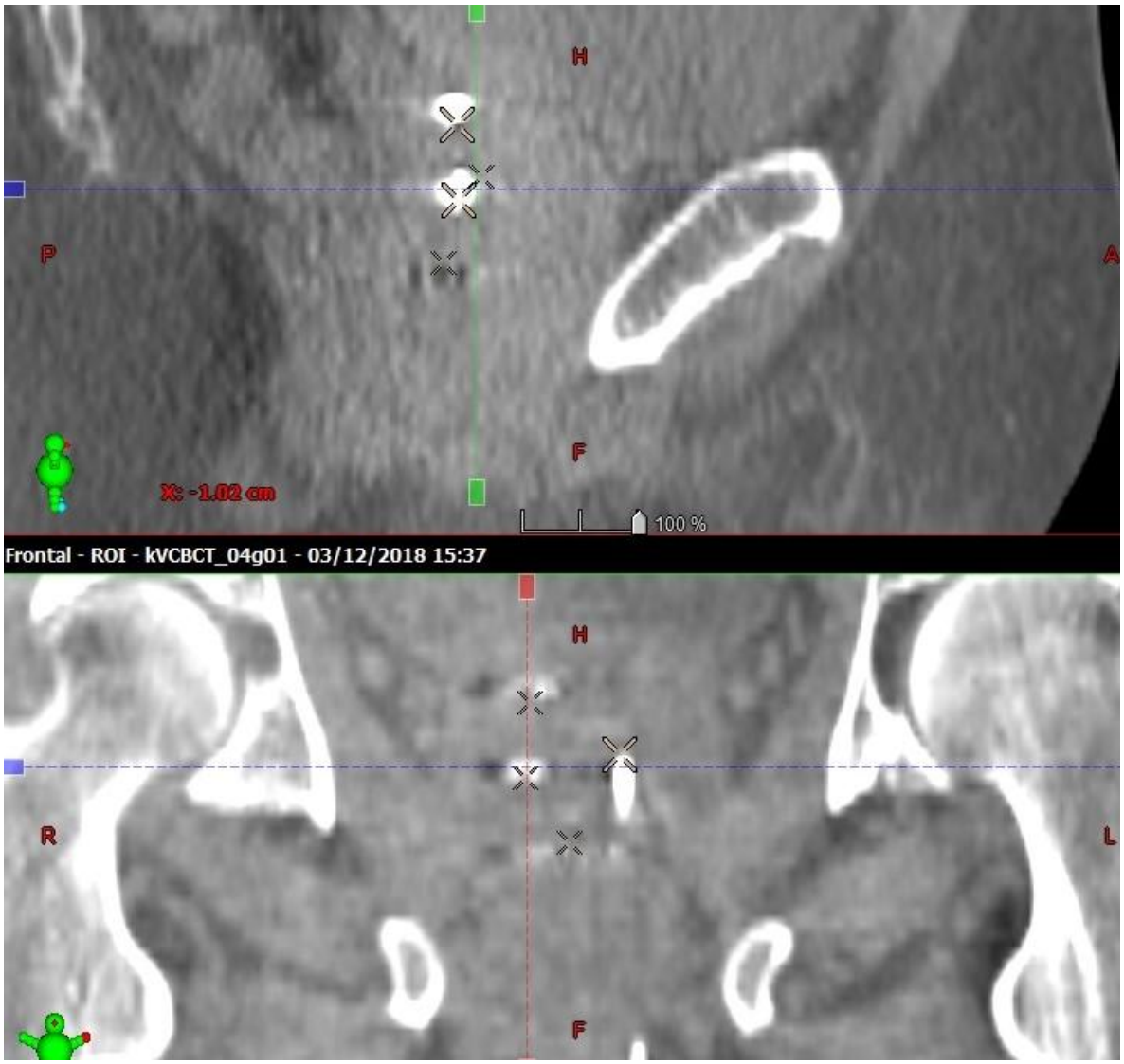


Fig A2(c)

Fig A2*: Example of transmitter and fiducial markers during co-ordinate point placement for a single patient from the study. A2(a) CT planning scan in the sagittal plane showing the tip of the transmitter A2(b) CBCT scan in the sagittal plane showing the tip of the transmitter, at the same point as A2(a). A2(c) CBCT image showing the fiducial markers and the tip of the transmitter during point placement in the Sagittal plane (top image) and coronal plane (bottom image).*

The relevant point co-ordinates for each fraction and each patient in the study were collated within Excel for the transmitter and each of the three fiducial markers. The displacement between the coordinates of each relevant point on the CT planning scan and each CBCT scan was recorded (Dataset A). Additionally, the differences between the pre and post fraction CBCT scans were recorded (Dataset B). Displacements greater than 0.2cm and 0.3cm were highlighted.

Statistical analysis was carried out using both an F-test and a Levene test to analyse the variance of displacement measurements of the RayPilot transmitter compared to the seeds. Both of these tests were applied to the displacement measurements from dataset A and dataset B respectively, comparing the variance of the RayPilot transmitter displacements against the individual displacements of each seed in the x, y and z direction. The F-test assumes the population data is normally distributed, and the Levene test is less sensitive to normality in the source data.

3.4 Results

The position of the transmitter tip and the fiducial markers on the planning CT was used as a reference for identifying the respective displacement from the pre and post-fraction CBCT images (Dataset A). This included 70 data points for the transmitter (2 CBCTs for 5 fractions over 7 patients) and 210 data points for the fiducials (with 3 fiducials in each image). The mean displacement (+/- standard deviation) of the RayPilot transmitter was -0.04cm, +/- 0.1cm (LR), 0.07cm +/- 0.2cm (AP) and 0.16cm +/- 0.5cm (SI). Isolating measurements for each patient (Table A1), all mean displacements were below 0.2cm except P3(LR) 1.2cm,

P4(AP) 0.33cm, P6(AP) 0.3cm and P6(SI) 0.2cm. The mean displacement (+/- standard deviation) of the fiducial markers for all patients was -0.03cm +/- 0.1cm (LR), -0.03cm +/- 0.14cm (AP) and -0.03cm +/- 0.14cm (SI). All of the fiducial mean displacements were below 0.2cm when calculated for each patient individually.

The position of the transmitter tip and the fiducials were analysed comparing the pre and post-fraction CBCT images (Dataset B). The pre-fraction CBCT was used as a reference image and the relevant displacement in the post-CBCT image noted, interpreted as a measure of the intrafraction motion. This dataset included 35 data points for the transmitter and 105 data points for the fiducials. The mean displacement (+/- standard deviation) of the transmitter was 0.02cm, +/- 0.11cm (LR), 0.00cm +/- 0.15cm (AP) & -0.02cm +/- 0.18cm (SI) with mean values for each patient below 0.2cm, except P3(SI) –0.24cm. The mean displacement of the fiducial markers was 0.02cm +/- 0.09cm (LR), -0.03cm +/- 0.13cm (AP) & 0.04cm +/- 0.11cm (SI) and no mean values for individual patients in any direction exceeded 0.2cm.

1. Paper A

		RayPilot			Fiducial Markers (mean)		
		x	***y***	***z***	***x***	***y***	***z***
Patient 1	CT Vs CBCT (cm)	-0.05	-0.08	-0.05	-0.02	-0.02	-0.11
	st dev	*0.05*	*0.08*	*0.29*	*0.08*	*0.10*	*0.21*
	Pre Vs Post CBCT (cm)	0.01	-0.02	0.07	0.02	-0.02	-0.02
	st dev	*0.06*	*0.13*	*0.11*	*0.06*	*0.09*	*0.07*
Patient 2	CT Vs CBCT (cm)	-0.10	0.06	0.02	-0.05	-0.14	-0.08
	st dev	*0.08*	*0.07*	*0.11*	*0.08*	*0.10*	*0.09*
	Pre Vs Post CBCT (cm)	-0.05	-0.06	-0.03	-0.03	-0.06	0.05
	st dev	*0.14*	*0.11*	*0.11*	*0.11*	*0.10*	*0.09*
Patient 3	CT Vs CBCT (cm)	-0.10	0.08	1.20	0.02	-0.05	-0.03
	st dev	*0.14*	*0.10*	*0.50*	*0.18*	*0.13*	*0.12*
	Pre Vs Post CBCT (cm)	-0.07	0.17	-0.24	0.02	0.06	0.03
	st dev	*0.11*	*0.07*	*0.21*	*0.08*	*0.09*	*0.12*
Patient 4	CT Vs CBCT (cm)	-0.06	0.33	-0.10	-0.08	-0.10	0.07
	st dev	*0.05*	*0.12*	*0.10*	*0.10*	*0.13*	*0.17*
	Pre Vs Post CBCT (cm)	-0.02	0.00	-0.10	0.03	-0.13	0.07
	st dev	*0.08*	*0.16*	*0.10*	*0.08*	*0.10*	*0.13*
Patient 5	CT Vs CBCT (cm)	-0.02	-0.11	-0.02	-0.02	0.03	-0.04
	st dev	*0.06*	*0.10*	*0.14*	*0.07*	*0.06*	*0.11*
	Pre Vs Post CBCT (cm)	-0.04	0.06	-0.08	0.01	0.03	0.05
	st dev	*0.08*	*0.13*	*0.11*	*0.07*	*0.06*	*0.08*
Patient 6	CT Vs CBCT (cm)	0.04	0.30	0.20	0.00	-0.08	0.02
	st dev	*0.05*	*0.12*	*0.19*	*0.02*	*0.17*	*0.08*
	Pre Vs Post CBCT (cm)	-0.04	-0.11	0.08	-0.01	-0.03	0.03
	st dev	*0.05*	*0.18*	*0.22*	*0.02*	*0.12*	*0.09*
Patient 7	CT Vs CBCT (cm)	-0.01	-0.11	-0.13	-0.05	0.12	-0.05
	st dev	*0.15*	*0.12*	*0.15*	*0.10*	*0.16*	*0.09*
	Pre Vs Post CBCT (cm)	0.07	-0.02	0.14	0.09	-0.07	0.07
	st dev	*0.16*	*0.16*	*0.15*	*0.09*	*0.21*	*0.12*
All patients	CT Vs CBCT (cm)	-0.04	0.07	0.16	-0.03	-0.03	-0.03
	st dev	*0.10*	*0.20*	*0.50*	*0.10*	*0.14*	*0.14*
	Pre Vs Post CBCT (cm)	-0.02	0.00	-0.02	0.02	-0.03	0.04
	st dev	*0.11*	*0.15*	*0.18*	*0.09*	*0.13*	*0.11*

Table A1: *Table of the mean displacements in the x (LR), y (AP) and z (SI) directions for Dataset A (CT Vs CBCT) and Dataset B (Pre Vs Post CBCT) for each patient and in total.*

1. Paper A

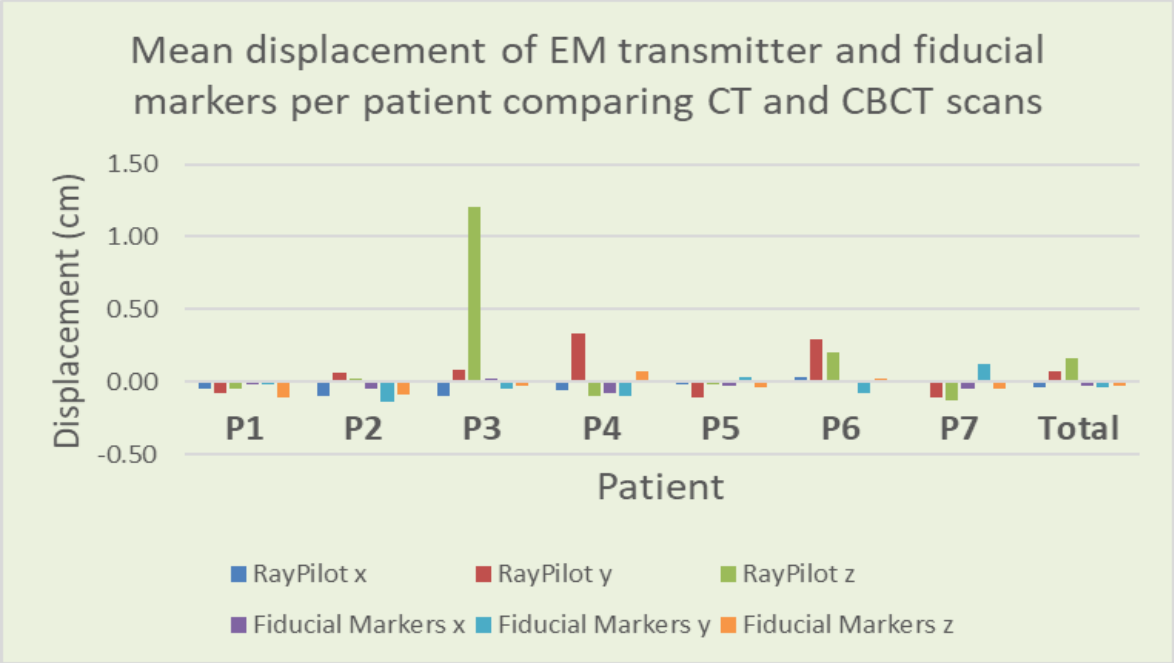


Fig A3(a)

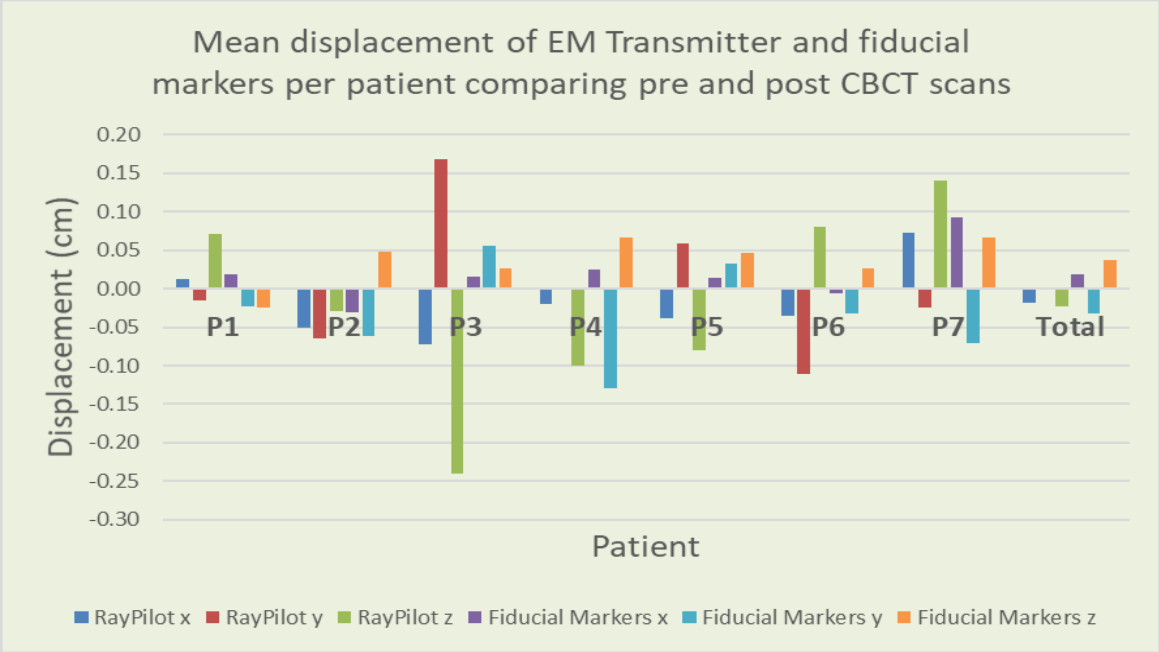


Fig A3(b)

Fig A3*: Graphs of the mean displacement for each patient of the transmitter and the fiducial markers in the x (LR), y (AP) & z (SI) directions. A3(a) Displacements of the points using the planning CT scan as a reference against the position in the pre and post CBCT scans (Dataset A). A3(b) Displacements of the points using the pre-treatment CBCT scans as a reference against the position in the post CBCT scans (Dataset B).*

1. Paper A

		RayPilot			Fiducial Markers (mean)		
		x	***y***	***z***	***x***	***y***	***z***
Percentage of displacements over 0.2cm	***CT Vs CBCT***	9.7%	31.9%	50.0%	10.2%	13.9%	19.4%
	Pre Vs Post CBCT	7.9%	15.8%	42.1%	3.5%	14.9%	14.0%
Percentage of displacements over 0.3cm	***CT Vs CBCT***	0.0%	5.6%	29.2%	0.5%	3.2%	9.3%
	Pre Vs Post CBCT	0.0%	0.0%	10.5%	0.0%	0.0%	1.8%

Table A2: *Table of the percentage of displacements of the RayPilot transmitter and fiducial markers measured to be exceeding 0.2cm and 0.3cm for Dataset A (CT Vs CBCT) and Dataset B (Pre Vs Post CBCT) in the x (LR), y (AP) and z (SI) directions*

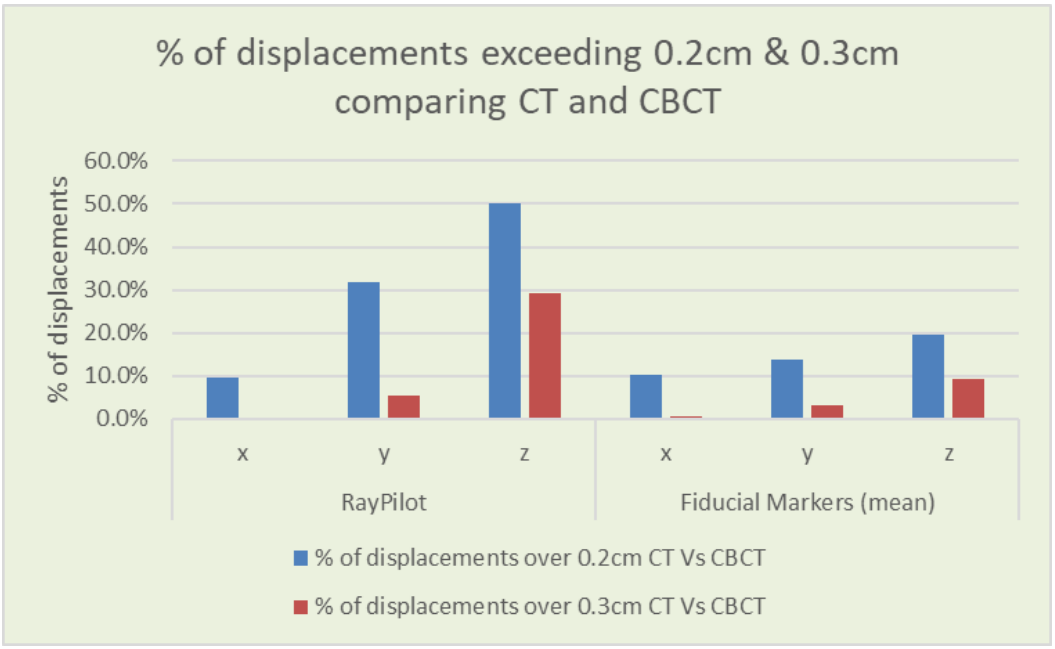


Fig A5(a)

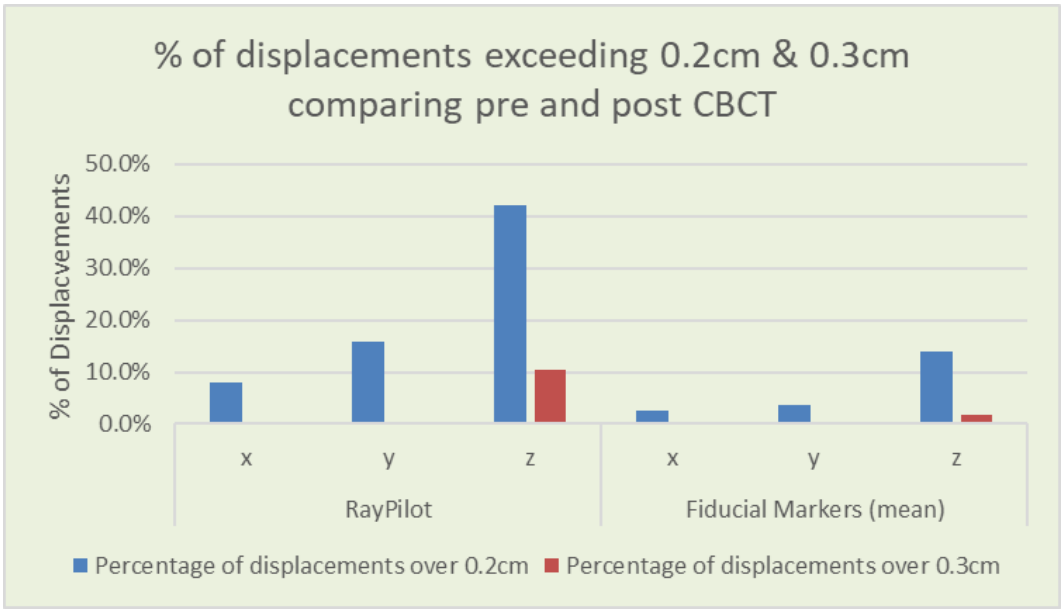


Fig A5(b)

Fig A5*: Graphs showing the percentage of measured displacements exceeding 0.2cm & 0.3cm in the x (LR), y(AP) and z(SI) direction. A5(a) Percentage of displacements exceeding 0.2cm & 0.3cm comparing planning CT scan and the pre and post CBCT scans. A5(b) Percentage of displacements exceeding 0.2cm & 0.3cm comparing pre and post CBCT scans.*

Statistical analysis was carried out by performing an F-test and a Levene test comparing the displacement data of the RayPilot transmitter and the seed displacements to test if there was a statistically significant difference between the variances of each data set. These were applied separately for the displacements in the x (L/R), y (A/P) and z (S/I) direction for Dataset A (results shown in table A3) and Dataset B (results shown in table A4) testing the hypothesis Ho, that the variances of the respective displacement data were equal. The threshold for the p value below which the hypothesis Ho would be rejected was set as p<= 0.05.

	F-Test		Levene Test	
	Ho	**p value**	**Ho**	**p value**
x	accept	0.801	accept	0.538
y	reject	0.001	reject	0.001
z	reject	0	reject	1.241E-10

Table A3*: F-test and Levene test results for dataset A. Tests comparing the variance of the measured displacement of the RayPilot transmitter in the x (L/R), y (A/P) and z (S/I) direction against the displacement of the individual seeds. This was testing the hypothesis Ho that the variances are equal.*

	F-Test		Levene Test	
	Ho	**p value**	**Ho**	**p value**
x	accept	0.073	accept	0.494
y	accept	0.200	accept	0.078
z	reject	0.000	reject	0.001

Table A4*: F-test and Levene test results for dataset B. Tests comparing the variance of the measured displacement of the RayPilot transmitter in the x (L/R), y (A/P) and z (S/I) direction against the displacement of the individual seeds. This was testing the hypothesis Ho that the variances are equal.*

For Dataset A, Ho was accepted for measurements in the x (L/R) direction, and rejected for the y (A/P) and z (S/I) directions. This means the variances in the x (L/R) direction were calculated to be equal and a statistically significant difference in the variances in the y (A/P) and z (S/I) direction was found. For dataset B, Ho was accepted in the x (L/R) and y (A/P) direction and rejected in the z (S/I) direction, which means a statistically significant difference in the variance in the z (S/I) direction was found. These findings were consistent for both the F-test and the Levene test. The p values for each calculation give an indication of the strength of the result, with a threshold of p<=0.05 indicating the hypothesis was rejected and with a lower p value giving increased confidence that a rejected hypothesis was true.

3.5 Discussion

In dataset A, the mean displacement of the transmitter was within 0.2cm for all data points except P3(SI), P4(AP) & P6(AP),(SI) (Fig A3). It was found in these results that both the magnitude of displacements and the percentage of displacements exceeding 0.2cm and 0.3cm respectively were consistently lower for the fiducial markers than the RayPilot transmitter.

In dataset A, displacements were most commonly noted in the SI direction, with measurements of 0.2cm or greater recorded for 50% of data points for the transmitter, whilst for the fiducials this was 19% (Fig A5). SI displacements of 0.3cm or greater accounted for 29.2% of the transmitter measurements and 9.3% for the fiducials. Theoretically both systems should remain in situ, and as such relative displacements should be comparable. These results may be pointing to differences in the relative position between the two systems. The fiducials are used for patient positioning, therefore closer correlation between

their position and the reference planning CT would be expected if there was a relative change in position between the systems. A 0.2cm imaging action level was in place during treatment, whereby target displacement below this value would not require correction. Therefore, the displacement values recorded in Dataset A may include any inherent displacement of up to 0.2cm that was uncorrected as per protocol.

Dataset A included 29% of measurements of the transmitter of 0.3cm or greater, which was greater than the number of fiducial measurements of this magnitude (9.3%). It would be useful in future studies to record the RayPilot system displacement when the kV imaging was being acquired for a direct comparison of the interpretation of the same anatomical conditions of the two systems.

The transmitter measurements for Dataset B showed that 42.1% of the SI displacements were 0.2cm or greater, with 10.5% of measurements 0.3cm or greater. The fiducial measurements in the SI direction had 14% of displacements measured 0.2cm or greater and 1.8% at 0.3cm or greater. Dataset B includes the difference in values between the pre and post-fraction CBCT images. This would be a good indicator for identifying intrafraction motion as the patient should be in their treated position for both. More transmitter measurements exceeded each threshold than for the fiducials. This difference between the systems may indicate that the displacements are not primarily due to intrafraction motion, but differences in the stability of the fiducials and the transmitter.

A larger number of displacements exceeded 0.2cm and 0.3cm in the SI direction than any other. This was consistent with results presented by Braide et al. (A14) who investigated stability of the RayPilot transmitter in 10 patients, and concluded that displacements in the SI direction were most common, noting that this was along the track where the device was inserted and may have influenced this. As this is the direction of the transmitter's insertion track this may have contributed to the positional instability. In Dataset A, the mean

displacement of the RayPilot transmitter for all patients in the SI direction was 0.16cm, with a standard deviation of +/- 0.5cm highlighting the degree of variability in the dataset. This is contrasted with the equivalent mean displacement of the fiducials in dataset A for all patients of 0.03 with a standard deviation of +/- 0.14cm. This data shows some evidence that the RayPilot transmitter is less stable than the fiducial markers in the S/I direction. This agrees with the conclusions from Braide et al. (A14) but a larger sample size would strengthen this hypothesis.

Analysis showed a statistically significant difference between the variances in the y & z direction for Dataset A and in the z direction for Dataset B. Although the F-test relies on the source data being drawn from a normal distribution, the Levene test is less sensitive to normality. The analysis from both tests was consistent, and indeed the low p values calculated for the measurements in the z direction for both data sets provide confidence in these results. With the seeds being used as the primary imaging tool for the treatments, this difference in variances highlights that the RayPilot transmitter relative position is not consistent to the seeds in they y & z direction for Dataset A and the z direction for Dataset B. For Dataset A this may be inferring interfraction variability of the transmitter, however it is interesting that this is also apparent in Dataset B which compares the position of the device in the pre and post CBCT images. This would therefore be inferring further instability of the device over the duration of the treatment. This statistical analysis provided further evidence from this study that the transmitter position may be unstable when benchmarked against the seeds. The patient numbers included in this study were low however, and therefore for stronger evidence base a larger cohort study would be required.

There are some limitations with the data collection in this study. When the measurement points were determined in Eclipse, this was done using the offline review module. The resolution of the available 2D images for point placement in each plane were 0.09cm LR & AP and 0.1cm SI. There was also a degree of subjectivity determining the point position on

the image. The fiducials for example were visible across more than one image in each plane and as such estimating the centre may have introduced some error to the results. Although the tip of the RayPilot casing does not correspond to the active measurement point of the transmitter, this was a more easily localised point and a more consistent point for placement and used to record the measurements. However, there may have been some subjectivity over the most position in the images of this point for some measurements.

The mean of the fiducials was calculated for each fraction based on the mean of the combined displacement of all three markers. This method was used as the patient position was determined using all three markers, whilst the RayPilot system relies on a single point of reference. However, it was not clear in the matching software how representative the mean position of all three markers would be to the calculated target position. The method of analysis in this study therefore may not correlate exactly with the kV orthogonal imaging system, however as it is based on the physical position of the seeds used in the match it gives a reasonable estimation for this. Each seed match was visually inspected by the radiographers who would investigate any outliers.

Patient P3 dislodged their transmitter by accidently pulling on the protruding wire before their first fraction was delivered. This was identified in the study as a disadvantage of the system, with the patients having their transmitter inserted two weeks before treatment there was an increased risk of this occurring. This risk could be reduced in future studies by reducing the required contouring and planning time. The tracking was continued with the reference marker for the RayPilot transmitter reset in eclipse using its position in the CBCT scan on fraction 1. The system is looking to track relative displacements, so this change should in theory be sufficient to continue and the relative displacements would remain stable throughout the treatment. However, the SI displacements of the transmitter in dataset A ranged from 0.8cm-1.7cm over all five fractions, and for the fiducial markers this range was -0.2cm to 0.2cm. In dataset B the SI displacement ranged from -0.5cm to 0.0cm, which may

indicate intrafraction motion of the transmitter was present relative to the prostate. The stability of the transmitter may have been compromised when dislodged as it is designed to be in a fixed position during treatment. However, the range of the SI fiducial displacements in dataset B was -0.2cm to 0.24cm which is similar to the transmitter, so this may be pointing to anatomical changes rather than instability. This could be investigated in further studies.

The electrical wire connector is left protruding from the patient to be connected to the table top array. This is inserted before the planning CT, and is left in situ until after the last fraction. As the wire is loose, it could be accidently moved by the patient and this was identified as a risk to the positional stability of the transmitter. The sample size in this study was not be large enough to draw strong conclusions around the frequency of this occurring, or indeed the impact on the position or stability of the transmitter. Future studies with a larger patient cohort could be used to look at this in more depth. It may be that after an adverse event as seen here, a modified imaging protocol is required.

In dataset A, the displacements were measured against the reference planning CT for both the pre and post-fraction CBCTS, giving two measurements per fraction. This method gave a representation of the treatment phase as a whole, however it does provide additional data points for the same number of fractions so comparisons with other studies should be mindful of this. Splitting the data to analyse the pre and post CBCT images separately would be of interest in future studies.

A technical fault within the couch-top array on P4 before fraction 3 prevented any further measurements from the transmitter for this patient. As the transmitter was still in situ and this study was focussed on its physical position, all the data for this patient was retained for this study. There may have been potential unconscious bias by the radiographers by not considering the position of the transmitter on the CBCT scans for this patient.

3.6 Conclusions

These initial results show that the RayPilot transmitter can be identified on CBCT imaging during Prostate SBRT and tested alongside other imaging modalities. The positional stability of the device when benchmarked against fiducial markers was variable. In order to understand the differences between the imaging modalities, some synchronicity between the measurements at the time of recording would be useful. Further work would be required to verify the RayPilot device as a stand-alone modality for SBRT.

3.7 Ethical approval

Ethical approval for this work to be presented was granted through the PRINToUT clinical trial ethical approval application.

3.8 References

(A1) Cancer Research UK. *Prostate cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer [accessed 01/11/20]

(A2) Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol.* 2016;17(8):1047–60. Available from: https://dx.doi.org/10.1016/S1470-2045(16)30102-4

(A3) M. Ritter, J. Forman, P. Kupelian, C. Lawton, and D. Petereit, Hypofractionation for prostate cancer, *Cancer J*. vol. 15, no. 1, pp. 321–329, 2009 Available from

1. Paper A

https://dx.doi.org/10.21037/tau.2017.12.07

(A4) Y. Alayed et al., Two Stereotactic ablative radiotherapy treatments for localized prostate cancer (2STAR): Results from a prospective clinical trial, *Radiother Oncol*, vol. 135, pp. 86–90, 2019, Available from: https://dx.doi.org/10.1016/j.radonc.2019.03.002

(A5) Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531–43. Available from: https://dx.doi.org/10.1016/S1470-2045(19)30569-8

(A6) A. Widmark, A. Gunnlaugsson, L. Beckman, C. Thellenberg-Karlsson, M. Hoyer, M. Lagerlund et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial, *Lancet*, vol. 394, no. 10196, pp. 385–395, 2019, Available from: https://dx.doi.org/10.1016/S0140-6736(19)31131-6

(A7) J. Murray et al., A randomised assessment of image guided radiotherapy within a phase 3 trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer *Radiother Oncol,* vol. 142, pp. 62–71, 2020, Available from https://dx.doi.org/10.1016/j.radonc.2019.10.017

(A8) A. G. M. O'neill, S. Jain, A. R. Hounsell, and J. M. O'sullivan, Fiducial marker guided prostate radiotherapy: A review, *Br J Radiol* vol. 89, no. 1068, pp. 1–18, 2016, Available from: https://dx.doi.org/10.1259/bjr.20160296

(A9) S Hossain, P. Xia, C. Chuang, L. Verhey, A. Gottschalk, G. Mu, L. Ma, Simulated real

time image guided intrafraction tracking-delivery for hypofractionated prostate IMRT, *Med Phys*, vol. 35, no. 9, pp. 4041–4048, 2008 Available from: https://dx.doi.org10.1118/1.2968333

(A10) Lovelock DM, Messineo AP, Cox BW, Kollmeier MA, Zelefsky MJ. Continuous monitoring and intrafraction target position correction during treatment improves target coverage for patients undergoing SBRT prostate therapy *Int. J. Radiat. Oncol. Biol. Phys.* 2015;91(3):588–94. Available from: https://dx.doi.org/10.1016/j.ijrobp.2014.10.049

(A11) S. Das, T. Liu, A Jani, P. Rossi, J. Shelton, Z. Shi, M. Khan, Comparison of image-guided radiotherapy technologies for prostate cancer, *Am. J. Clin. Oncol*, vol. 37, no. 6, pp. 616–623, 2014, Available from: https://dx.doi.org/10.1097/COC.0b013e31827e4eb9

(A12) Varian Medical Systems *Radiotherapy products* Available at: https://www.varian.com/en-gb/products/radiotherapy [accessed 06/11/20]

(A13) O. Holmes, J. Gratton, J. Szanto, E. Vandervoort, J. Doody, E. Henderson et al. Reducing errors in prostate tracking with an improved fiducial implantation protocol for CyberKnife based stereotactic body radiotherapy (SBRT), *J Radiosurg SBRT*, vol. 5, no. 3, pp. 217–227, 2018.

(A14) Braide K, Lindencrona U, Welinder K, Götstedt J, Ståhl I, Pettersson N, et al. Clinical feasibility and positional stability of an implanted wired transmitter in a novel electromagnetic positioning system for prostate cancer radiotherapy *Radiother Oncol.* 2018;128(2):336–42. Available from: https://doi.org/10.1016/j.radonc.2018.05.031

(A15) McLaren D. Using breath analysis to PRedIct Normal TissUe and Tumour response during prostate cancer SBRT. Version 1.0 May 2018, IRAS Number: 240335

4. Paper B: Target Journal - International Journal of Radiation Oncology, Biology, Physics

Analysis of the intrafractional motion of the prostate during SBRT using an EM Transmitter

Authors: Michael Trainer[1], William H Nailon[1,3], Linda J Carruthers[1], Susan Adamson[4] Mike Kirby[2]

[1]Department of Oncology Physics, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK

[2]Directorate of Radiotherapy, Liverpool University, Liverpool, UK

[3]School of Engineering, The University of Edinburgh, Edinburgh, UK

[4]Department of Radiotherapy, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK

2. Paper B

4.1 Abstract

Purpose/Objectives: Intra-fraction motion during hypofractionated radiotherapy can lead to clinically significant differences between planned and delivered dose to the target and organs at risk. The purpose of this study was to establish the efficacy of RayPilot for real-time positional verification in prostate SBRT and to assess target displacement.

Materials/Methods: The RayPilot tracking system uses a transmitter inserted into the prostate which is detected by a table-top array containing antennae. This study included 7 prostate cancer patients who had the RayPilot device inserted and were treated with SBRT (36.25Gy in 5#). The primary positional verification imaging method was kV orthogonal pairs matched to fiducial markers with additional CBCTs. In parallel, changes in the transmitter position during treatment were monitored by the RayPilot system with the beam halted manually if the displacement was more than 0.2cm. The RayPilot software records the position of the device every second and its displacement from a reference position is calculated. This positional data was analysed in Excel, where the maximum, minimum and mean position of the device along with the % of displacements exceeding 0.1, 0.2, 0.3 & 0.5cm were recorded.

Results: Of the 35 fractions in the study, the EM transmitter position was recorded successfully in all except #3, 4 & 5 for patient 4 due to technical issues. Over the whole study, displacements measured every second exceeded 0.2cm for 2.64%, 2.18% and 5.10% of all measurements in the lateral, longitudinal and vertical directions respectively. The mean displacement did not exceed 0.03cm

Conclusions: RayPilot is a viable means for tracking the prostate during SBRT. The position of the target was within 0.2cm for 94.9% of the patient's treatment time. Synchronising the software with the linac would enable data collection only while the

treatment beam is on, thus strengthening the validity of the data. Further work is planned to assess the efficacy of RayPilot with respect to current X-ray based IGRT methods and determine if it could be used as the primary monitoring device.

4.2 Introduction

Prostate cancer remains the most common cancer for males in the UK, accounting for 26% of all new male cancer diagnoses in 2017 (B1). Of these patients, 30% received radiotherapy as part of their primary treatment. Radiotherapy treatments can be highly conformal, therefore the accurate delivery of the dose to the target is essential for the treatment to be as effective as possible. Discrepancies between the planned and delivered position can impact the dosimetry of the treatment.

Interfraction motion is where anatomical changes occur between fractions and can often be mitigated by established on-board imaging techniques (B2). These include cone-beam CT (CBCT), and 2D kV orthogonal imaging aligned to fiducial markers in the prostate. Intrafraction motion occurs during the treatment delivery and there have been studies where this was identified. For example, prostate motion was been noted by Mah et al. (B3), where imaging was carried out on 42 patients using CINE MRI over 9 minutes, which they saw as analogous to a single fraction treatment time. They reported that displacements were generally small, with the largest mean displacement being recorded as 0.02cm in the a/p direction and only 3% of motions being greater than 1.0cm.

Hypofractionation in prostate radiotherapy is where a higher dose per fraction than the standard regime is delivered. The two primary advantages of this are the lower alpha/beta ratio of prostate cancer lending itself to a greater sensitivity to fraction size (B4) and the potential for resource saving by reducing the number of fractions for a high-volume site

group such as prostate. This can involve moderately hypofractionated treatments (2.4-3.4Gy per fraction), which are becoming more commonly used such as in the CHIIP trial, which has published favourable results (B5). Fractionations with at least 5 Gy per fraction are classified as ultra-hypofractionated or alternatively prostate SBRT (B6). Currently there are no published large scale randomised clinical trials that evaluate prostate SBRT but two recent trials have published early results. HYPO-RT-PC was a large phase 3 trial where 42.7Gy in 7 fractions was delivered. Widmark et al. reported that this technique was non-inferior to their standard arm of 78Gy in 39 fractions for outcomes, however they did see higher early toxicities in the hypofractionated arm (B7). Brand et al. (B8) reported acute toxicity 12 weeks after radiotherapy for the PACE B trial was published for their regime of 36.25Gy in five fractions. They reported that acute toxicity in their hypo fractionated regime is not greater than for the patients receiving standard fractionation (78Gy/39#) or a moderately hypofractionated (62Gy/20#) fractionation in the same trial.

Due to the higher dose per fraction for SBRT, the impact on the plan dosimetry from any geometric displacements of the target during individual fractions can be greater. Lovelock et al. reported that intrafraction motion would lead to 10% of patients in their study having a target D95 less than the required 90% without positional correction (B9). On-treatment imaging such as CBCT and 2D planar kV imaging can verify that the target is positioned correctly before the fraction is delivered reducing the impact of any interfraction motion, however this will not provide positional information during the beam delivery.

Techniques to track the target position in real-time during treatment are available and have been utilised successfully within prostate radiotherapy and SBRT. The Calypso motion management system (B10) involves three electronic transponders, which are implanted into the prostate and the position of these are tracked during treatment. Lovelock et al. investigated the use of this system for prostate SBRT and found the target displacement

exceeding their 0.2cm imaging threshold for one-third of the fractions delivered, with the beam delivery being halted in each instance (B9).

The Cyberknife system uses a robotic radiosurgery system and dynamic image guidance utilising kV imaging to track the position of fiducial markers in real-time during treatment (B11). A study by Choi et al. (B12) investigating Cyberknife tracking during prostate SBRT showed that for 21% of patients, the target volume was displaced by more than 0.1cm with no displacements exceeding 0.2cm.

This study aimed to examine the efficacy of the RayPilot system as a real-time imaging tracker verifying target displacement during prostate SBRT delivery alongside locally established imaging solutions. This involved assessment of the technical aspects of the tracking capability of the system, interpretation of the measured data and how it integrated into the workflow for this type of treatment.

4.3 Methods and Materials

This study included seven prostate patients (P1-7) enrolled in the PRINToUT (B13) trial between November 2018 and December 2019. PRINToUT is a locally run trial, aiming to establish biomarkers for tumour response and normal tissue effects from high dose per fraction prostate radiotherapy. Radiotherapy causes the release of volatile organic compounds, which were measured in breath samples immediately after each fraction in the trial. Analysis will investigate if a statistically significant correlation between the biomarker data and patient outcomes exists. The PRINToUT trial aligned to the clinical and treatment protocol of the PACE trial (B14).

The age range of the patients was 53-81 (mean 70.7) with five patients having a Gleason score of 6 and two having a score of 7. Six of the patients were staged at T2 and the remaining patient was T1. PSA was measured at the time of participation, with a range of 6-13 ng/ml.

Tumour tracking was carried out using the RayPilot real-time positional verification system (B15). This consists of a small electromagnetic transmitter, which connects via a couch-top sensor plate housing 16 antennae. Geometric positioning information of the transmitter is collected 30 times per second using the antennae and interpreted by a data processing unit to calculate differences from a reference position. The connectivity to the linac does not facilitate automatically triggering and halting of the beam during treatment, but this can be performed manually based on the readout displacements.

Fig B1: *Image of the set up for the RayPilot system on a linac. The patient is positioned on the couchtop sensor plate which is connected by cable to the transmitter.*

Prior to the planning CT, the patient received a multi-parametric prostate MRI scan. Following this, the RayPilot transmitter was inserted transperineally into the prostate. This was carried out under local anaesthetic by a radiologist, guided by ultrasound imaging. The transmitter remained in situ until after the last fraction was completed. The planning CT scan

was with a Philips wide bore scanner using 0.1cm slices. The MR and the CT images were registered using rigid mapping in the Eclipse treatment planning system (v13.6) (B10) and used by the clinical oncologist for delineation of the prostate. The CTV was defined as the prostate for low-risk patients, and for intermediate risk the CTV was defined as the prostate plus 1cm of seminal vesicles. The CTV was expanded by 0.5cm sup, inf, right, left & ant and 0.3cm post to create the PTV.

The treatment protocol aimed to deliver 36.25Gy in 5# to the prostate on alternate days with OAR tolerance doses taken from the PACE trial (Appendix 2). The treatment plans aimed to deliver at least 95% of the prescribed dose to the PTV, with the CTV boosted to receive at least 100%. Each patient had a treatment plan created using the Eclipse treatment planning system v13.6 (B10) with the final dose calculation performed with the AAA algorithm (v10.0.28). The treatment was planned as VMAT, delivering the dose in 3 full rotation arcs.

The imaging protocol aligned to the PACE protocol for centres with no real-time tracking, with the RayPilot system (B16) acting as a supplementary monitoring tool. 2D kV orthogonal imaging, matching to three gold seeds inserted into the prostate was the primary imaging method for patient positioning, with images taken before treatment and between each arc. If the displacement of the fiducial seeds was 0.2cm or above in any direction, the patient position would be corrected. CBCT images were taken directly before and after each fraction was delivered to verify the anatomy and the position of the transmitter was consistent with the planning scan.

2. Paper B

The RayPilot software provided real-time measurement of the displacement of the transmitter in the longitudinal, lateral and vertical directions from a reference position. The pitch and the yaw are also displayed but this was not considered in this study. The reference position is taken from a marker, manually positioned in Eclipse. The displacement recorded in the software during treatment would be relative to this reference position. Hence, a “zero” reading would mean that the device was in the same position as in the CT planning image. Therefore, some patients may begin their treatment with a displacement greater than zero. When the patient was connected to the software but still being positioned correctly, measurements were recorded but labelled as “set-up” in the software. After the first orthogonal kV image pair, the patient would be in the correct treatment position, the software would start to label recorded measurements as “treatment”. The measurements labelled “treatment” didn’t correspond to the beam delivery and would therefore include data collected if the patient moved after this time or required to be taken off the treatment couch. The reading was monitored during the fraction by a radiographer. If the displacement was 0.2cm or greater, the beam was interrupted manually and additional 2D kV orthogonal images taken to re-position the patient before resumption of the beam.

Positional readouts every second for all fractions were stored in the software, and these were exported into an Excel spreadsheet for analysis. The readouts were analysed for each patient, with filters being used to exclude measurements labelled as “set-up” and include those labelled as “treatment”. The maximum, minimum and mean displacement for each fraction and as a total for each patient were calculated along with the percentage of readings recorded with a displacement exceeding 0.1cm, 0.2cm, 0.3cm & 0.5cm.

Readings that were identified as anomalies such as those with large displacements during re-set up, were removed for the final analysis. This was carried out with advice from a treatment radiographer for clinical context.

4.4 Results

The measured data for each patient and each fraction was collated in Excel for analysis. A summary of these finding is presented in Table B1, with the overall maximum, minimum and mean displacement measured for all patients and all fraction. The percentage of measurements exceeding 0.1cm, 0.2cm, 0.3cm and 0.5cm were also calculated. P4's measurements were only recorded for fractions 1 and 2 due to technical issues, so this patient was excluded from any overall totals. The number of data points labelled as "treatment" per fraction was used to determine time taken for each fraction. This ranged from 369 seconds to 3500 seconds (mean 1155 seconds, standard deviation 640 seconds).

	LR	SI	AP
Min (cm)	-0.38	-0.47	-0.50
Max (cm)	0.29	0.42	0.59
Mean (cm)	0.02		
Standard		0.01	0.01
Deviation	0.05		
(cm)		0.06	0.07
% outside			
0.1cm	15.9%	11.0%	25.2%

% outside 0.2cm	2.6%	2.2%	5.1%
% outside 0.3cm	0.1%	0.3%	1.4%
% outside 0.5cm	0.0%	0.0%	0.0%

Table B1: *Summary table of displacement measurements recorded in the RayPilot software, Included is the overall minimum, maximum and mean displacement and the percentage of data points recorded to be outside 0.1cm, 0.2cm, 0,3cm and 0.5cm respectively*

Patient	Mean transmitter displacement (standard deviation) - cm		
	Left / Right	Sup / Inf	Ant / Post
P1	0.04 (0.06)	-0.02 (0.07)	0.01 (0.12)
P2	0.04 (0.06)	-0.01 (0.05)	0.03 (0.05)
P3	0.01 (0.06)	0.01 (0.07)	0.04 (0.08)
P5	0.01 (0.03)	-0.03 (0.07)	0.02 (0.04)
P6	0.00 (0.05)	0.01 (0.08)	0.02 (0.1)
P7	-0.01 (0.12)	0.03 (0.08)	-0.06 (0.15)
Total	0.02 (0.05)	0.01 (0.06)	0.01 (0.07)

Table B2*: The mean transmitter displacement and standard deviation (cm) measured per patient.*

Fraction	Mean transmitter displacement (standard deviation) - cm		
	Left / Right	Sup / Inf	Ant / Post
Fraction 1	0.03 (0.05)	0.01 (0.04)	0.04 (0.07)
Fraction 2	0.00 (0.04)	0.00 (0.04)	0.02 (0.07)

Fraction 3	0.03 (0.06)	0.01 (0.08)	0.02 (0.08)
Fraction 4	0.04 (0.07)	0.02 (0.06)	-0.01 (0.08)
Fraction 5	0.01 (0.05)	-0.01 (0.05)	0.01 (0.07)

Table B3: *The mean transmitter displacement and standard deviation (cm) measured per fraction.*

Patient	Percentage of displacement data points exceeding 0.2cm (%)		
	Left / Right	Sup / Inf	Ant / Post
P1	1.1	3.0	6.4
P2	1.9	0.1	0.1
P3	0.0	0.4	5.1
P5	0.0	4.8	0.0
P6	0.3	4.3	5
P7	11.1	4.9	17.8
Total	3	2	5

Table B4: *The percentage of displacement measurement points exceeding 0.2cm per patient*

Fraction	Mean transmitter displacement (standard deviation) - cm		
	Left / Right	Sup / Inf	Ant / Post
Fraction 1	0.01	0.01	0.06
Fraction 2	0.01	0.00	0.02
Fraction 3	2.41	6.45	2.87
Fraction 4	6.11	1.53	9.39
Fraction 5	2.08	1.91	4.79

Table B5: *The percentage of displacement measurement points exceeding 0.2cm per fraction*

2. Paper B

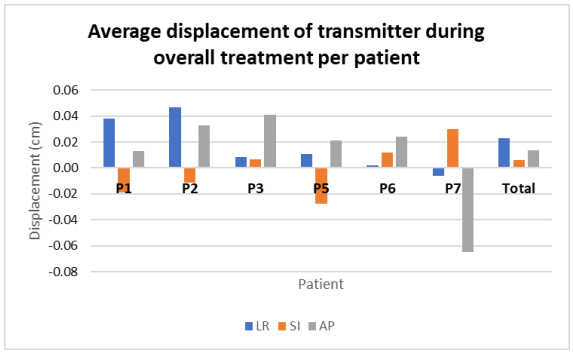


Fig B2(a)

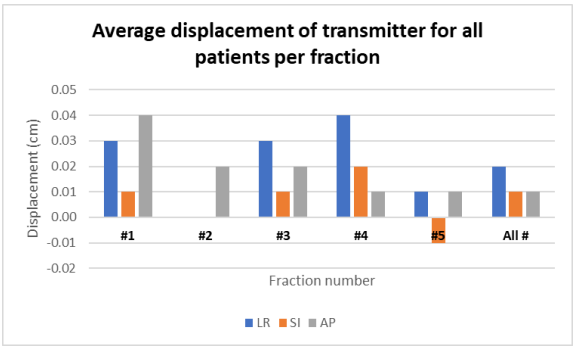


Fig B2(b)

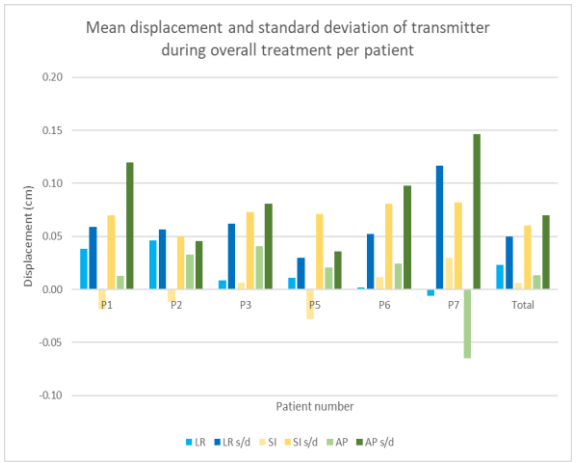


Fig B2(c)

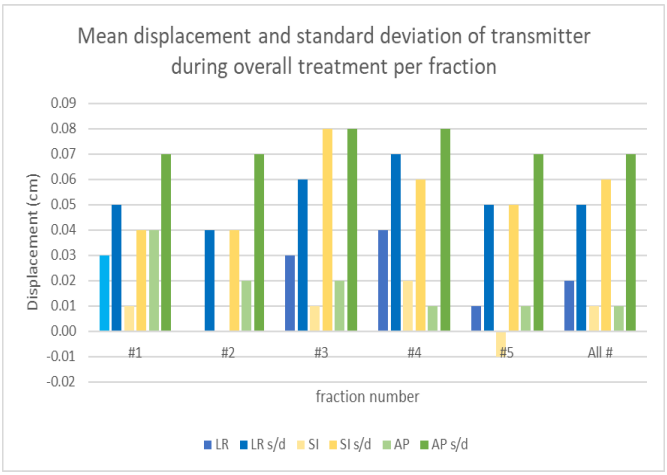


Fig B2(d)

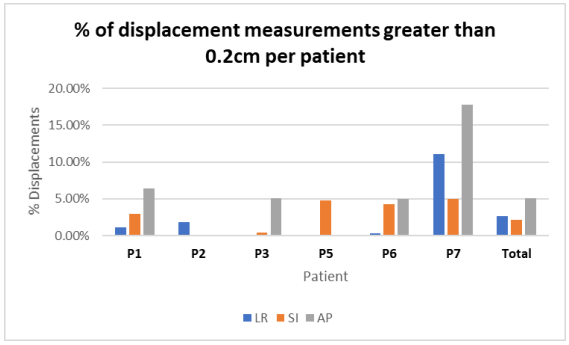


Fig B2(e)

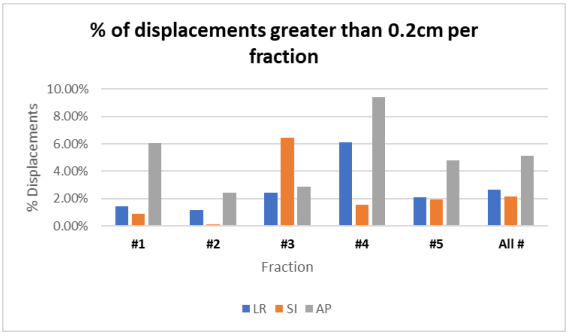


Fig B2(f)

Fig B2: *Graphs summarising the analysis of the RayPilot readout data recorded for 7 patients. The mean displacement of the transmitter for each patient over all fractions (Fig B2a) and for each fraction for all patients (Fig B2b) and with standard deviations (Fig B2c & Fig B2d). The percentage of displacements exceeding 0.2cm during the treatment phase is presented for each patient (Fig B2e) and for each fraction (Fig B2f).*

2. Paper B

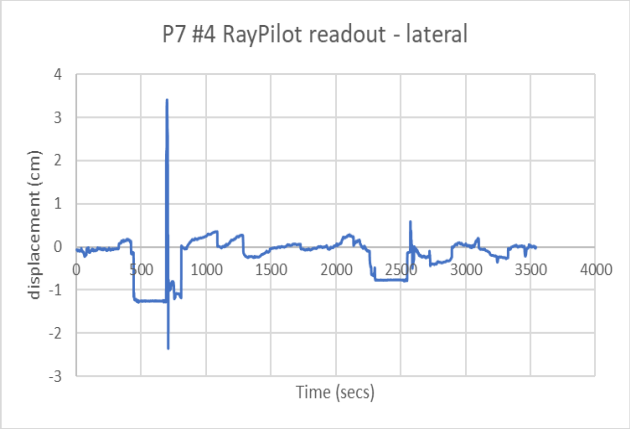


Fig B3(a)

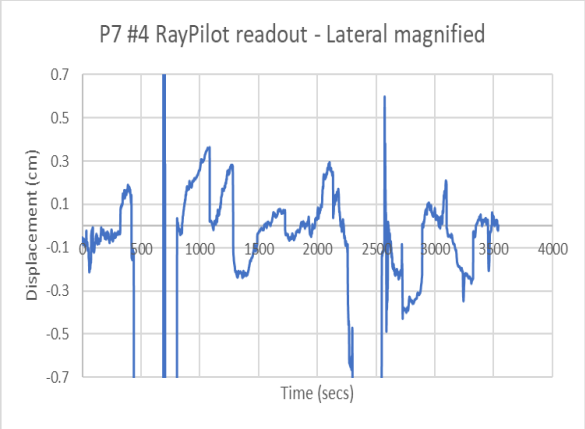


Fig B3(d)

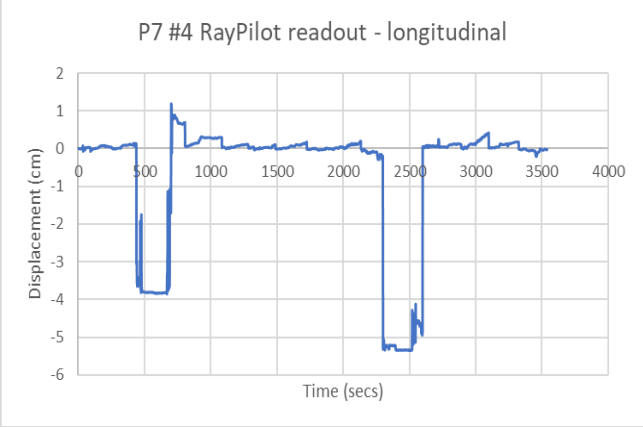


Fig B3(b)

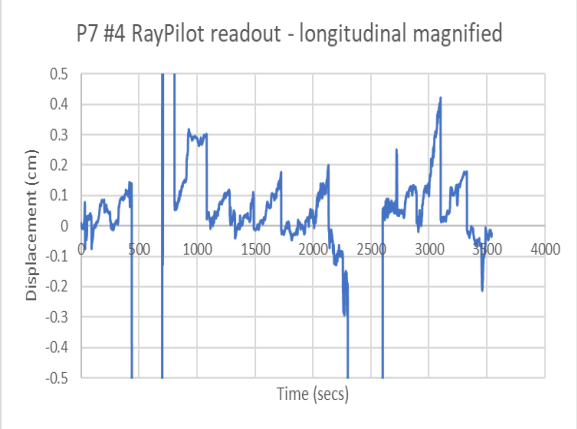


Fig B3(e)

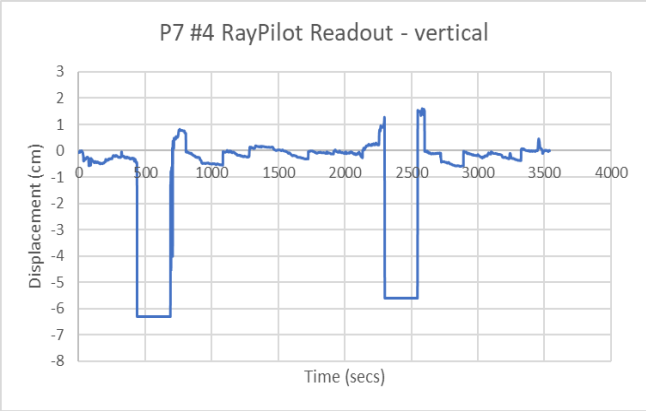


Fig B3(c)

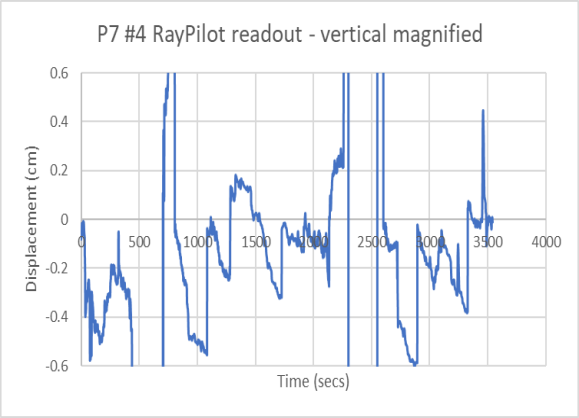


Fig B3(f)

Fig B4: *Example of RayPilot readout data measured for P7 during fraction 4. Fig B3 a b & c display the full measured readout for this fraction in the lateral (LR), longitudinal (SI) and vertical (AP) directions. Fig B3 d, e, & f show the same data with the axis scaled to magnify some of the detail.*

2. Paper B

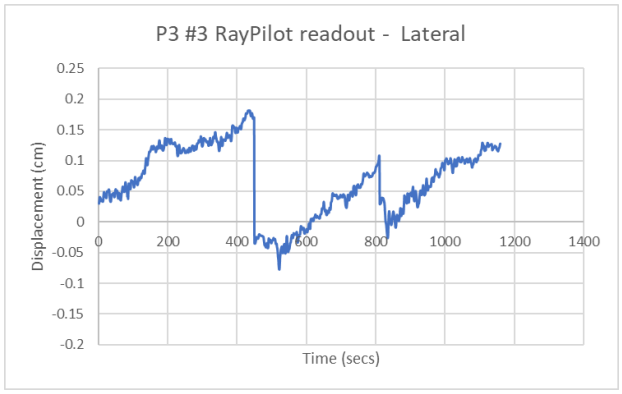


Fig B4(a)

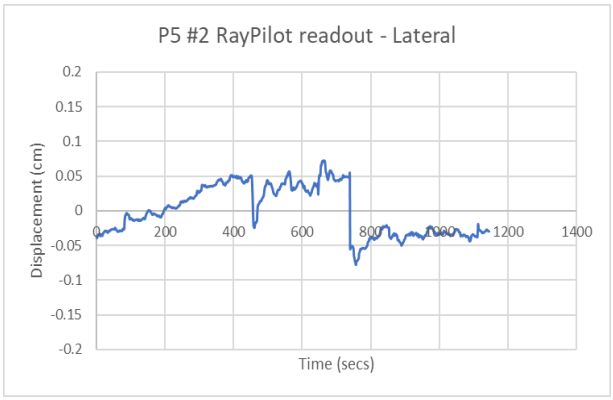


Fig B4(d)

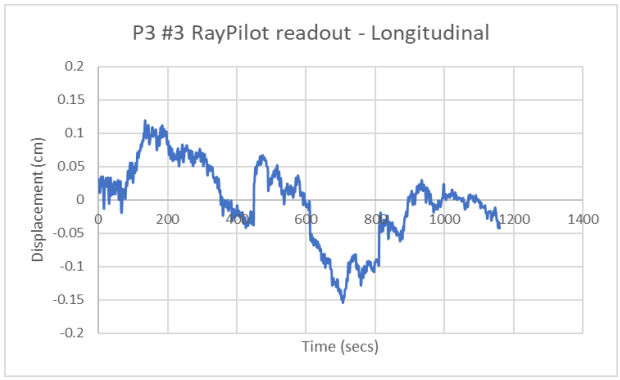


Fig B4(b)

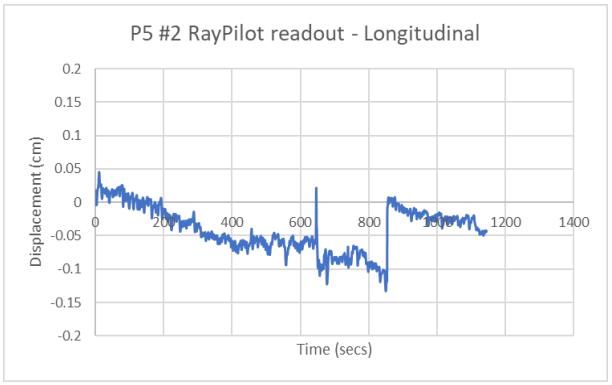


Fig B4(e)

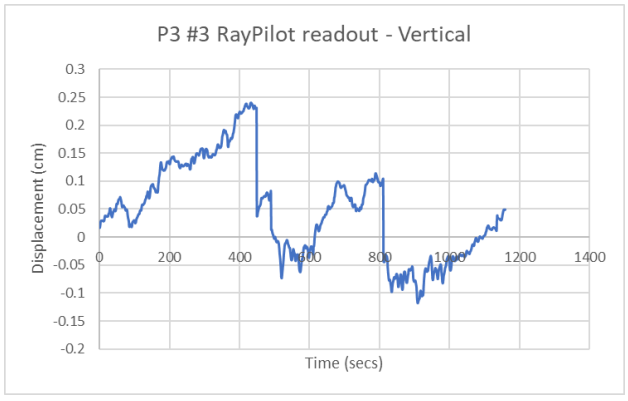


Fig B4(c)

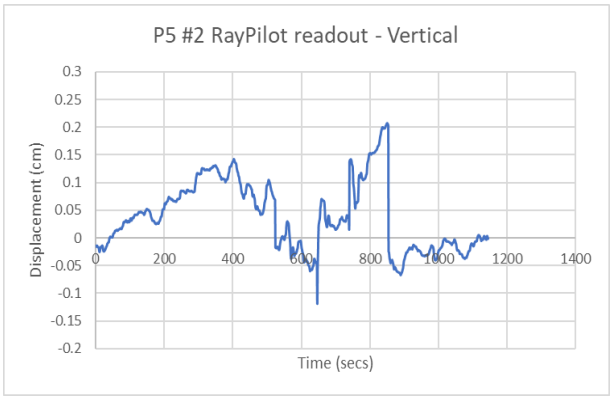


Fig B4(f)

Fig B4: *Example of Raypilot readout data measured for P3 #3 (Fig B4 a, b & c) and P5 #2 (Fig B4 d, e & f) during showing the full measured readout for these fractions in the lateral (LR) longitudinal (SI) and vertical (AP) directions respectively.*

2. Paper B

Patient	fraction	Treatment time (secs)	mean displacement & *Standard deviation (cm)*					
			L/R		S/I		A/P	
P1	1	810	0.05	*0.09*	0.02	*0.07*	-0.03	*0.19*
	2	440	0.01	*0.01*	-0.05	*0.02*	0.01	*0.06*
	3	480	0.00	*0.04*	0.01	*0.02*	0.04	*0.06*
	4	360	0.12	*0.04*	0.08	*0.04*	-0.14	*0.06*
	5	2560	0.05	*0.05*	-0.06	*0.07*	0.04	*0.11*
P2	1	1000	0.05	*0.07*	-0.02	*0.03*	0.04	*0.03*
	2	1000	0.03	*0.03*	0.01	*0.01*	0.03	*0.04*
	3	950	0.06	*0.07*	0.02	*0.09*	0.01	*0.07*
	4	1550	0.06	*0.07*	0.01	*0.07*	0.01	*0.06*
	5	910	0.02	*0.04*	-0.02	*0.04*	0.04	*0.03*
P3	1	810	-0.01	*0.04*	-0.01	*0.07*	0.01	*0.04*
	2	1000	-0.02	*0.03*	0.05	*0.08*	0.01	*0.05*
	3	1170	0.07	*0.06*	0.00	*0.06*	0.05	*0.09*
	4	1190	0.02	*0.07*	-0.02	*0.08*	0.08	*0.07*
	5	1300	-0.03	*0.03*	0.02	*0.07*	0.04	*0.10*
P5	1	425	0.12	*0.02*	0.04	*0.03*	0.14	*0.04*
	2	1150	0.00	*0.04*	-0.04	*0.03*	0.04	*0.06*
	3	880	0.00	*0.03*	0.00	*0.06*	-0.01	*0.04*
	4	1080	0.00	*0.04*	-0.03	*0.05*	0.06	*0.06*
	5	2000	0.01	*0.03*	-0.03	*0.07*	0.02	*0.04*
P6	1	675	0.01	*0.02*	0.01	*0.02*	0.03	*0.04*
	2	1250	-0.03	*0.04*	0.00	*0.05*	0.01	*0.12*
	3	1700	0.01	*0.07*	0.03	*0.12*	0.02	*0.13*
	4	875	0.04	*0.03*	0.02	*0.05*	0.06	*0.03*
	5	870	0.00	*0.03*	-0.02	*0.03*	0.01	*0.03*
P7	1	1090	-0.01	*0.07*	0.03	*0.05*	-0.03	*0.07*
	2	1550	-0.01	*0.10*	0.00	*0.06*	0.02	*0.09*
	3	1075	0.06	*0.08*	0.02	*0.12*	0.00	*0.10*
	4	990	-0.01	*0.14*	0.05	*0.09*	-0.13	*0.18*
	5	3500	-0.01	*0.12*	0.03	*0.04*	-0.06	*0.08*

***Table B6**: Table presenting the overall designated treatment time in seconds for each patient and each fraction and the mean displacement value of the RayPilot transmitter (left/right, sup/inf, ant/post) during this time, in cm*

4.5 Discussion

There has been more interest in recent years in prostate radiotherapy treatments being delivered using hypofractionation. Whilst there are proposed radiobiological benefits as well

as potential resource savings through this technique, there are also potential issues surrounding the safe and accurate delivery of radiotherapy to this site. Due to the high dose per fraction, geometric discrepancies for individual fractions in SBRT can result in a clinically significant reduction in target dose (B12). Accurate real-time positional information of the prostate intrafractionally, can assist in ensuring it remains within the PTV for the duration of the treatment and therefore receives the intended dose. Small studies such as these can help to test the efficacy of such equipment alongside established imaging methodologies and inform how they are utilised in future studies and protocols.

The readout information of the RayPilot system allowed analysis of how the system fits within a prostate SBRT delivery, and provided further insight into the system and the target position during treatment. The graph in Fig B3a shows the mean position of the transmitter was recorded as less than 0.1cm for each patient, with the greatest mean displacement in any direction being P7 AP (-0.06cm). When this data was calculated for all patients per fraction, the largest mean displacement was 0.04cm (Fraction 1 vertical & Fraction 4 lateral). These figures are relatively low, and would ensure that the prostate's mean position remained well within the treated volume, with the CTV (prostate) to PTV margin 0.5cm SIRLA and 0.3cm P.

These low values may be attributed to the stability of the anatomy or the robustness of the imaging protocol, as positional displacements would have been identified either by the RayPilot software or the kV imaging. The patient bowel and bladder preparation protocol can also contribute to maintaining consistent anatomy. The imaging protocol mandated that a positional correction should only be instigated if the displacement exceeded 0.2cm. Correcting the patient position adds additional time to the treatment delivery and so if the

threshold is too tight, this may lead to a large increase in beam interruptions. As smaller displacements would still infer the prostate remained within the PTV margins, 0.2cm was adopted. Choi et al. (B12) reported on the outcome data from prostate SBRT, delivered using the Cyberknife system. They reported small displacements had no impact to prostate coverage, however they did note increased toxicity when displacements exceeding 0.073cm AP. This was greater than the mean displacements recorded in this study (Fig B2) however analysis of toxicity for these patients would be useful in a future study.

The recorded graphs of the motion (Fig B3 & B4) provided a visual assessment of the trajectory of the transmitter displacement in each plane. These were created retrospectively from the readout data and were not available to the treatment staff at the time of delivery. This may have been useful in some cases, but with this method of retrospective analysis, building up experience could help to identify trends such as displacements when certain conditions exist. No obvious trends were noted from this dataset however.

The displacements were also analysed to show the percentage of measurement points exceeding designated levels. The software recorded the positional data of the transmitter every second which can be used as a surrogate for the time the target was displaced assuming the relative target and transmitter position remains consistent. The data points used were those labelled “treatment” within the system, which included measurements taken between arcs and during repositioning of the patient if this was required. This led to a difference in the time recorded for some fractions, with a range of 369 to 3500 seconds.

Isolating the data points recorded only when the beam is on would improve the methodology for estimating dose to the target, however this is not the intended use of the

equipment. The system should highlight changes after the patient is positioned correctly. For this purpose, the current set up for labelling data points is more suitable, and recommended by the manufacturer. After the initial kV orthogonal image is taken and used to correctly position the prostate, any displacements would require correction from this baseline position. Future versions of the software however, may also allow data points acquired during the beam delivery to be filtered which would be useful for more accurate dosimetric analysis.

The imaging protocol of the study utilised RayPilot as a supplementary system for real-time tracking, alongside the PACE imaging protocol for centres with no real-time tracking. This involved additional kV orthogonal imaging between arcs, instigating positional correction if required. This slightly conservative approach was taken whilst experience using the RayPilot system was developed, allowing safe introduction and testing of the software and for fractions where the RayPilot system could not be used (eg P4 #3, #4 & #5) to still be delivered within the protocol.

The RayPilot system only tracks the displacement of the target, not the OARs, such as the bladder or rectum. Although this is consistent with other tracking systems (B15), changes in the size or position of these organs for one fraction can have a impact on the plan dosimetry. For this study anatomical information was assessed before treatment on the CBCT image, but changes during treatment may still have an impact. The Rectal tolerance for this study included a limit on the volume receiving 36Gy to 0.2cc. This is analogous to a point dose, however the planning approach was not the same as for serial organs such as the spinal cord. Further work would be useful to look at the impact of changes to the rectum over the course of treatment. If rectum tolerance was close to being exceeded then small changes could see the rectum dose go over tolerance. Whilst the use of a PRV around the rectum could minimise this risk, this would lead to a dose compromise of the target volume, which is something that the tracking system is trying to avoid. Also setting an appropriate PRV

around a mobile structure such as the rectum may be difficult and vary from patient to patient.

2D kV orthogonal imaging matching to fiducial markers was chosen as the primary imaging modality for the technique, with extensive local experience using this method of positional verification. This was used successfully alongside the RayPilot system, and CBCT imaging. Although the 2D orthogonal images provided no volumetric information, the images were a lower dose than CBCT scans and much quicker to acquire. This was especially useful as there where a number of concomitant images required for each fraction.

P7 exhibited the largest percentage of measured displacements outside of the imaging interventional threshold of 0.2cm, with 17% of the measured points in the vertical direction exceeding this (Fig B3c). If this was a reflection of the position of the target during treatment, this could have impacted the target volume, as 6.7% of these measurements exceeded the posterior PTV margin of 0.3cm. These results were strongly influenced by fraction 4 for this patient, where 38% of the measurements in the vertical direction were displaced by more than 0.2cm.

The overall time measured for this fraction was the longest in the study, 3300 seconds, and significantly longer than the overall mean time of 1155 seconds for one fraction. During P7 #4, significant issues with set up were found, with the RayPilot system instigating the beam to be halted twice followed by kV orthogonal imaging and positional adjustments. The actual time to deliver 3 arcs for this patient was approximately 180 seconds so this hints at significant additional set-up time. However, with these interventions this would reduce the risk that these displaced data points were recorded during beam delivery and impact the plan dosimetry. The overall number of data points for all fractions was used to calculate the overall mean values. This does not lend an equal waiting to each fraction. If a more accurate

dose estimate was required, the displacement values for each fraction should be weighted equally as the treatment delivery time for each would be the same.

The relationship between intrafraction target motion and time in prostate radiotherapy was discussed in Mutanga et al (B17) where they noted a displacement of approximately 0.02cm per minute. The range in fraction times in this study are presented in Table B6 along with the respective mean displacements and standard deviation for each fraction. From the data presented, there does not appear to be an obvious correlation between increased treatment time and the mean or standard deviation of the displacements. The RayPilot system was tracking the position of the target during the treatment phase, with periodic positional corrections being applied using the IGRT system if the target was noted to be outside the imaging interventional tolerance. Therefore, one would not expect to see the displacement drift such as that described in Mutanga et al. over the whole treatment phase without a correction being instigated.

Fractions with longer treatment times would not necessarily indicate problems with the patient set up. A number of prolonged fraction times were related to the patient's bladder filling where the patient was required to be taken off the bed. The system does not allow for the treatment time to be reset or paused when this occurs. Although the data presented does not correspond to the actual treatment delivery, this data does give an indication of the behaviour of the target from when the patient is first positioned correctly in the treatment position. Interestingly, all of the patients first fraction treatment times were less than the overall mean treatment time, and the three longest treatment times all occurred on a patient's last fraction. This could be something that is investigated in further studies.

Erroneous data points were excluded from the calculations. These were identified through the graphs where extreme displacements, some as large as 6cm were noted during the treatment phase. These were attributed to occasions where the patient was taken off the bed

between arcs, and were easily identified due to the large step change as seen in Fig B3a, b & c. However, for P7 #4 there also appears to be a number of measured displacements in the region of 0.2-0.4cm as shown in Fig B3f. These smaller deviations may have been what was observed for this patient, but it does show that over the fraction there was a lot of movement. This should have been identified through the imaging protocol, and the beam only delivered when the displacement of the transmitter was within 0.2cm.

Data from P3 #3 and P5 #2 are presented in Fig B4. These readouts are typical of the fractions where no displacements exceeding the 0.2cm imaging threshold tolerance were noted. No positional corrections were required during P5 #2, which is reflected in the graph where all data points remain within 0.2cm. For P3 #3, the data points on the vertical (AP) graph (Fig B4c) have a spike where a small number of points exceeding the 0.2cm. Although this exceeds the imaging tolerance, there was no evidence of the beam being halted or positional intervention for this fraction. These points may have occurred when the beam was off and as such not been corrected. If it occurred during the treatment beam, it may still not have been the case that the beam should have been halted. The protocol stated that a beam should be halted manually when a displacement of 0.2cm or greater was noted. This was resource intensive, as it required an additional radiographer to carry out this task, and it also led to a delay in halting the beam due to the reaction time, which may have been the case for this fraction as the tolerance was only breached very briefly. This would not be expected to impact the delivered dose significantly.

Keall et al. (B18) discuss using an interventional tolerance of 0.3cm for longer than 5 seconds for their prostate treatments, which takes into account the low impact of target displacements which occur very quickly. This would also prevent unnecessary stoppages and delays. In practice this is an advantage of the manual system used in this study as there

is a natural delay due to reaction times. However, a more consistent and automated approach would be more advantageous if this could be possible in future versions of the RayPilot system.

Patient P1 was the first patient treated locally with prostate SBRT and using the RayPilot tracking system. As the study progressed, one would expect a learning curve within the department relating to aspects of the treatment workflow and delivery as the staff gain more confidence and experience in the technique. The patient treatments in the study were spaced over 12 months, which was allowed review of technique and an opportunity for learning. Whilst this may have had an impact on the study, with staff experience and knowledge being increased as the study progressed, as this was part of a clinical trial the key aspects of data collection and treatment could not be changed without amending the trial protocol, and hence would have been consistent throughout.

The number of patients in the study (N=7) limits the options for statistical tests, with the low numbers reducing the statistical power and therefore the confidence in any results. O'Neil et al. (B2) carried out a review of published literature on fiducial guided prostate radiotherapy. They excluded studies with N<20. Although this led to a large number of studies being excluded, their rationale was based on published guidance from BIR (B19) recommending at least 20 patients, and preferably 25 for a study to have a patient population deemed representative. As a pilot study showing the efficacy of the system for prostate SBRT however the numbers were seen as sufficient, with further work identified to improve the system further.

With further advancements in modern planning systems adaptive tools, it may be possible to simulate dosimetric impact using displacement from individual fractions, for example using the percentage time that the target moves outside of the treated volume. This would

however have to be linked to the actual beam on time and not include time before or between arcs. Although this study has shown that the imaging protocol and PTV margins used were appropriate for this group of patients, this data could also be used to investigate the potential dosimetric impact of any change to the CTV to PTV planning margin.

Further studies could be designed to refine the workflow involving RayPilot. If the system were to be used to inform positional changes, this could remove the additional kV orthogonal images acquired between each arc and or when displacements had been identified in RayPilot. The readout from the RayPilot system could theoretically provide the displacement in each direction, and this used to reposition the patient. This would have to be investigated very carefully before implementation. The system of matching the kV orthogonal images to fiducials is well established and the physical couch movements are linked to those determined by the matching software. The risk of a geometric error would increase if this became a manual task using the RayPilot system readout. Further work looking at the positional sensitivity of the RayPilot system for identifying these shifts, along with a comparison against the established imaging method would be useful to support this change.

4.6 Conclusion

RayPilot was utilised successfully in this study and is a viable means for tracking the prostate during SBRT, alongside established imaging techniques. The position of the target was within 0.2cm for 94.9% of the measurements in the study. Synchronising the software to isolate only measurements taken during radiation delivery to be used would strengthen the validity of the data. Linking the system to automatically halt the beam when displacements are recorded would improve the efficiency of the treatment workflow. Further work should be

carried out to asses if RayPilot could be the primary positioning technology during prostate SBRT.

4.7 Ethical approval

Ethical approval for this work to be presented was granted through the PRINToUT clinical trial ethical approval application.

4.8 References

B1. Cancer Research UK. *Prostate cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer [accessed 01/11/20]

B2 A. G. M. O'Neill, S. Jain, A. R. Hounsell, and J. M. O'sullivan, Fiducial marker guided prostate radiotherapy: A review, *Br J Radiol* vol. 89, no. 1068, pp. 1–18, 2016, Available from: https://dx.doi.org/10.1259/bjr.20160296

B3. Mah D, Freedman G, Milestone B, Hanlon A, Palacio E, Richardson T, et al. Measurement of intrafractional prostate motion using magnetic resonance imaging. *Int. J. Radiat. Oncol. Biol. Phys.*2002;54(2):568–75. Available from: https://dx.doi.org/10.1016/S0360-3016(02)03008-0

B4. Xiong W, Li J, Ma CM. Effect of patient variation on standard- and hypo-fractionated radiotherapy of prostate cancer. *Phys Med Biol*. 2005;50(7):1483–92. Available from: https://dx.doi.org/10.1088/0031-9155/50/7/011

B5. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial.

Lancet Oncol. 2016;17(8):1047–60. Available from: https://dx.doi.org/10.1016/S1470-2045(16)30102-4

B6. Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, et al. Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA evidence-based guideline. J. Clin. Oncol. 2018;36(34):3411–30. Available from: https://dx.doi.org/10.1200/JCO.18.01097

B7. A. Widmark, A. Gunnlaugsson, L. Beckman, C. Thellenberg-Karlsson, M. Hoyer, M. Lagerlund et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial, *Lancet*, vol. 394, no. 10196, pp. 385–395, 2019, Available from: https://dx.doi.org/10.1016/S0140-6736(19)31131-6

B8. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531–43. Available from: http://dx.doi.org/10.1016/S1470-2045(19)30569-8

B9. Lovelock DM, Messineo AP, Cox BW, Kollmeier MA, Zelefsky MJ. Continuous monitoring and intrafraction target position correction during treatment improves target coverage for patients undergoing SBRT prostate therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;91(3):588–94. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.10.049

B10. Varian Medical Systems. https://www.varian.com/ [accessed 01/11/20]

B11. Accuray. *Cyberknife S7* https://www.accuray.com/cyberknife [accessed 04/11/20]

B12. Choi HS, Kang KM, Jeong BK, Song JH, Lee YH, Ha IB, et al. Analysis of motion-dependent clinical outcome of tumor tracking stereotactic body radiotherapy for prostate

cancer. *J. Korean Med. Sci*. 2018;33(14):1–13. Available at: https://doi.org/10.3346/jkms.2018.33.e107

B13. McLaren D. *Using breath analysis to PRedIct Normal TissUe and Tumour response during prostate cancer SBRT*. Version 1.0 May 2018, IRAS Number: 240335

B14. C. Griffin, V. Hinder, S. Burnett, S. Brown, and O. Naismith, *PACE: Radiotherapy planning and delivery guidelines* V2.1 2020 pp1–26

B15. S. Das, T. Liu, A Jani, P. Rossi, J. Shelton, Z. Shi, M. Khan, Comparison of image-guided radiotherapy technologies for prostate cancer, *Am. J. Clin. Oncol*, vol. 37, no. 6, pp. 616–623, 2014, Available from: https://dx.doi.org/10.1097/COC.0b013e31827e4eb9

B16. Micropos *Raypilot solution* Available at: https://micropos.se/healthcare-professionals/raypilot-solution [accessed 29/10/20]

B17. Mutanga TF, Sc M, Boer HCJ De, Ph D, Rajan V, Ph D, et al. Day-to-Day Reproducibility of Prostate Intrafraction Motion Assessed by Multiple kV and MV Imaging of Implanted Markers During Treatment. *Int. J. Radiat. Oncol. Biol. Phys.*2012;83(1):400–7. Available from: https://dx.doi.org/10.1016/j.ijrobp.2011.05.049

B18. Keall PJ, Ng JA, Juneja P, O'Brien RT, Huang CY, Colvill E, et al. Real-Time 3D Image Guidance Using a Standard LINAC: Measured Motion, Accuracy, and Precision of the First Prospective Clinical Trial of Kilovoltage Intrafraction Monitoring-Guided Gating for Prostate Cancer Radiation Therapy. Int *Int. J. Radiat. Oncol. Biol. Phys.* 2016;94(5):1015–21. Available from: http://dx.doi.org/10.1016/j.ijrobp.2015.10.009

B19. BIR. *Geometric uncertainties in radiotherapy: defining the planning target volume*. London, UK: British Institute of Radiology; 2003.

5 Paper C: Target journal – International Journal of Radiation Oncology Biology Physics

Investigating a planning solution and the dosimetric impact of intrafraction motion for dose escalated prostate SBRT using the RayPilot Tracking system

Authors: Michael Trainer[1], William H Nailon[1,3], Linda J Carruthers[1], Mike Kirby[2]

[1]Department of Oncology Physics, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK

[2]Directorate of Radiotherapy, Liverpool University, Liverpool, UK

[3]School of Engineering, The University of Edinburgh, Edinburgh, UK

5.1 Abstract

Aim: To investigate whether clinically acceptable dose escalated SBRT plans could be created for patients enrolled in the PRINToUT trial and whether the RayPilot tracking system could be used in their treatment.

Methods and materials: A retrospective planning study (arm A) was carried out on seven patients in the PRINToUT trial. Plans were created on the Eclipse treatment planning system (v13.6), aiming to deliver 36.25Gy in 5#to the prostate and to boost the dose to the dominant intraprostatic lesion to 45Gy, in 5#. Using intrafraction motion data measured during treatment using CBCT images and the RayPilot tracking system respectively, two additional plans were created for each patient (arm B & arm C respectively), with the isocentre displacement per fraction simulated for each and the plans summed.

Results: In arm A, the PTV, CTV and PTV(boost) dose coverage was within the trial objectives for all plans. The bladder dose constraints were met for all patients in the study. The rectum V3600cGy exceeded the tolerance of 2cc for three out of the seven patients and only two patients met all of the rectum dose constraints. The plans in arm B (CBCT data) met the PTV dose targets for three out of seven patients, CTV dose targets for six out of seven patients and the PTV(boost) targets for one out of seven patients. The rectum V3600cGy tolerance was exceeded for three patients. In arm C (RayPilot data) the dose targets for all plans for the PTV, CTV and PTV(boost) were met. The bladder doses were within tolerance for all patients in this group. The rectum V3600cGy exceeded 2cc for three patients.

Conclusion: The addition of a boost to prostate SBRT treatment plans can be achieved with adequate target coverage. However, this can lead to exceeding OAR tolerances for some

patients. Intrafraction motion can impact plan dosimetry of prostate SBRT plans with a boost in some cases.

5.2 Introduction

The most common cancer diagnosis in the UK is prostate, where it is estimated that one in eight men will be diagnosed in their lifetime (C1). Radiotherapy plays a key role in the treatment of prostate cancer, with 30% of patients having radiotherapy as part of their treatment (C2). Standard protocols for prostate radiotherapy focus on treating the whole prostate rather than the largest malignant component known as the dominant intraprostatic lesion (DIL) as this does not necessarily represent the extent of the disease (C3). Studies have discussed a correlation between the location of the DIL and subsequent disease recurrence (C3), (C4), and the dose delivered to the DIL can be of interest.

Hypofractionation and SBRT for prostate radiotherapy are emerging as a favoured treatment options, with trials such as CHIIP (C5) or PACE (C6). There have been found to be radiobiological advantages of hypofractionation due to the lower alpha/beta ratio of prostate cancer (C7). Due to the proximity of the prostate and the rectum, the limiting factor to dose escalation can often be the OAR doses. It has been suggested that increased escalation to the DIL alone could allow higher treatment doses to be achieved whilst still maintaining safe OAR doses (C8), (C9).

Planning studies have shown that acceptable prostate SBRT DIL boost plans can be achieved. Kim et al. (C4) replanned 15 prostate SBRT patients treated with Cyberknife to include a boost to the DIL. Plans aimed to prescribe 35Gy/5# to the prostate and 40Gy/5# (5Gy boost) or 45Gy/5# (10Gy boost) to the DIL. Each patient had two boost plans created, one for each dose level. They reported 73% of their 40Gy plans and 60% of their 45Gy/5# plans met their desired clinical objectives, and concluded that the location of the DIL in the

prostate was the limiting factor in the efficacy of the solution. In Feng et al. (C10), a retrospective planning study was carried out on 14 patients who had their DIL identified through MR imaging. This study simulated a linac based delivery aiming to treat the prostate with 36.25Gy/5# and boost the dose to the DIL to 47.5Gy/5#, whilst keeping within OAR constraints from the PACE trial. They reported that all of the clinical constraints for each plan were met and noted that variation in the position of the DIL didn't impede the ability to produce acceptable plans.

The impact of inter and intrafractional target motion on hypofractionated treatment schedules can be greater than conventional fractionations, and therefore the accuracy of the delivery can be important to treatment efficacy (C11). However, De Muinck Keizer et al. (C12) reported intrafraction motion can be captured within suitable target margins. Tracking systems such as Cyberknife (C13) and Calypso (C14) have been successfully utilised to track the position of the target in real-time during prostate SBRT treatments (C15),(C16) including where there has been a boost to the DIL (C17). Boosting the DIL has also been carried out without the use of real-time tracking (C9).

This retrospective planning study aimed to investigate the effects on dose distributions to dose escalated prostate SBRT plans when intrafractional motion from real IGRT data is applied, and whether the RayPilot tracking system could be used to support the delivery of this technique.

5.3 Methods and materials

Seven patients who were enrolled in the PRINToUT clinical trial (C18) between November 2018 and January 2019, with a mean age of 70.7 (range 53-81) were included in this retrospective study. PRINToUT is investigating the relationship between volatile organic

compounds released in patient's breath and their normal tissue and tumour response to radiotherapy. Patients receive prostate SBRT and have breath samples taken for analysis. The dose fractionation (36.25Gy in 5#) and organ at risk tolerances used for the trial (Appendix 2) were closely aligned to PACE (C6). The treatment plans aimed to cover the CTV with 100% of the prescribed dose (PD) and the PTV with 95% of the PD.

Treatments were delivered on Varian Truebeam linacs, using three 6MV VMAT arcs. Positional verification was with kV orthogonal pairs as the primary imaging modality for positioning the patient, taken before each fraction and between each arc delivery. A CBCT image was taken directly before and after the beam was delivered to assess anatomical changes and the RayPilot real-time positional tracking system (C19) was used to monitor the target during treatment. The RayPilot system consists of a table top array with an electromagnetic transmitter connected via a cable. The 3-D positional vector of the transmitter is used to calculate its displacement from a reference position in real-time. Each patient in the study had the transmitter inserted transperineally into the prostate before their planning CT. Positional displacements were calculated 30 times per second, and if noted to be 0.2cm or greater, the treatment was halted manually and kV orthogonal pairs were used to verify the displacement and correct the position if necessary. After the treatment, data including the positional information recorded every second, was available for analysis.

The main planning study (arm A) used the PRINToUT study dose, fractionation and OAR tolerances, but with an addition of a boost of 125% of the PD (45Gy / 5#) to a DIL PTV(boost) – aiming for D99% to receive 95% of the boost dose. The DIL(s) for each patient had been delineated by a clinician prior to their treatment using multi-parametric MR images fused to the treatment planning CT scan using rigid mapping using the Eclipse

treatment planning system (v13.6) (C14). All other clinical volumes from the clinical plan remained consistent. The CTV to PTV margin from PRINToUT was 0.3cm posteriorly and 0.5cm in all other directions. For this study, a PTV(boost) was created by expanding directly from the DIL contour by 0.2cm posteriorly and 0.3cm in all other directions.

The plans were all created using the Eclipse treatment planning system (v13.6) (C14), based on beam models for the Truebeam linac and the final dose was calculated using the AAA dose algorithm (v10.0.28). The plans aimed to meet the mandatory target coverage, whilst minimising dose to the OARs. However, no compromise to the target dose was instigated if OARs exceeded their tolerance once fully optimised. The plans were normalised to CTV D99%. An additional two plans for each patient were created, using data from two previous studies (C20), (C21). These studies each used different methods of determining positional displacement during treatment but were acquired on the same patients.

The source data for arm B of the planning study was investigating the displacement of the RayPilot transmitter from the reference planning CT and each of the pre and post-fraction CBCT images (C20), (Paper A). The positional displacement of the transmitter tip for each fraction for the planning study was calculated by the mean displacement between the two CBCT scans for each individual fraction.

The source positional data for arm C of the planning study was based on RayPilot readout data acquired during treatment (C21), (Paper B). The system recorded the position of the transmitter every second and calculated its displacement from a reference position. Using the data from this study, the mean displacement for each patient during each individual fraction was used as a surrogate for the intrafraction displacement. There were technical difficulties which prevented the recording of the RayPilot data for P4 during treatment, and

as such this patient was not included in arm C of the planning study. In Arm B, patient P3's data was seen as an outlier due to a physical displacement of the RayPilot transmitter caused by the patient accidently pulling on the protruding wire. This occurred after their planning CT scan but before the first fraction. This was noted during the treatment, with the coordinates of the transmitter tip in the software renormalised using the CBCT image from fraction 1. However, as the source data for this study compared the CBCT images to the CT scan, the coordinates of the physical position of the transmitter tip would have an inherent difference. Therefore analysis excluding results from P3 was also carried out.

Arm A included the original prostate SBRT with boost plans with no changes. In both arm B & arm C, the impact of displacements on the treatment plan was simulated in Eclipse by using the plans from Arm A and creating individual plans for each fraction (five single fraction plans per patient for both arm B and arm C) and displacing the isocentre by the displacement from the respective clinical source data. The plans were recalculated using the same MUs as the original plan, and the dose from each single fraction plan was summed to simulate the dose over a whole 5# course. The dosimetry of all plans in arms A, B & C were assessed using parameters from the PRINToUT plan assessment form (PAF) (Appendix 2), with the addition of the target dose to the PTV(boost).

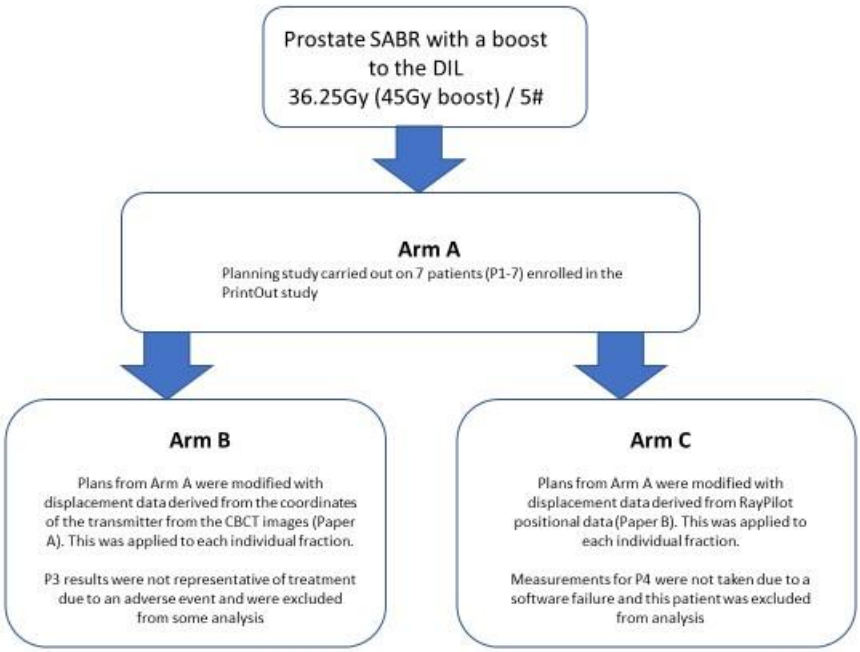


***Fig C1**: Flow diagram illustrating the detail of Arm A, Arm B and Arm C of the planning study*

5.4 Results

In arm A, the PTV, CTV and PTV(boost) mandatory dose constraint was met for all plans. The D99% of the PTV ranged between 97.7%-98.5% of the PD, with a mean value of 98.1%. The D99% of the PTV(boost) ranged between 120.9%-122.5% of the PD with a mean of 121.8%. The bladder dose constraints were met for all patients in the study. The Rectum V1810cGy exceeded the mandatory dose constraint of 50% for three out of the seven patients, with a range of 31.3%-62.2%. The rectum V3600cGy exceeded 2cc for three out of the seven patients, with a range of 1.3cc-2.9cc. Only two patients in the study met all of the rectum dose constraints.

The plans in arm B met the PTV dose targets for three out of seven patients (range 27.8%-97.6%), CTV dose targets for six out of seven patients (range 46.1%-100.7%) and the PTV(boost) targets for one out of seven patients (range 65.4%-119.3%). The bladder V1810cGy exceeded 40% for one patient. The rectum V1810cGy exceeded 50% for three patients (range 31.2%-62.5%), and the V3600cGy tolerance of 2cc was exceeded for three patients (range 0.6cc-4.5cc).

The plans in arm C met the dose targets for all plans for the PTV (range 97%-98.2%), CTV (range 100%-100.1%) and PTV(boost) (range 119.3%-122%). The bladder doses were within tolerance for all patients in this group. The rectum V1810cGy exceeded 50% for three out of the six patients (range 31.2%-62.5%), and the V3600cGy exceeded 2cc for three patients (range 1.2cc-2.7cc).

3. Paper C

		Arm B (cm)			Arm C (cm)		
		x	y	z	x	y	z
P1	#1	-0.05	-0.05	0.40	0.05	0.02	-0.03
	#2	0.00	-0.05	0.15	0.01	-0.05	0.01
	#3	-0.09	-0.10	-0.40	0.04	0.02	0.06
	#4	-0.09	0.00	-0.20	0.04	-0.05	0.04
	#5	-0.05	-0.10	-0.30	0.04	-0.02	0.01
P2	#1	-0.09	0.00	0.10	0.05	-0.02	0.04
	#2	-0.10	0.09	0.10	0.03	0.01	0.03
	#3	-0.09	0.00	0.15	0.06	0.02	0.01
	#4	-0.05	0.10	-0.05	0.06	0.01	0.01
	#5	-0.10	0.10	-0.05	0.02	-0.02	0.04
P3	#1	0.11	0.12	1.40	-0.01	-0.01	0.01
	#2	-0.06	0.06	0.40	-0.01	0.05	0.01
	#3	-0.24	0.06	1.25	0.07	0	0.05
	#4	-0.12	0.06	1.50	0.02	-0.02	0.08
	#5	-0.18	0.12	1.35	-0.03	0.01	0.04
P4	#1	-0.05	0.25	-0.10			
	#2	0.00	0.37	-0.20			
	#3	-0.10	0.23	0.00			
	#4	-0.05	0.42	-0.10			
	#5	-0.05	0.42	-0.15			
P5	#1	0.00	0.00	-0.20	0.12	0.04	0.14
	#2	0.00	-0.15	0.10	0	-0.04	0.03
	#3	-0.10	-0.10	-0.10	0	0	-0.01
	#4	0.00	-0.20	0.00	0	-0.02	0.06
	#5	0.00	-0.10	0.10	0.01	-0.03	0.02
P6	#1	0.00	0.25	0.20	0.01	0.01	0.03
	#2	0.00	0.37	-0.05	-0.03	0	0.01
	#3	0.05	0.24	0.25	0.01	0.03	0.02
	#4	0.09	0.37	0.40	0.04	0.02	0.06
	#5	0.05	0.26	0.20	0	-0.02	0.01
P7	#1	0.12	-0.06	-0.05	-0.01	0.03	-0.03
	#2	0.00	-0.18	-0.15	-0.01	0	0.02
	#3	0.00	-0.06	0.00	0.06	0.02	0
	#4	0.08	0.00	-0.15	-0.01	0.05	-0.13
	#5	-0.23	-0.24	-0.30	0.03	0.05	-0.11

***Table C1**: Table of displacement values (cm) for each patient and each individual fraction applied to the planning study in Arm A to produce displacement corrected treatment plans based on positional data from the CBCT images (Arm B) and the positional data from the RayPilot system (Arm C).*

Volume	Parameter	Optimal	Mandatory	P1	P2	P3	P4	P5	P6	P7	mean	mean excluding P3	mean excluding P4
CTV	D99.0%		>=100%	100	100	100	100	100	100	100	100.0	100.0	100.0
PTV	D99.0%		>=95%	97.8	98.3	98.3	98.3	97.8	98.5	97.7	98.1	98.1	98.1
PTV (boost)	D99.0%		>=119%	122.5	122.3	121.6	121.7	122	121.6	120.9	121.8	121.8	121.8
DIL (GTV)	D99.0%			124.4	123.7	123.6	122.7	127.1	124.5	124.1	124.3	124.4	124.6
Bladder	V1810cGy		<40%	12.8	16.3	20.6	8.3	12.2	5.5	17.1	13.3	12.0	14.1
	V3700cGy	<5cc	<10cc	1.2	1.9	2.2	0.5	1	1.7	1.1	1.4	1.2	1.5
Rectum	V1810cGy		<50%	47.5	54	54.3	47.4	41.5	62.2	31.3	48.3	47.3	48.5
	V2900cGy		<20%	16.3	15.5	14.6	15.7	13.5	13.1	10.7	14.2	14.1	14.0
	V3600cGy	<1cc	<2cc	2.9	1.6	2.8	1.9	1.3	1.9	2.1	2.1	2.0	2.1

Fig C2(a) Arm A: mean excluding P4 added for direct comparison with Arm C

Volume	Parameter	Optimal	Mandatory	P1	P2	P3	P4	P5	P6	P7	mean	mean excluding P3	mean excluding P4
CTV	D99.0%		>=100%	100.7	100.2	46.1	100	100	100.3	100.1	92.5	100.2	91.2
PTV	D99.0%		>=95%	92.6	97.6	27.8	91.8	95.6	88.2	97	84.4	93.8	83.1
PTV (boost)	D99.0%		>=119%	116.3	118.8	65.4	110.3	118.3	107.6	119.3	108.0	115.1	107.6
DIL (GTV)	D99.0%			123.8	124	82.8	123.5	126.7	121.6	124.4	118.1	124.0	117.2
Bladder	V1810cGy		<40%	11.9	16.3	42.9	6.4	12.1	6.9	16.2	16.1	11.6	17.7
	V3700cGy	<5cc	<10cc	0.1	1.1	13.5	0	0.6	2	0.7	2.6	0.8	3.0
Rectum	V1810cGy		<50%	45.6	54.1	51.2	48.7	40.8	65.5	31.2	48.2	47.7	48.1
	V2900cGy		<20%	15.3	16.4	8.7	22.7	11.7	16.8	11	14.7	15.7	13.3
	V3600cGy	<1cc	<2cc	2.2	1.8	0.6	4.5	0.7	3.2	2.5	2.2	2.5	1.8

Fig C2(b) Arm B: P3 dislodged their transmitter in an adverse event before treatment which may have significantly impacted these measurements. These results were viewed as an outlier, and mean excluding P3 added due to adverse event and mean excluding P4 added for direct comparison with Arm C.

Volume	Parameter	Optimal	Mandatory	P1	P2	P3	P5	P6	P7	Average
CTV	D99.0%		>=100%	100	100	100	100.1	100	100.1	100.0
PTV	D99.0%		>=95%	97.6	97.9	98.1	97.5	98.2	97	97.7
PTV (boost)	D99.0%		>=119%	122	121.7	121.1	120.7	121.2	119.3	121.0
DIL (GTV)	D99.0%			124.4	123.7	123.6	127.3	124.5	124.4	124.7
Bladder	V1810cGy		<40%	13	16.6	21.2	13	5.7	16.2	14.3
	V3700cGy	<5cc	<10cc	1.3	2	2.4	1.2	1.9	0.7	1.6
Rectum	V1810cGy		<50%	47.4	54	54.4	41.6	62.5	31.2	48.5
	V2900cGy		<20%	15.9	15.3	14.6	13.2	13	11	13.8
	V3600cGy	<1cc	<2cc	2.6	1.5	2.7	1.2	1.9	2.5	2.1

Fig C2(c) Arm C: P4 positional data was not recorded due to technical issues so this patient was excluded from this arm of the study.

Fig C2: *Target and organ at risk doses from retrospective planning study looking at prostate SBRT with a dose boost to the dominant intraprostatic lesion. Out of tolerance results in red. (a) Results from Arm A of the study - no displacement simulated, (b) Results from Arm B of the study - displacements simulated using the RayPilot transmitter position determined from CBCT imaging data, (c) Results from Arm C of the study - plans displaced using positional information from the RayPilot tracking system.*

3. Paper C

Comparing arms A and B, the mean absolute difference between the percentage of the PTV D99% was 13.7 (-4.3 excluding P3), with a range between -70.7 & -0.7. The mean absolute difference in the percentage of CTV D99% was -7.5 (0.2 excluding P3) with a range between -53.9 & 0.7 and the mean absolute difference in the PTV(boost) D99% was -13.8 (-6.7 excluding P3) with a range between -56.2 & -1.6.

Comparing arms A and C, the absolute difference in percentage for PTV D99% was within 1 for all patients, with a mean value of -0.3 and a range between -0.7 & -0.2. The mean absolute difference in the percentage of CTV D99% was 0.0, with a range between 0.0 & 0.1 and the mean absolute difference in the PTV(boost) D99% was -0.8, with a range between -1.6 & -0.4.

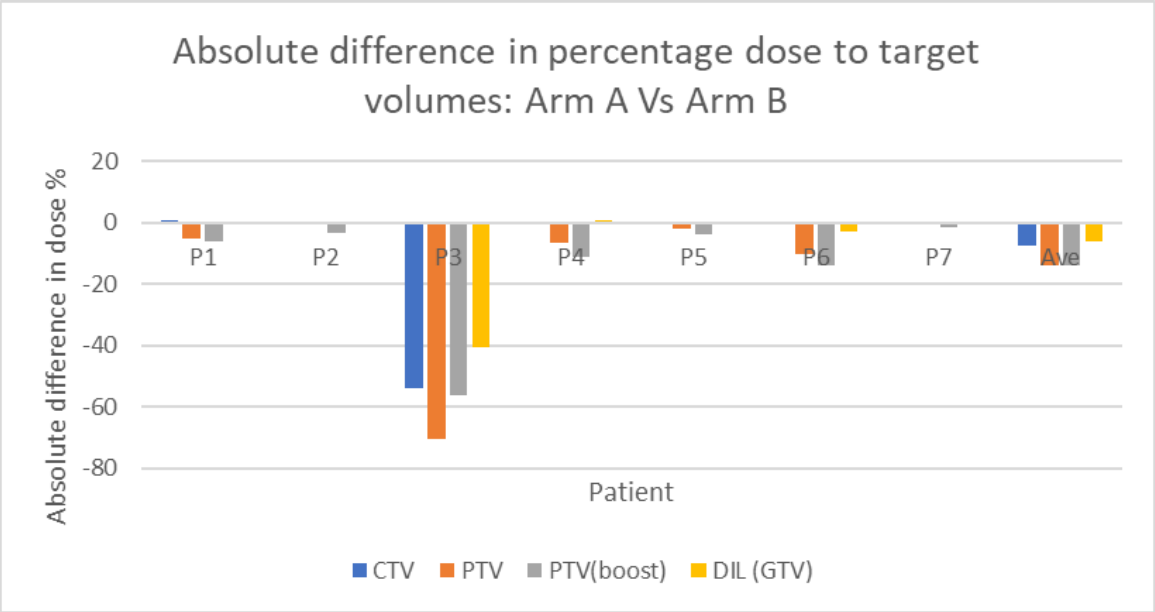


Fig C3(a)

3. Paper C

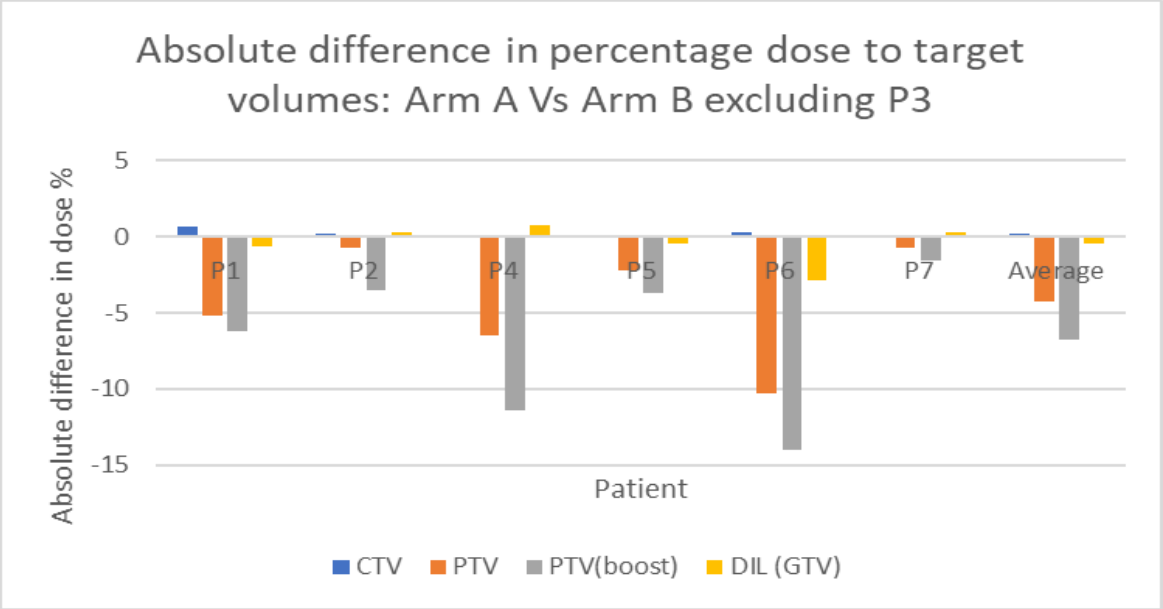


Fig C3(b)

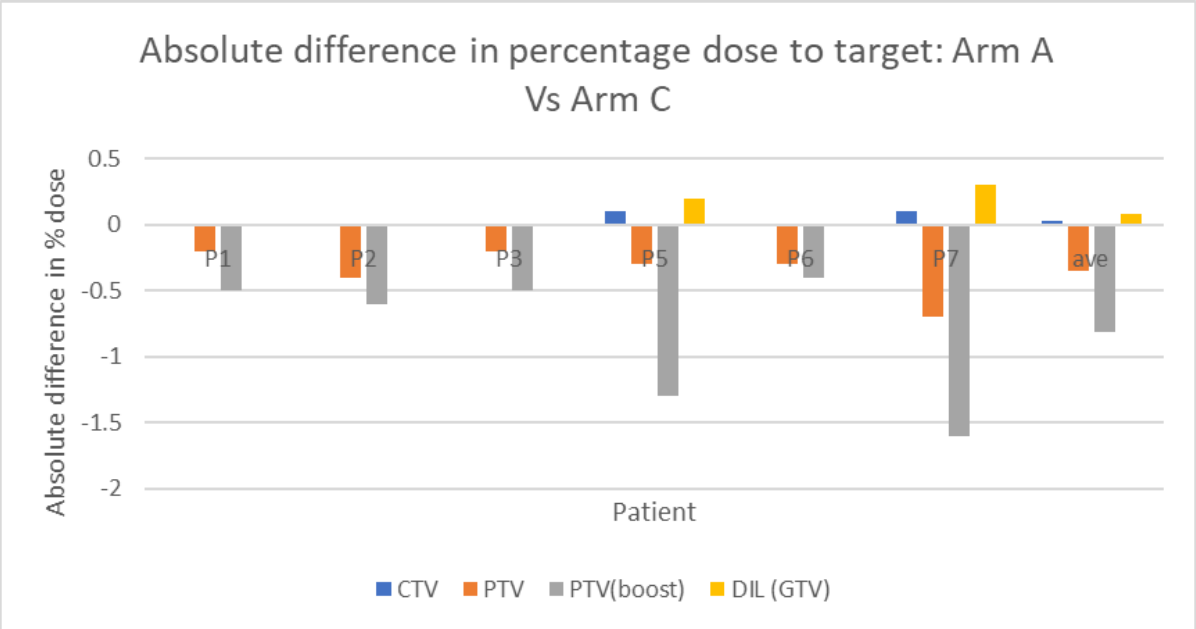


Fig C3(c)

Fig C3: *Graphs showing the absolute difference of the percentage dose of the CTV, PTV, Focal PTV and DIL, comparing two arms of the planning study: (a) comparing arm A and arm B (b) comparing arm A and arm B, excluding P3 (c) comparing arm A and arm C.*

5.5 Discussion

The treatment plans in arm A achieved acceptable target coverage for all patients. The OAR doses however, were only acceptable for two out of the seven patients in the study. The rectum tolerance of V3600cGy being <2cc was exceeded with P1 (2.9cc), P3 (2.8cc) & P7 (2.1cc) whilst P4 (1.9cc) and P6 (1.9cc) were only marginally below this level. As this was a mandatory tolerance, the plans for P1, P3 and P7 would have been deemed unacceptable for clinical use. The DIL for P1 and P3 were located quite posteriorly and their PTV(boost) overlapped with the rectum, shown in Fig C4 a & c respectively. The DIL of P7 is placed quite centrally and but due to its size involves a volume of the PTV(boost) that is close to(0.4cm) the rectum inferiorly as shown in Fig C4 g & h. The DIL for P4 (PTV(boost) was 0.6cm from the rectum) and P6 (PTV(boost) overlapping the rectum) were also positioned posteriorly. The PTV(boost) for P2 and P5 were located further from the rectum (0.8cm and 1cm respectively) and these plans were below tolerance. All of the plans in the study exceeded the optimal dose tolerance for rectum V3600 of <1cc.

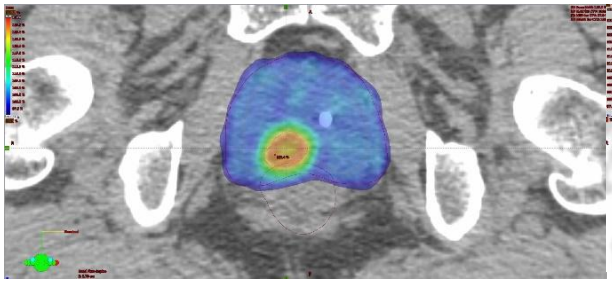


Fig C4 (a) P1

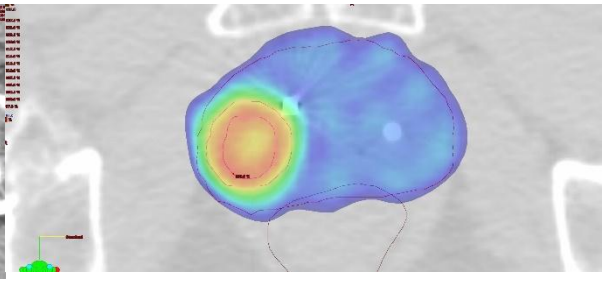


Fig C4 (b) P2

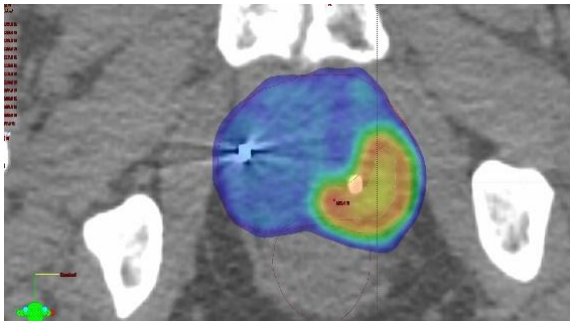


Fig C4 (c) P3

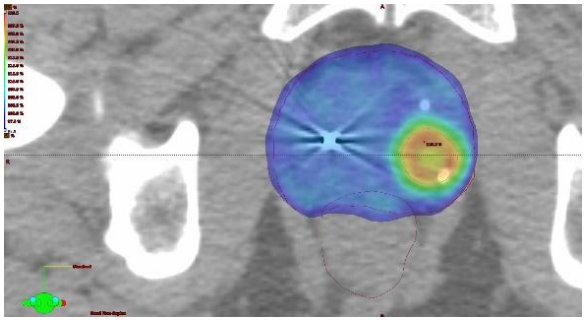


Fig C4 (d) P4

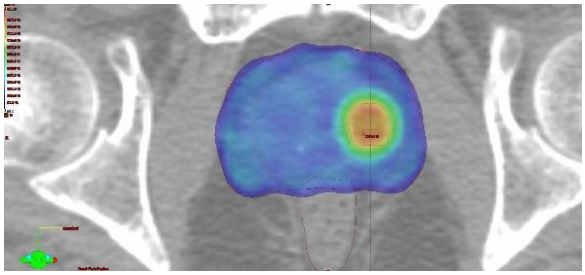


Fig C4 (e) P5

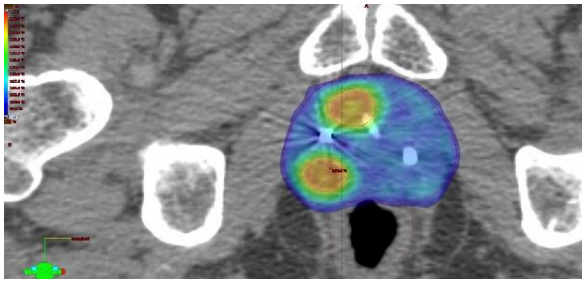


Fig C4 (f) P6

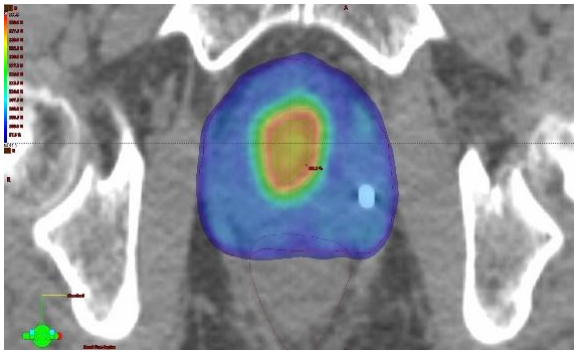


Fig C4 (g) P7 transverse

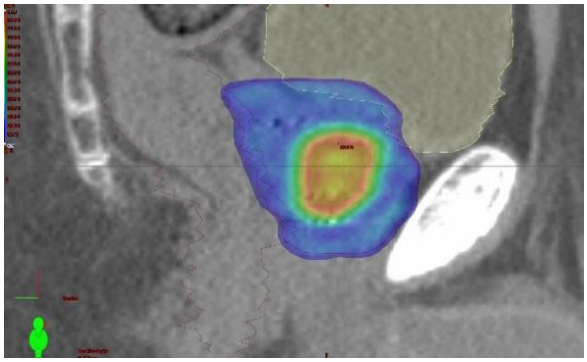


Fig C4 (h) P7 sagittal

Fig C4: *Image showing the high dose region and rectum volume a) transverse plane for P1 b) transverse plane for P2 c) transverse plane for P3 d) transverse plane for P4 e) transverse plane for P5 f) transverse plane for P6 g) transverse plane for P7 h) sagittal plane for P7.*

It would seem feasible that the location and volume of the DIL relative to the rectum would have an impact on whether the OAR tolerances were achievable. When delivering the prescription dose of 3625cGy, reducing the rectum to below 3600cGy is achievable whilst also maintaining the 95% coverage of the PTV, which was demonstrated in the original (non-boosted) clinical plans for the patients in this retrospective study. For patients with boost volumes in close proximity or abutting the rectum, this can be more challenging as it requires a larger dose transition over a relatively small distance. This could be a limiting factor for achieving clinically acceptable doses as seen in Kim et al. (C4).

Some studies have discussed the advantages of spacers to reduce rectum doses during prostate SBRT delivery (C22) (C23). This could be considered either for all patients, or if a

correlation between DIL position and rectum dose was identified, patients could be identified before their planning scan as requiring a spacer.

Although all plans were optimised to produce the lowest OAR doses achievable, the coverage of each of the PTVs was prioritised during the planning process. For clinical patients, the clinician may have requested the rectum dose to be reduced by compromising the DIL PTV coverage. For the lesions that were closest to the rectum, this may have led to a compromise of the dose to the target. Lowering the total dose to the PTV boost may also have been suitable. The approach taken in this study allowed investigation of the impact of intrafraction motion on PTV coverage and a direct comparison between patients, which would not have been possible if plans had been compromised. There was also no established approach to allowing target compromise in this adapted protocol. The impact of proximity of the boost PTV to rectum dose could be investigated further, and a consistent approach to this would be useful for clinical implementation.

Arm B of this study investigated the dosimetric impact of displacements using only the physical position of the RayPilot transmitter seen in the CBCT images. The source data would not be a suitable surrogate for intrafraction motion, as there was evidence showing a statistically significant difference in the positional stability of the RayPilot transmitter compared to the seeds for this limited patient group. These measurements are therefore assumed to be an overestimate of the intrafraction motion, and direct comparisons with the data in Arm A or Arm C may not be representative of the clinical situation but are useful for analysis of the impact of more extreme intrafraction displacements. The treatment plans based on the displacements from arm B showed the dose coverage of the PTV to be below the mandatory tolerance for P1 (92.6%), P3(27.8%), P4(91.8%) & P6(88.2%).

Based on this data, the target coverage for P3 would not be deemed clinically acceptable if delivered. This patient's transmitter was dislodged sometime between their treatment

planning scan and their first fraction. The position of the transmitter in subsequent CBCT images was therefore offset from that seen in the planning scan. This was mitigated for treatment by assigning a new reference coordinate based on a re-scan of the patient. However, the physical position of the transmitter was noted as being variable throughout the treatment, ranging from 0.4cm to 1.5cm displacement. As the data collected for this study used the physical position of the transmitter, this would not be representative of the treated position and this patient should be considered an outlier. If the transmitter had remained stable, a systematic shift from this point could have been used. Inclusion of this patient's results are useful however to highlight the impact on the dosimetry using only the physical position of the RayPilot transmitter. As the kV orthogonal imaging was used for patient positioning this study would not represent a test of using the RayPilot transmitter as the sole imaging modality.

The PTV dose for P1, P4 and P6 was also below the target dose coverage in arm B, with the mean for all plans in the study (excluding P3 being less) than 95%. However, for each of these calculations the minimum expected CTV coverage was maintained. If these represented the actual treatment position, the prostate organ would still have received the prescribed dose. Therefore, this shows the planning solution and margins to be robust to this level of intrafraction motion for the prostate. Although the PTV(boost) only meets the required dose coverage for one patient (P7), the DIL GTV is covered by 95% of the boost dose in all patients excluding P3, which again would demonstrate that the margins and planning solution for these patients are robust to this level of intrafraction motion.

The impact to OARs based on the displacements in arm B was variable. The rectum V3600cGy for P4 and P6 moved from being under the 2cc tolerance in arm A to exceeding it, with the rectum V2900cGy value for P4 also exceeding tolerance in arm B. This highlights the potential impact positional changes can have on the delivered dose to OARs, especially those close to tolerance. This should be investigated and a consistent approach within a

department for dealing with changes in anatomy would be useful before implementing a clinical solution. Adaptive tools such as those utilising deformable registration could be used to more accurately estimate the cumulative dose to structures based on changes seen in each fraction. Creating a PRV volume for such a moveable structure would not necessarily be appropriate and could lead to additional compromise for the target.

In theory, each of the pre and post-fraction CBCT images would be acquired with the patient positioned correctly for treatment. The mean of the pre- and post-treatment CBCT displacements was calculated for each fraction and this was used to represent the relevant displacement in the planning study. There were some limitations of this method of data collection. The variance of the positional displacement of the RayPilot transmitter was not equal to that of the seeds in some directions, in other words some positional instability was noted. This in itself would exclude this data as suitable for assessing intrafraction motion. There were also limitations in the method of data collection, for example the sensitivity of the measurements was limited by the resolution of the images in each plane which was 0.09cm-0.1cm. Additionally, there was an imaging threshold of 0.2cm in the study, which meant positional displacements just below this would not be corrected for. Combined with the image resolution, there is potential for an inherent error of nearly 0.3cm in the measurements before any other variations are accounted for. With the Posterior PTV margin in the plans 0.3cm, and the PTV boost 0.2cm posteriorly and 0.3cm in all other directions this would be seen as significant.

The coordinate position to be used to determine the displacement was measured manually, also the reference coordinates in the planning scan. Although a consistent approach was devised this was not seen as a precise process and may have led to some additional uncertainty. As the CBCT scans were taken directly before and after the beam delivery, they would not represent the position of the patient anatomy during treatment. Using the mean displacement value of the pre and post CBCT scans, this should give a representation of the

intrafraction motion and mitigate any discrepancies. Measurements of the displacement of the fiducial markers could be used in further work to repeat arm B of the study and use the displacement noted by the markers for each fraction, which were noted in the source data to exhibit less overall displacement.

Arm C was investigating the effect on displacements using the real-time positional readouts acquired by the RayPilot system during each patient's treatment. Doses were clinically acceptable for the PTV, CTV and PTV(boost) coverage for all patients in the study. There were also no changes in status of any of the OAR doses, with those values over tolerance being so in arm A too. This would mean that the clinical viability of the plans would be consistent with the original plan based on the simulated displacements. There were technical issues which meant that the RayPilot system didn't record positional data during P4's treatment, and therefore this patient was omitted from this arm of the study.

The displacements used in arm C could be seen as more representative of the treatment, with data being acquired during the delivery of the beam. The data is also collected over time giving positional information during the fraction. However, the system was not synchronised with the actual treatment delivery, and as such contains measurements collected before the treatment delivery and in between arcs. This could include positional variations that were corrected before beam delivery. By using the mean displacement for each fraction, it was hoped that this would mitigate any impact on the plan calculations from this.

If the target had been particularly mobile but oscillating around a point, the mean displacement may have incorrectly pointed towards a stable target. The source data for this study reported information on the percentage of measurement points collected where the transmitter had displaced by more than 0.1cm, 0.2cm and 0.3cm. This allowed the validation that the mean value was representative of the treated position. Measurements taken when

the beam was not on would not be representative of the treated position of the patient anatomy, however it does provide positional information over a longer period of time. As any positional discrepancies would have been corrected, without the beam being delivered, it would be expected therefore that this data set would represent a slightly worst case than the true case. To model the true impact of intrafraction motion, one would have to vary the isocentre position over the whole treatment time. However, this was not feasible with the planning systems available in this study.

Although arm B and arm C were calculated based on the same clinical data, they resulted in very different dose results. This would not be unexpected, with notable differences in the magnitude of the displacement source data for each study. For arm B (excluding P3) the range of mean displacements for each fraction was between -0.4 and 0.4, with 15 fractions out of 35 fractions 0.2cm or greater. In arm C, the measured displacement was generally low, with only P7 exhibiting displacement that exceeded 0.1cm (#4(AP), -0.13) & (#5(AP), -0.11).

Although the data in Arm B was shown to not represent intrafraction motion due to instability and limitations in the data collection, this arm of the study highlights the impact of a more extreme scenario for motion in these types of plans. It should also be noted that by using the RayPilot system as a positional tracker during treatment, systematic intrafraction motion larger than 0.2cm should be identified and corrected, whereas some of the data in arm B suggests systematic displacement in some fractions exceeding this but not corrected for. Although there were limitations in the collection method of displacements noted in arm C this could be considered a worst case, due to the inclusion of measurements collected when corrective positional set up may have been required.

The margins used for the PTV (0.3P 0.5SIRLA) and PTV(boost) (0.2P 0.3SIRLA), would be sufficient based on the displacements in arm B. Based on the data used in arm C alone, a

reduction in these margins could be considered. Although adequate coverage of the DIL would be identified as a priority within the study, it was noted earlier that the rectum V3600cGy tolerance was exceeded for three plans within arm A. A reduction in margins could be looked at to help mitigate this impact. This would be assuming that the fiducial marker system is correct and that the position of the DIL relative to these remains consistent. Without any image verification during the treatment this would be difficult to confirm and as such it would seem unwise to reduce the margins without this evidence base. It may at first be feasible to reduce margins on the PTV and keeping the PTV(boost) margins. Further planning studies would also have to look at whether this would have the desired impact on reducing OAR doses or if the unchanged boost volume would be solely contributing to this.

The imaging tolerance for this study was set to 0.2cm, whereby the patient was only repositioned if their positional displacement exceeded this figure. A change to margins would also have to be carried out within the context of this threshold, as they should be set to account for some variation within the PTV. If reducing the margins required adjusting the imaging sensitivity down, this could have implications on treatment times, leading to more treatment interruptions. The positional data used in arm C showed low variation, with little evidence of systematic displacements larger than 0.1cm during the course of treatment. Increasing the quantity of measurements in future studies may help to inform margins in this technique going forward.

Further studies prioritising dose compromise to the DIL PTV for patients where OAR tolerances are exceeded could be also looked at, or consideration of a reduction to the dose of the escalated boost. Both of these may have clinical implications or may not be permitted as part of particular clinical trials.

This study also assumes that the position of the DIL with respect to the rest of the prostate anatomy and positional aids remains consistent. Some verification of this position during

treatment would be useful. An example of this would be using an MR linac would allow real-time image analysis (C24). This would be assuming that the image quality would be equivalent to the parametric MR images used for delineation of the DIL in planning.

The OAR doses in the study have been calculated assuming they maintain the same volume from the treatment planning scan. It would be expected that there would be some variation in the size and shape of these organs during treatment, and so this would be unlikely to represent their true dose, although bowel and bladder preparation protocols would mitigate this. The V3600cGy for the rectum is recorded in absolute volume, not percentage volume so changes to the organ outside of the high dose region would not impact this parameter. This dose overlap would be expected to occur at the interface between the rectum and the prostate, which if the prostate was positioned correctly would not be expected to alter dramatically ant or post, although some changes laterally could be noted. As such the V3600cGy calculated in this study could be assumed to be a reasonable estimate for the actual dose received. This could be verified in further studies using the data from the CBCT images.

As this a planning study and was not delivered clinically, there would be no survival or toxicity data to analyse. Confidence could be gained by looking to follow some established clinical trials for dose escalated prostate SBRT where early toxicity results have been published.

5.6 Conclusions

The addition of a DIL boost to prostate SBRT treatment plans is feasible and target doses can be met. This led to OAR doses exceeding clinical tolerances set within the study for some cases. The anatomical position of the DIL may be a limiting factor when trying to meet OAR tolerances. The dosimetric impact of intrafraction motion measured using the RayPilot

system was not significant but based on CBCT imaging data some plans may have been compromised.

5.7 Ethical approval

Ethical approval for this work to be presented was granted through the PRINToUT clinical trial ethical approval application.

5.8 References

C1. Prostate Cancer UK. *About prostate cancer: facts and figures.* Available from: https://prostatecanceruk.org/prostate-information/about-prostate-cancer [accessed 01/11/20]

C2. Cancer Research UK. *Prostate cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer [accessed 01/11/20]

C3. Cellini, N, Morganti, A, Mattiuci, G, Valentini, V, Leone, M, Luzi, S et al., Analysis of Intraprostatic Failures in Patients Treated With Hormonal Therapy and Radiotherapy :Implications for Conformal Therapy Planning *Int. J. Radiat. Oncol. Biol. Phys.* 2002;53(3):595–9.

C4. Kim YJ, Yoon KJ, Kim YS. Simultaneous integrated boost with stereotactic radiotherapy for dominant intraprostatic lesion of localized prostate cancer: a dosimetric planning study. *Sci. Rep*. 2020;10(1):1–7. Available from: https://doi.org/10.1038/s41598-020-71715-2

3. Paper C

C5. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol.* 2016;17(8):1047–60. Available from: https://dx.doi.org/10.1016/S1470-2045(16)30102-4

C6. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531–43. Available from: https://dx.doi.org/10.1016/S1470-2045(19)30569-8

C7. Kuperman VY, Lubich LM. Effect of reoxygenation on hypofractionated radiotherapy of prostate cancer. *Med Phys*. 2020;47(10):5383–91. Available from: https://doi.org/10.1002/mp.14343

C8. Arrayeh E, Westphalen AC, Kurhanewicz J, Roach M, Jung AJ, Carroll PR, et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal MRI and MRSI study. *Int. J. Radiat. Oncol. Biol. Phys.* 2012;82(5):787–793. Available from: https://dx.doi.org/10.1016/j.ijrobp.2011.11.030

C9. McDonald AM, Dobelbower MC, Yang ES, Clark GM, Jacob R, Kim RY, et al. Prostate stereotactic body radiation therapy with a focal simultaneous integrated boost: acute toxicity and dosimetry results from a prospective trial. *Adv. Radiat. Oncol.* 2019;4(1):90–5. Available from: https://doi.org/10.1016/j.adro.2018.09.007

C10. Feng Y, Welsh D, McDonald K, Carruthers L, Cheng K, Montgomery D, et al. Identifying the dominant prostate cancer focal lesion using image analysis and planning of a simultaneous integrated stereotactic boost. *Acta Oncol.* 2015;54(9):1543–50. Available from: https://dx.doi.org/10.3109/0284186X.2015.1063782

3. Paper C

C11. Lovelock DM, Messineo AP, Cox BW, Kollmeier MA, Zelefsky MJ. Continuous monitoring and intrafraction target position correction during treatment improves target coverage for patients undergoing SBRT prostate therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;91(3):588–94. Available from: https://dx.doi.org/10.1016/j.ijrobp.2014.10.049

C12. De Muinck Keizer DM, Kontaxis C, Kerkmeijer LGW, Van Der Voort Van Zyp JRN, Van Den Berg CAT, Raaymakers BW, et al. Dosimetric impact of soft-tissue based intrafraction motion from 3D cine-MR in prostate SBRT. *Phys. Med. Biol.* 64 (2019) 235008. https://dx.doi.org/ 10.1088/1361-6560/ab6241

C13. Accuray. *Cyberknife S7* https://www.accuray.com/cyberknife [accessed 04/11/20].

C14. Varian Medical Systems *Radiotherapy products* Available at: https://www.varian.com/en-gb/products/radiotherapy [accessed 06/11/20]

C15. Choi HS, Kang KM, Jeong BK, Song JH, Lee YH, Ha IB, et al. Analysis of motion-dependent clinical outcome of tumor tracking stereotactic body radiotherapy for prostate cancer. *J. Korean Med. Sci*. 2018;33(14):1–13. Available at: https://doi.org/10.3346/jkms.2018.33.e107

C16. Mantz C. A phase II trial of stereotactic ablative body radiotherapy for low-risk prostate cancer using a non-robotic linear accelerator and real-time target tracking: Report of toxicity, quality of life, and disease control outcomes with 5-year minimum follow-up. *Front Oncol.* 2014;4(279):1–8. Available at: https://doi.org/10.3389/fonc.2014.00279

C17. Aluwini S, Van Rooij P, Hoogeman M, Kirkels W, Kolkman-Deurloo IK, Bangma C. Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: Early results. *Radiat. Oncol.* 2013;84(8):1–7. Available at: https://doi.org/10.1186/1748-717X-8-84

C18. McLaren D. *Using breath analysis to PRedIct Normal TissUe and Tumour response during prostate cancer SBRT*. Version 1.0 May 2018, IRAS Number: 240335

C19. Micropos *Raypilot solution* Available from: https://micropos.se/healthcare-professionals/raypilot-solution [accessed 29/10/20]

C20. Trainer M, Carruthers L, Nailon B, Kirby M *Investigating the use of RayPilot for motion management during prostate SBRT: initial experience* ESTRO 2020 available from: https://www.estro.org/Congresses/ESTRO-2020/279/ph

C21. Trainer, M, Adamson, S, Carruthers, L, Nailon, B, Kirby, M Analysis of the Intra-Fractional Motion of the Prostate During SBRT Using an EM Transmitter, *Int. J. Radiat. Oncol. Biol. Phys.* 2020;108(3):e340 Available from: https://dx.doi.org/10.1016/j.ijrobp.2020.07.812

C22. Hwang ME, Mayeda M, Liz M, Goode-Marshall B, Gonzalez L, Elliston CD, et al. Stereotactic body radiotherapy with periprostatic hydrogel spacer for localized prostate cancer: Toxicity profile and early oncologic outcomes. *Radiat. Oncol*. 2019;14(1):1–9. Available at: https://doi.org/10.1186/s13014-019-1346-5

C23. Ruggieri R, Naccarato S, Stavrev P, Stavreva N, Fersino S, Giaj Levra N, et al. Volumetric-modulated arc stereotactic body radiotherapy for prostate cancer: Dosimetric impact of an increased near-maximum target dose and of a rectal spacer. *Br J Radiol*. 2015;88(1054):7–10. Available at: https://doi.org/10.1259/bjr.20140736

C24. De Muinck Keizer DM, Kerkmeijer LGW, Maspero M, Andreychenko A, Van Der Voort Van Zyp JRN, Van Den Berg CAT, et al. Soft-tissue prostate intrafraction motion tracking in 3D cine-MR for MR-guided radiotherapy. *Phys. Med. Biol.* 2019;64(23). Available at: https://doi.org/10.1088/1361-6560/ab5539

6. Critical Appraisal

6.1 Introduction

A research study acquires evidence in a systematic way to address a particular problem. In clinical research this evidence base can be used to inform or change clinical practices. For decisions affecting patient's treatments and care, it is essential that a critical appraisal of any applied research is carried out. This is a way of interpreting the relevance of results or conclusions and putting them within the context of their intended clinical use.

Having a consistent and systematic framework for critical appraisal is important, and some guidance on established critical appraisal methods are available. The critical appraisal skills programme (CASP) (71) is a training course for healthcare professionals, aiming to provide them with the skills and knowledge to analyse research. The CASP checklist (18) is a tool that provides a clear methodology to be followed whilst carrying out a critical appraisal. Al-Jundi et al. (72) discussed the importance of critical appraisal of research when clinicians are integrating new evidence and techniques into clinical practice. Their review provided guidance on critical appraisal techniques, and explored the idea that this is a vital clinical tool and developing these skills is as important as developing the skills used in technical aspects of clinical roles.

In addition to critical appraisal of available research, it is important to employ these techniques to self-appraise one's own research, especially when used to inform clinical practice decisions. This chapter aims to critically appraise the research project investigating the use of the RayPilot system to track and correct intrafraction motion for prostate SBRT with an escalated boost.

The important aspects of the research are highlighted, noting where it aligns with published research and where its novel aspects can be found. The strengths and areas of development within the project are discussed, alongside the implications of the project within the wider field of study and the proposed direction of future work. This critical review offers insight into the impact of the research within the local department and to the specific field.

6.2 Context within wider research and practice

6.2.1 Imaging approach

The imaging approach used within this research study was to use kV orthogonal images as the primary imaging modality for patient positioning, with the RayPilot system as a supplementary tracking system and to verify the 3-D position of the transmitter on CBCT images. This was a similar method to that discussed in Braide et al. (25), a study investigating the RayPilot system in long course prostate patients. One difference noted was the method in Braide et al. for assessing relative positional differences between the fiducial markers and transmitter. For this they used MATLAB software (26) to calculate this which is a more quantifiable method, and may have reduced the potential error in sensitivity of the CBCT measurements discussed in section 3.5. However, patient's in Braide's study received 39 fractions so intrafraction target motion of a single fraction would have less impact than in prostate SBRT, but did provide a larger base of measurement points for each patient.

6.2.2 Application of data to a planning study

Real clinical positional data was used to inform the planning study in Paper C. Lovelock et al.(33) used a similar approach to their planning study, using clinical positional data from the Calypso tracking system (29) to simulate the dosimetric impact to a target. However, the use

of the data in each study was different. Whilst Paper C focussed on the dosimetric impact of the treated position of the patient, Lovelock et al. focussed on the impact of the tracking system, simulating the dosimetry on treatments if no positional intervention had been available. This reflects the different research aims for each study with the research in this thesis looking to test the robustness of the imaging and tracking system as a whole, whereas Lovelock et al. aimed to validate the use of a tumour tracking system within the delivery.

Bijina et al. (59) published a planning study comparing delivery methods for prostate SBRT with integrated boost. They assessed the dose distributions using not only DVH data but also conformity indices. This method of plan analysis was not used in Paper C, but would be a useful metric to analyse the dose gradient of the boosted lesion. This may provide further evidence on the impact of the position or volume of the lesion discussed in section 5.5. Bijina et al. (62) provides a degree of validation to the linac delivery method in this study as they found plans based on linac delivery to be superior to Cyberknife and Tomotherapy, albeit without taking into account intrafraction motion. However, their study included limited patient numbers (N=13), so strong conclusions about this superiority could not be drawn.

6.2.3 Tracking system comparison

A comparison between the positional data of the RayPilot transmitter detected in CBCT images in Paper A and the RayPilot readout data in Paper B showed differences. This was reflected in the variation in results from the planning studies, with Fig C1(b) using the data from Paper A which resulted in more parameters being outside tolerance than using the data from Paper B shown in Fig C1(c). However, this doesn't appraise one method over the other. In Hamilton et al. (31), a comparison between the Calypso tracking system, CBCT and kV orthogonal imaging was carried out using a phantom. Using a phantom was useful as a

direct comparison between the imaging systems. Although using a phantom gives clear quantifiable results, the acquired clinical positional data is more representative to simulate the delivery of a simultaneous integrated boost plan and therefore supports the research aims formed from the literature review for this project (Table 5).

6.2.4 Focal lesion clinical trials

Draulans et al. (65) published updated results for the hypo-FLAME trial, treating prostate SBRT with an escalated boost. The toxicity for a group of 100 patients enrolled in the trial was reported, with promising results. The strength of this paper is not only the patient numbers but that they are reporting toxicity data. One would expect that this would have an impact on informing clinical practice, and also give clinicians confidence to follow the trial methodology. Their patient sample size of 100 was chosen specifically to gain 82% power on a one-sided significance level of 0.05. One of the advantages of this large trial was that they start to analyse once the required patient numbers were gained, meaning their statistical analysis would be more robust. The PRINoUT study was designed to be a small pilot study, with 7 patients at the time of this research study and as such there was no expectation that this number of patients would be recruited.

Whilst this research project was based on the clinical protocol of the PACE trial, the hypo-FLAME trial includes a simultaneous boost and may be of interest for future studies or clinical implementation. They reported a large number of patients and found that a boosted prostate SBRT treatment resulted in acceptable toxicity. One difference in the approach within hypo-FLAME was the addition of a 0.2cm PRV around the rectum, whilst the PRINToUT solution included no PRV. Hypo-FLAME did not include a PTV margin for the boost volume, whereas the planning study in paper C did. Paper C discusses how the boost PTV margin helped the GTV to receive the required dose in cases where significant

displacement was noted (Section 5.5), but would have contributed to the inability to meet the rectum dose constraints on some plans (Fig C1(b)). There was also no specific mention in Draulans et al. (61) that the centres involved in FLAME had used any tumour tracking systems during the delivery, but one centre was noted as treating with rectal spacers. Some of these differences in approach should be investigated before adopting these practices for future studies.

6.3 Appraisal of the research process as a whole

6.3.1 Study design and set-up

The research process for this project was robust, however there were some logistical factors within the study design that led to limitations. The data was collected from clinical patients enrolled in a locally run clinical trial, PRINToUT (12). With this trial representing the first implementation of prostate SBRT locally, the technique commissioning and set up of the research project were carried out concurrently. Due to a strong multi-disciplinary collaborative approach, this was completed in a timely manner. The range of contributors increased the strength of the data collection, as this research was not solely carried out with Physics input, but drew on suggestions from radiographers, medics and the clinical trials administrators. One of the main strengths of gathering data within a clinical trial, was that the quality of the data collected was high. The trial was reviewed and approved by the Academic and Clinical Central Office for Research and Development (ACCORD) (73). This ensured that the methodology for data collection was of a high standard and that any deviations would be investigated. The patient demographic had to meet the inclusion criteria for the trial, and the treatment protocol ensured a high level of consistency in the beam delivery, imaging and data collection by the team treating the patient. There were some disadvantages to setting up this research project alongside the PRINToUT trial. For example, the timeline for collecting the data and indeed starting the study were tied to the

trial. It also meant significant changes to the treatment protocol could not be made after the trial had started as this would require further ethics approval. One of the consequences of the required start date was that the study was set up for clinical treatments and data collection before the literature review for this project could be completed or the research questions formed. The consequence of this was that the study and data collection was carried out in a more general manner and the research questions would not inform the detail of this. There was a large amount of data available for each treatment however, which was one of the advantages of aligning with PRINToUT. This allowed flexibility when defining the research question and significant deviations would not have been expected if the literature review was carried out earlier. There are positive aspects in having the opportunity to supplement and support a locally run clinical trial. When a trial such as this is devised, it may be a prompt for a department to look at other avenues of research that can be carried out alongside the gathering of high-quality data. However additional data collection within a trial may invalidate the ethics and governance around the original trial and so must only be carried out with this in mind.

6.3.2 Site visits

The team setting up the PRINToUT clinical trial had visited another centre using this tracking system and also visited the manufacturer. This was aimed to get some exposure of using the equipment and generate ideas for integrating the system into a clinical technique. However, this was carried out before this research study was devised. It would have been useful to have carried out a site visit such as this but this was not feasible due to time constraints and staffing resources. A site visit looking at research of tracking systems would have been advantageous and may have informed the design of the project differently. Visits may have included centres using alternative tracking systems or with significant research output. The

experience from the local team that had carried out the site visits was available, and the manufacturers were available to give technical support.

6.4 Data collection: Strengths and areas for improvement

One of the strengths of this research was the multi-disciplinary approach to gathering the data. The team involved in setting up the treatment protocols and trial were drawn from a wide range of disciplines. There were regular update meetings with all groups where trial progress along with associated research studies were discussed and reviewed. Because all the data was collected from clinical patients, the requisite checks and audit were carried out to national standards and staff training was robust and evidenced clearly. As the data used in this research was already within a clinical trial, this was covered by the existing ethics approval.

6.4.1 Patient numbers

One of the areas of improvement for the project was the low patient numbers included in the study. Patient recruitment relied on patient's agreeing to not only the fractionation, but also the procedure to insert the tracking device. This may have also impacted the demographic of potential patients enrolling in the study. Patient recruitment was limited by the availability of theatre sessions and radiologist to insert the device. This proved to be difficult to facilitate in some cases and as such the projected 12 patients in the first year was not met, and not all patients who were eligible and willing to participate could be enrolled.

Low patient numbers in the study also meant that the power of any statistical significance of any tests would not provide suitable levels of confidence. Examples tests included looking at a correlation between the co-ordinates of the fiducial markers and the co-ordinates of the

Raypilot transmitter tip. This would have been a way of validating the stability of the transmitter against an established method. A study to investigate any correlation between displacement and fraction number would also have been interesting. Although the patient numbers didn't allow strong conclusions from the numerical results, it was originally devised as a small pilot study and were sufficient to fulfil this remit. Striking a balance between spending years collecting sufficient data for statistical significance and publishing data early is key when devising research projects. One of the advantages of a large multi-centre approach to research studies is the potential to access large patient numbers in a shorter timescale.

6.4.2 Data collection

The approach to gathering data was flexible and could be carried out using readily available software such as Excel. Therefore, the collection and the analysis of the data could be done at various locations and times rather than relying on the availability of particular computer terminals. No additional training or support to manipulate the data using Excel was required, which helped the collection and analysis of data to be within the required timelines. There was a large amount of data available for each patient. Whilst patient toxicity data was also being collected in the trial, this was not utilised for this project. Whilst this may have added to the study conclusions, it wasn't necessarily appropriate to use within Paper C due to the focus on integrated boost dosimetry for which the PRINToUT toxicity would not be relevant. It would be an interesting follow up study to look at the patient's toxicity results in the context of the positional data reported in Paper A and Paper B.

The first patient in this study was the first patient locally to be both treated with prostate SBRT and also using the RayPilot tracking system. This meant that the department was building up experience in the technique as the trial went on. This may have led to differences

in the approach to imaging, treatment and the decision process as experience was built up, which could have influenced the results. However, this also meant that a small team were involved through the pathway, including the planning and treatment staff and the treatments were all carried out on a single linac. This would have helped maintain consistency.

6.4.3 Contouring

The dominant intraprostatic lesion (DIL) was outlined using multi-parametric MR images. This was carried out using a combination of the MR images available. This may have led to some variability in the lesion contour, as preferencing one of the multi-parametric images over the other can impact the defined volume. It may be that this method also doesn't capture all of the lesions in the prostate. Johnson et al. (50), carried out a large study where they found that only 45% of all prostate lesions can be detected using multi-parametric MRI. For this research project, the lesion delineation was carried out using rigid registration, as deformable registration wasn't available but may be more accurate (53). The position and volume of the lesion was thought to influence the ability to meet clinical OAR tolerances in Paper C (Section 8.5), these factors combined may have had an impact on the results.

Outlining was carried out on the plans by the clinician responsible for that patient. However, the prostate lesion was outlined for all patients by a single clinician for research only. Having only one clinician involved in the lesion outlining could have introduced some user bias, and as these volumes weren't to be used in the clinical planning process, they were not subject to the same audit and checking as the rest of the volumes.

6.4.4 Collection of empirical data

The data collection was quite resource intensive. With more available time at the beginning of the study, or with access to advanced computer programming skills, some of this could

have been automated. This may have allowed more in-depth analysis of the values or to highlight trends. A large portion of the data analysis involved manually recording data in spreadsheets. Although the study was only carried out on seven patients, there were a large number of data points gathered and much of the data from the RaypPilot system had to be manipulated manually to remove outliers as described in section 4.3. To expand the scope of this study, it would be a requirement for much of this work to be automated. This would be achievable but would require additional support, such as from a computer scientist, which was not available for this project.

The Edinburgh Cancer Centre has a research agreement with the manufacturer of the RayPilot tracking system, Micropos (11). This was advantageous throughout the project, allowing access to technical information and receiving additional support throughout the commissioning process. Access to the system's raw data was also easily attained, which isn't the case with all commercial radiotherapy systems. This helped for there to be some flexibility in determining the use of the data. There was minimal input from the manufacturers in the actual research aspect of the project or study design which helped to maintain independence.

The displacement data from two systems, CBCT and RayPilot were analysed within the study. There were differences noted between this data and limitations with each method of collection. The limitations of the CBCT method discussed in paper A included potential error due to slice thickness and some evidence of instability of the transmitter, whereas the RayPilot data discussed in Paper B had a higher level of geometric precision but could not be synchronised to the beam delivery times. It may be that the planning study in Paper C could have only used the RayPilot data, but the CBCT images were useful for the whole study to assess the stability of the transmitter device. An improved method for a direct

comparison would have been for the RayPilot readout displacement to be recorded during the CBCT acquisition. Although useful for this research, this may have added an extra layer of complexity to the treatment and imaging process for the radiographers, with this being recorded manually, and as such may not have been practical to have included in this pilot study.

The empirical results within this project were taken from clinical data, but only analysed by one operator. Although for some aspects of the data collection this would have given a more consistent approach, this may have introduced bias as the interpretation of the measurements were not peer reviewed. This was mitigated through discussions and updates with experienced members of the research team. Identifying the data to collect was straightforward, but there were instances such as determining outlier points from the Raypilot readout in Paper B that were more subjective and would have been improved by some peer review. Also, the treatment plans in the planning study in Paper C did not go through the same rigorous checking process that would be carried out if they were to be delivered clinically, and as such do not exactly replicate a clinical situation.

6.5 Broad methodological approach

6.5.1 Novel aspects to the research

There was an opportunity for a novel approach to this research project through the use of the particular tracking system. The Raypilot system is not widely used across clinical departments at the time of the study, with the Edinburgh Cancer Centre being the first UK centre to use this equipment clinically. Subsequently, there wasn't a large body of published data on this system and while there were studies looking at the viability of Raypilot as a tracking device, there was little evidence found where positional information from the system

was used to inform a planning study such as in Paper C, or for simultaneous integrated boosts. Although this provided opportunities for this project, the lack of a large body of previous research studies about the tracking system could also be seen as a disadvantage. However, there were many studies found within the systematic review that involved other tracking devices and systems such as Calypso (29) and Cyberknife (34) and the principles could be applied to inform this research study.

6.5.2 Qualitative Vs Quantitative analysis

The methodological approach to the research in this project was mainly through quantitative analysis. For scientific studies this would be a more familiar method for data collection, with a large amount of the empirical data being numerical. There may be a tendency for scientists to view qualitative data collection as being less precise, and they may not have had the same exposure to this methodology throughout their training. McCusker et al. (74) suggests advantages to designing clinical research using a mixed methodology with qualitative and quantitative analysis. There may have been opportunities in this project for some of the data to be collected in using a more qualitative approach. For example, this could have focussed on the experiences of the radiographers using the equipment. The patients could have recorded how they felt on each fraction to see if there was a correlation between this and their set up data. Some qualitative data was collected and available within the clinical trial, but was not considered for inclusion in this research. This may have added some additional context to the conclusions and help to understand some of the clinical results.

6.5.3 Single centre study

There may have be limitations to this research being conducted as a single centre study. This may have led to enforced bias in the data collection, only based on the experience of

one group of staff. That being said, for this small pilot study with the low overall patient numbers expected, it may have been that the addition of other centres for data collection would have reduced the consistency in the data collection. By the same rationale, introducing centres with other equipment such as planning systems or linacs would have been an advantage for a larger study but may have diluted the results of this study in its final form. The addition of another centre with an alternative tracking system would have allowed a direct practical comparison between this system and RayPilot.

6.6 Line of enquiry

A set of three research questions were devised within this study (Table 5), which were used to guide and inform the direction of the study as a whole. These questions were devised based on a literature review carried out looking at current practice and available research for tracking devices and the treatment of prostate SBRT.

6.6.1 Research question 1: *What is the accuracy and stability of RayPilot for prostate motion management during SBRT?*

The first research aim identified was to investigate the accuracy and stability of the RayPilot tracking system during prostate SBRT delivery. This was carried out within the study, but there were limitations as to how definitive this could be answered. As the RayPilot system was used alongside the existing imaging system, the results do not necessarily isolate the tracking system's role in the placement of the patient. The stability of the RayPilot system relative to the seeds was assessed in paper A, with statistical analysis showing a significant difference in the variances of the measured displacements in some directions and hence instability. As this was only carried out on a limited number of patients, further studies would be required to provide strong evidence of instability. The accuracy was validated somewhat through the commissioning and ongoing QA of the system, along with its combined use with

the kV system to position the patient. The positional measurements in Paper B showed that the patients were positioned successfully using the combined imaging protocol and the system was able to detect target fluctuations when they occurred.

6.6.2 Research question 2: *How does RayPilot compare against other motion management systems for SBRT?*

The second research question was to compare the RayPilot system against other available tracking and imaging systems. This was fulfilled in part but with lots of areas where further research would have been useful. A direct comparison of practical measurements against other tracking systems was not feasible, as RayPilot was the only available tracking system available for this study. The range of research and reading within the study allowed for comparative analysis on the use of other tracking systems (33)(38)(46)(59), and an understanding of the strengths and weaknesses of the RayPilot system for delivering prostate SBRT compared to these was attained through this.

Due to the logistics of commissioning, additional QA and revenue costs associated with tracking systems, radiotherapy centres would typically only use one type of system. However, as the RayPilot system is only currently available for research and for one linac at the Edinburgh Cancer Centre, there are plans to supplement this by commissioning a triggered imaging system on the Truebeam, which uses the kV imager to track patients (75). This may provide some direct comparisons between tracking systems in future studies. Expanding this research to include other centres with alternative tracking systems would also provide opportunities for direct comparison and validation of RayPilot.

6.6.3 Research question 3: *Can RayPilot be used for dose escalated prostate SBRT?*

The study showed that in some patients, dose escalated SBRT would be possible but could be restricted in meeting the OAR tolerances by the location of the lesion. A limitation identified in this line of enquiry was that there would be no clinical patients treated using

dose escalated prostate SBRT. Therefore, data from the non-escalated prostate SBRT patients was used and applied to the study in Paper C. As a feasibility planning study this was useful, looking at the current clinical imaging protocols in a situation where a dose escalated plan could be delivered. However, what this was not able to simulate was the additional clinical processes that would take place if the dose escalated protocol was to be used. For example, the more rigorous checking process, patient reaction to the dose escalated doses and how the decision process of the clinical staff would change to displacements from this technique. There were five out of seven patient plans in Arm A of Paper C that didn't meet the OAR tolerances. As the planning study had a focus on impact from displacements on target coverage, the approach for plans where OAR tolerance was exceeded was not resolved but would be a component to answering the research question fully.

None of the imaging or tracking systems used in the study were able to verify the position of the lesion during treatment. Although this was a consistent feature noted in a number of studies and trials found in the systematic review, it would also be seen as a limitation to fully addressing the research question in this study and would be useful to look into further.

6.7 Study implications for clinical practice and theory

6.7.1 Clinical implications for the study locally

Locally, this study has built up confidence treating prostate SBRT and using a tracking system. The Edinburgh Cancer Centre is actively looking to increase the number of prostate SBRT treatments it delivers, and this research provides evidence on the impact of the imaging protocol, and shows the reliability of the RayPilot tracking system, providing confidence the target is positioned correctly. There were also some questions highlighted from the study which could be investigated locally, such as the margins used in the study.

For the target margins, the practical measurements showed that the target remained stable for much of the treatment data points (Fig B3), and displacements were identified and corrected in a timely manner. A reduction to the margins and its potential impact could be investigated based on this data.

There were limitations on using the RayPilot tracking system for wider use in the department due to this only being available for one linac and funding issues regarding the transmitters for non-trial patients. However, this research can be used to help inform the proposed use of triggered imaging (75), where the kV orthogonal imager is used as a tracking device. This is a commercial system replicating the KIM solution described in section 2.4.6. Although this system tracks the position during the treatment phase it does require the beam to be interrupted whilst imaging, and this occurs a designated number of times throughout the treatment arc. This would mean that unlike RayPilot this system would not provide real-time tracking throughout the beam delivery. These differences and their impact could be investigated. There would also be an additional concomitant radiation dose to the patient from the triggered imaging. The system is however available to use of each of the Truebeam linacs within the department and would need no capital investment and so be used to expand access to SBRT to a greater number of patients.

The positional variation of the transmitter and hence the target over a fraction was small, based on the RayPilot readout data from Paper B. The dosimetric impact to the target volumes in the focal boost planning technique using these measurements in Paper C was not significant (Fig C1(c)), with the dose values consistent with the plans with no displacement (Fig C1(a)). This can give confidence that the standard prostate SBRT plans delivered within the PRINToUT trial would also have acceptable delivered dosimetry. There could be an argument that the additional kV imaging between arcs could be removed from

the protocol if tracking is being carried out. However, as all of the data points in this research study were acquired following this imaging protocol the results would be applied to these conditions. To reduce the frequency of any imaging within this protocol would require further work. This could include an audit to investigate when the kV orthogonal system highlighted a patient displacement that required adjustment between arcs.

6.7.2 Dose calculation algorithm

The algorithm used for dose calculation in the planning study was the Analytical Anisotropic Algorithm (AAA) which may have influenced the outcome of the study. Acuros XB is an alternative dose calculation algorithm available within Eclipse (76), which uses a different method of dose calculation to AAA by discretely solving the linear Boltzman transport equation. Kim et al. (77) showed that recalculating prostate VMAT plans with Acuros XB instead of AAA resulted in a statistically significant difference to the dose parameters of the plans. Koo et al. (78) compared prostate VMAT plans, calculated using Acuros XB and AAA in a phantom and found that plans using Acuros XB calculated the dose within an air cavity such as the rectum more accurately. Whilst the Acuros XB algorithm is available locally, it has not yet been commissioned for either clinical use or research studies. This study has shown there would be a use for an additional planning algorithm to help benchmark research studies in the department. This would help to provide extra context and validate calculations and may be a useful method for comparison to other centres where more advanced calculation algorithms are used within research studies.

6.7.3 Research output and impact

This research study has so far produced two posters which have been peer reviewed and accepted for display at the ESTRO 2020 (13) (Appendix 3) and ASTRO 2020 (14) (Appendix 4) conferences respectively. The three papers included within the thesis will be submitted to

an appropriate journal for peer-review and potential publication. It is important for research studies such as this to aim to have some kind of scientific output to increase research impact beyond the local department to the wider academic and clinical looking to utilise similar work or practices. The advantage of submitting work in this way, is that it allows peer review by an expert in the field who can critique and hopefully endorse the work as of a quality suitable for inclusion in a leading scientific conference or journal.

This research would interest centres looking to implement a prostate SBRT service or looking to introduce a simultaneous integrated boost. The methodology of the research and in particular the use of actual clinical measurements to feed into a planning study could be used as a framework for using imaging data to validate a change in process. This methodology could be utilised in studies involving other anatomical sites where real-time tracking is used and a change of practice is being considered. Centres looking to implement the use of the RayPilot system would be interested in this research, with one of the novel aspects of this research being the use of this system where limited published studies exist. The set of papers within this thesis provide a framework for clinicians in cancer centres to implement the RayPilot system and can be used to inform future research study design.

6.8 Suggestions for future work or implementation

Clinical research should be seen as an ongoing process, whereby the end points of studies not only provide answers to a question, but also identify further questions to be explored. There is a large body of further work identified within this study. These suggestions were derived through background reading, from issues that arose during collection of the empirical data, time restrictions that didn't allow lines of enquiry to be followed through, technical limitations in the study and suggestions from clinical users of the system. A subset of future work identified within the study is summarised below.

The PRINToUT trial has been amended but will continue, albeit with a different system for inserting the Raypilot transmitter – known as Hypocath(79). This will allow the transmitter to be inserted by the patient self-catheterising through the urethra and avoiding the need for a theatre session. It is hoped this will allow the patient numbers able to participate in the study to be increased. This change of system provides an opportunity to use the results from this research to validate this change. The stability of the device will be of particular interest due to the change in method of insertion, this may have an influence on the intrafraction changes in the transmitter and could be investigated.

With data continuing to be collected within the study this would be an opportunity to follow a larger patient cohort over a longer time. This may provide the opportunity for statistically significant analysis and to correlate some of the medium or long-term outcome data and toxicity with the positional data. The primary results from the PRINToUT trial will be the analysis of the volatile organic compounds from patient breath samples caused by radiotherapy and its relationship to normal tissue and disease response. Once this data has been analysed it may be useful to correlate any findings within the results in this research, or future patients using this methodology. The CBCT data could be used to supplement this. However, to facilitate a large increase in patient numbers a more efficient method for data collection and analysis would be advantageous.

Other anatomical sites could be treated with tracking using the Raypilot transmitter. Although designed for use in the prostate, there have been discussions about its future use for bladder radiotherapy. This could be looked at within the context of a simultaneous integrated boost to the GTV in the bladder. Other mobile sites in the body would be feasible for this technology too, although limitations around its suitability for insertion in some sites may prove a limiting factor.

To verify the RayPilot transmitter as a means to tracking the focal lesion, some verification of the transmitter position relative to the focal lesion would be useful. This could be done on an MR Linac, or indeed on an MR sim. The composition of the transmitter may interfere with the MR image, however the Hypocath system allows the catheter to be inserted without the transmitter and this could allow some verification of its position. Investigating if the focal lesion is identifiable on the images of an MR Linac would be useful, along with investigating whether an additional tracking system is required with this technology.

There has been interest internationally in delivering hypo-fractionated prostate SBRT in a single fraction (80). If this was the direction of future development in the UK and for the Edinburgh Cancer Centre, further work could be carried out on this system to assess its efficacy for this use such as a feasibility study looking at positional information from individual fractions. Delivering the whole dose of radiotherapy in one fraction has risks, for example intra-fraction motion of a single fraction would impact the dosimetry of the whole treatment. As such, this should only be considered after extreme confidence is gained from the positional imaging system, and ideally within an established clinical trial.

7 Concluding remarks

This research study has provided confidence to support the continuation and expansion of prostate SBRT at the Edinburgh Cancer Centre. The RayPilot tracking system provided a novel approach to the work, and the use of actual patient displacements applied to a planning study provided clinical context and strength to these results. This project was an excellent example of strong multi-disciplinary collaboration and fostered the development of a broad range of research skills and techniques in the production of this thesis. It is hoped that these skills can be developed further and applied in future work to support and lead research activity through a collaborative approach at the Edinburgh Cancer Centre and beyond.

References

1. Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: A review of current literature and clinical use in practice. *Br J Radiol*. 2011;84(1007):967–96. Available from: https://dx.doi.org/10.1259/bjr/22373346

2. Michalski A, Atyeo J, Cox J, Rinks M. Inter- and intra-fraction motion during radiation therapy to the whole breast in the supine position: A systematic review. *J Med Imaging Radiat Oncol*. 2012;56(5):499–509. Available from: https://dx.doi.org/10.1111/j.1754-9485.2012.02434.x

3. Saito N, Schmitt D, Bangert M. Correlation between intrafractional motion and dosimetric changes for prostate IMRT: Comparison of different adaptive strategies. *J. Appl. Clin. Medical Phys* 2018;19(4):87–97. Available from: https://dx.doi.org/10.1002/acm2.12359

4. Van Herk M. Errors and Margins in Radiotherapy. *Semin Radiat Oncol* 2004;14(1):52–64. Available from: https://dx.doi.org/10.1053/j.semradonc.2003.10.003

5. Guo W, Sun YC, Bi JQ, He XY, Xiao L. Hypofractionated radiotherapy versus conventional radiotherapy in patients with intermediate- To high-risk localized prostate cancer: a meta-analysis of randomized controlled trials. *BMC Cancer*. 2019;19(1):1–8. Available from: https://dx.doi.org/10.1186/s12885-019-6285-x

6. Nahum AE. The Radiobiology of Hypofractionation. *Clin Oncol* 2015;27(5):260–9. Available from: http://dx.doi.org/10.1016/j.clon.2015.02.001

7. Thomson DJ, Yom SS, Saeed H, El Naqa I, Ballas L, Bentzen SM, et al. Radiation Fractionation Schedules Published During the COVID-19 Pandemic: A Systematic Review of the Quality of Evidence and Recommendations for Future Development. *Int. J. Radiat. Oncol. Biol. Phys* 2020;108(2):379–89. Available from: https://doi.org/10.1016/j.ijrobp.2020.06.054

8. Stemkens B, Glitzner M, Kontaxis C, De Senneville BD, Prins FM, Crijns SPM, et al. Effect of intra-fraction motion on the accumulated dose for free-breathing MR-guided stereotactic body radiation therapy of renal-cell carcinoma. *Phys Med Biol*. 2017;62(18):7407–24. Available from: https://dx.doi.org/10.1088/1361-6560/aa83f7

9. Shirato H, Shimizu S, Kunieda T, Kitamura K, Van Herk M, Kagei K, et al. Physical aspects of a real-time tumor-tracking system for gated radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys*. 2000;48(4):1187–95. Available from: https://dx.doi.org/10.1016/S0360-3016(00)00748-3

10. Keall P, Poulsen P, Booth JT. See, Think, and Act: Real-Time Adaptive Radiotherapy. Semin Radiat Oncol. 2019;29(3):228–35. Available from: https://dx.doi.org/1016/j.semradonc.2019.02.005

11. Micropos *Raypilot solution* Available from: https://micropos.se/healthcare-professionals/raypilot-solution [accessed 29/10/20]

12. McLaren D. Using breath analysis to PRedIct Normal TissUe and Tumour response during prostate cancer SBRT. Version 1.0 May 2018, IRAS Number: 240335

13. Trainer M, Carruthers L, Nailon B, Kirby M *Investigating the use of RayPilot for motion management during prostate SBRT: initial experience* ESTRO 2020 available from: https://www.estro.org/Congresses/ESTRO-2020/279/ph [accessed 17/01/21]

14. Trainer, M, Adamson, S, Carruthers, L, Nailon, B, Kirby, M Analysis of the Intra-Fractional Motion of the Prostate During SBRT Using an EM Transmitter, *Int. J. Radiat. Oncol. Biol. Phys.* 2020;108(3):e340 Available from: https://dx.doi.org/10.1016/j.ijrobp.2020.07.812

15. NCBI. *PubMed* https://www.ncbi.nlm.nih.gov/pubmed [accessed 01/09/18-13/12/20]

16. Google. *Google Scholar* https://scholar.google.co.uk/ [accessed 01/09/18-13/12/20]

17. Pinchbeck GL, Archer DC. How to critically appraise a paper. *Equine Vet Educ* (2020) 32 (2) 104-109 Available from: http://dx.doi.org/10.1111/eve.12896

18. CASP. Systematic review checklist. https://casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf [accessed 11/12/20]

19. Downs S, Black N, The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions *J. Epidemiology Community Health.*1998;52(2):377–384. Available from: http://dx.doi.org/10.1136/jech.52.6.377

20. Hooper P et al. Age-related macular degeneration and low-vision rehabilitation: a systematic review *Can. J. Ophthalmol.* 2008;43:180-7 Available from: http://dx.doi.org/10.3129/i08-001

21. Mah D, Freedman G, Milestone B, Hanlon A, Palacio E, Richardson T, et al. Measurement of intrafractional prostate motion using magnetic resonance imaging. *Int. J. Radiat. Oncol. Biol. Phys.*2002;54(2):568–75. Available from: http://dx.doi.org/10.1016/S0360-3016(02)03008-0

22. Mutanga TF, Sc M, Boer HCJ De, Ph D, Rajan V, Ph D, et al. Day-to-Day Reproducibility of Prostate Intrafraction Motion Assessed by Multiple kV and MV Imaging of Implanted Markers During Treatment. *Int. J. Radiat. Oncol. Biol. Phys.*2012;83(1):400–7. Available from: https://dx.doi.org/10.1016/j.ijrobp.2011.05.049

23. Micropos Medical http://www.micropos.se [accessed 06/11/20]

24. Vanhanen A, Kapanen M. The effect of rectal retractor on intrafraction motion of the prostate. *Biomed. Phys. Eng. Express*. (2016) 2 035021 Available from: http://dx.doi.org/10.1088/2057-1976/2/3/035021

25. Braide K, Lindencrona U, Welinder K, Götstedt J, Ståhl I, Pettersson N, et al. Clinical feasibility and positional stability of an implanted wired transmitter in a novel electromagnetic positioning system for prostate cancer radiotherapy *Radiother Oncol.* 2018;128(2):336–42. Available from: https://doi.org/10.1016/j.radonc.2018.05.031

26. Mathworks *Math graphics programming* https://www.mathworks.com/products/matlab.html [accessed 14/11/20]

27. Biston M, Zaragori T, Delcoudert L, Gorsse C, Sarrut D, Comparison of electromagnetic transmitter and ultrasound imaging for intrafraction monitoring of prostate radiotherapy *Radiother Oncol.* 2019;136:1–8. Available from: https://doi.org/10.1016/j.radonc.2019.03.020

28. Vanhanen A, Syrén H, Kapanen M. Localization accuracy of two electromagnetic tracking systems in prostate cancer radiotherapy : A comparison with fiducial marker based kilovoltage imaging. *Phys. Med*. 2018 Dec;56:10-18 Available from: http://dx.doi.org/10.1016/j.ejmp.2018.11.007

29. Varian. *Calypso*. https://www.varian.com/products/radiotherapy/real-time-tracking-motion-management/calypso. 2020 [accessed 30/11/20]

30. Bell LJ, Eade T, Kneebone A, Mrt B, Hruby G, Alfieri F, et al. Initial experience with intra-fraction motion monitoring using Calypso guided volumetric modulated arc therapy for definitive prostate cancer treatment *J Med Radiat Sci* 2017;64:25–34. Available from: https://doi.org/10.1002/jmrs.224

31. Hamilton DG, Mckenzie DP, Perkins AE. Comparison between electromagnetic transponders and radiographic imaging for prostate localization: A pelvic phantom study with rotations and translations. *J. Appl. Clin. Medical Phys*. 2017;18(5):43–53. Available from: https://doi.org/10.1002/acm2.12119

32. McBride G. *A Proposal for Strength of Agreement Criteria for Lin's Concordance Correlation Coefficient*. National Institute of Water & Atmospheric Research (NZ). 2005.

33. Lovelock DM, Messineo AP, Cox BW, Kollmeier MA, Zelefsky MJ. Continuous monitoring and intrafraction target position correction during treatment improves target coverage for patients undergoing SBRT prostate therapy *Int. J. Radiat. Oncol. Biol. Phys.* 2015;91(3):588–94. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.10.049

34. Accuray. *Cyberknife*. https://www.accuray.com/cyberknife/ [accessed 09/12/20]

35. King C, Brooks J, Gill H, Presti J Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low risk prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2012;82(2):877–82. Available from: http://dx.doi.org/10.1016/j.ijrobp.2010.11.054

36. Holmes OE, Gratton J, Szanto J, Vandervoort E, Doody J, Henderson E, et al. Reducing errors in prostate tracking with an improved fiducial implantation protocol for CyberKnife based stereotactic body radiotherapy (SBRT). *J. Radiosurg SBRT* 2018;5(3):217–227

37. Murphy MJ. Fiducial-based targeting accuracy for external-beam radiotherapy. *Med Phys.* 2002;29(3):pp334-344. Available from: http://dx.doi.org/10.1118/1.1448823

38. Choi HS, Kang KM, Jeong BK, Song JH, Lee YH, Ha IB, et al. Analysis of motion-dependent clinical outcome of tumor tracking stereotactic body radiotherapy for prostate cancer. *J. Korean Med. Sci.* 2018;33(14):1–13. Available from: https://doi.org/10.3346/jkms.2018.33.e107

39. Kruijf WJM De, Verstraete J, Neustadter D, Corn BW, Hol S, Venselaar JLM, et al. Patient Positioning Based on a Radioactive Tracer Implanted in Patients with Localized Prostate Cancer: A Performance and Safety Evaluation *Int. J. Radiat. Oncol. Biol. Phys.* 2013;85(2):555–60 Available from: https://doi.org/10.1016/j.ijrobp.2012.03.064

40. Ng JA, Booth JT, Poulsen PR, Fledelius W, Worm ES, Eade T, et al. Kilovoltage Intrafraction Monitoring for Prostate Intensity Modulated Arc Therapy: First Clinical Results. *Int. J. Radiat. Oncol. Biol. Phys.* 2012;84(5):e655–61. Available from: https://doi.org/10.1016/j.ijrobp.2012.07.2367

41. Balter JAM, Wright JNE, Newell LAJ, Friemel BA, Dimmer ST, Cheng YUKI, et al. Accuracy of a wireless localization system for radiotherapy *Int. J. Radiat. Oncol. Biol. Phys.* 2005;61(3):933–7. Available from: https://doi.org/10.1016/j.ijrobp.2004.11.009

42. Shchory TAL, Schifter DAN, Lichtman RI, Neustadter DA, Corn BEW. Tracking Accuracy of a Real-Time Fiducial Tracking System for Patient Positioning and Monitoring in Radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2010;78(4):1227–34. Available from: https://doi.org/10.1016/j.ijrobp.2010.01.067

43. Korpics MC, Rokni M, Degnan M, Aydogan B, Liauw SL, Redler G. Utilizing the TrueBeam Advanced Imaging Package to monitor intrafraction motion with periodic kV imaging and automatic marker detection during VMAT prostate treatments. *J. Appl. Clin. Medical Phys*. 2020;21(3):184–91. Available from: https://dx.doi.org/10.1002/acm2.12822

44. Royal college of radiology: radiotherapy board (2021) On target 2: updated guidance for image-guided radiotherapy Available at: www.rcr.ac.uk/radiotherapy-board-on-target-2-updated-guidance-image-guided-radiotherapy.pdf accessed: August 2021

45. Kirby M, Calder K 2019 On-treatment verification imaging: A study guide for IGRT CRC Press, Boca Raton FL, pp. 43-48

46. Keall PJ, Ng JA, Juneja P, O'Brien RT, Huang CY, Colvill E, et al. Real-Time 3D Image Guidance Using a Standard LINAC: Measured Motion, Accuracy, and Precision of the First Prospective Clinical Trial of Kilovoltage Intrafraction Monitoring-Guided Gating for Prostate Cancer Radiation Therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2016;94(5):1015–21. Available from: http://dx.doi.org/10.1016/j.ijrobp.2015.10.009

47. Colvill E, Booth JT, Brien RTO, Eade TN, Kneebone AB, Poulsen PR, et al. Multileaf Collimator Tracking Improves Dose Delivery for Prostate Cancer Radiation Therapy: Results of the First Clinical Trial. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;92(5):1141–7. Available from: https://doi.org/10.1016/j.ijrobp.2015.04.024

48. Das S, Liu T, Jani AB, Rossi P, Shelton J, Shi Z, et al. Comparison of image-guided radiotherapy technologies for prostate cancer. *Am. J. Clin. Oncol.* 2014;37(6):616–23. Available from: https://doi.org/10.1097/COC.0b013e31827e4eb9

49. Goldman H, Singh N, Harding C, McGirr J, Seal A, Duncan I, et al. Accuracy of multiparametric magnetic resonance imaging to detect significant prostate cancer and index lesion location. *ANZ J. Surg* 2019;89(1–2):106–10. Available from: https://doi.org/10.1111/ans.14754

50. Johnson DC, Raman SS, Mirak SA, Kwan L, Bajgiran AM, Hsu W, et al. Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging. Eur. Urol. 2019;75(5):712-720. Available from: https://doi.org/10.1016/j.eururo.2018.11.031

51. Accuray, https://www.accuray.com/ [accessed 13/12/20]

52. Aluwini S, Van Rooij P, Hoogeman M, Kirkels W, Kolkman-Deurloo IK, Bangma C. Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: Early results. *Radiat. Oncol.* 2013;84(8):1–7. Available at: https://doi.org/10.1186/1748-717X-8-84

53. Feng Y, Welsh D, McDonald K, Carruthers L, Cheng K, Montgomery D, et al. Identifying the dominant prostate cancer focal lesion using image analysis and planning of a simultaneous integrated stereotactic boost. *Acta Oncol.* 2015;54(9):1543–50. Available from: http://dx.doi.org/10.3109/0284186X.2015.1063782

54. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate

cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531–43. Available from: http://dx.doi.org/10.1016/S1470-2045(19)30569-8

55. McDonald AM, Dobelbower MC, Yang ES, Clark GM, Jacob R, Kim RY, et al. Prostate stereotactic body radiation therapy with a focal simultaneous integrated boost: acute toxicity and dosimetry results from a prospective trial. *Adv. Radiat. Oncol.* 2019;4(1):90–5. Available from: https://doi.org/10.1016/j.adro.2018.09.007

56. Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, et al. Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;92(5):971–7. Available from: http://dx.doi.org/10.1016/j.ijrobp.2015.04.030

57. Murray LJ, Lilley J, Thompson CM, Cosgrove V, Mason J, Sykes J, et al. Prostate stereotactic ablative radiation therapy using volumetric modulated arc therapy to dominant intraprostatic lesions. *Int. J. Radiat. Oncol. Biol. Phys.* 2014;89(2):406–15. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.01.042

58. Monninkhof EM, van Loon JWL, van Vulpen M, Kerkmeijer LGW, Pos FJ, Haustermans K, et al. Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial. *Radiother Oncol* 2018;127(1):74–80. Available from: https://doi.org/10.1016/j.radonc.2017.12.022

59. Bijina TK, Ganesh KM, Pichandi A, Muthuselvi CA. Cyberknife, helical, tomotherapy and rapid-ARC SIB-SBRT treatment plan comparison for carcinoma prostate. *Asian Pac. J. Cancer Prev.* 2020;21(4):1149–54. Available from: http://dx.doi.org/10.31557/APJCP.2020.21.4.1149

60. Kim YJ, Yoon KJ, Kim YS. Simultaneous integrated boost with stereotactic radiotherapy for dominant intraprostatic lesion of localized prostate cancer: a dosimetric

planning study. *Sci. Rep*. 2020;10(1):1–7. Available from: https://doi.org/10.1038/s41598-020-71715-2

61. Draulans C, De Roover R, van der Heide UA, Haustermans K, Pos F, Smeenk RJ, et al. Stereotactic body radiation therapy with optional focal lesion ablative microboost in prostate cancer: Topical review and multicenter consensus. *Radiother Oncol* 2019;140:131–42. Available from: https://doi.org/10.1016/j.radonc.2019.06.023

62. Cabrera AR, Lee WR. Hypofractionation for clinically localized prostate cancer. *Semin Radiat Oncol* 2013;23(3):191–7. Available from: http://dx.doi.org/10.1016/j.semradonc.2013.01.005

63. Kim DWN, Cho LC, Straka C, Christie A, Lotan Y, Pistenmaa D, et al. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2014;89(3):509–17. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.03.012

64. Strom TJ, Wilder RB, Fernandez DC, Mellon EA, Saini AS, Hunt DC, et al. A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy ± intensity modulated radiation therapy. *Radiother Oncol*. 2014;111(1):126–31. Available from: https://doi.org/10.1016/j.radonc.2014.02.011

65. Draulans C, van der Heide UA, Haustermans K, Pos FJ, van der Voort van Zyp J, De Boer H, et al. Primary endpoint analysis of the multicentre phase II Hypo-FLAME trial for intermediate and high-risk prostate cancer. *Radiother Oncol.* 2020;147:92–8. Available from: http://dx.doi.org/10.1016/j.radonc.2020.03.015

66. Colvill E. DMLC tracking and gating can improve dose coverage for prostate VMAT. *Med Phys.* 2014;41(9). Available from: https://doi.org/10.1118/1.4892605

67. Chiesa S, Placidi L, Azario L, Mattiucci GC, Greco F, Damiani A, et al. Adaptive optimization by 6 DOF robotic couch in prostate volumetric IMRT treatment: rototranslational

shift and dosimetric consequences. *J. Appl. Clin. Medical Phys.* 2015;16(5):35–45. Available from: https://doi.org/10.1120/jacmp.v16i5.5525

68. Han B, Najafi M, Cooper DT, Lachaine M, Eyben R Von, Hancock S. Evaluation of transperineal ultrasound imaging as a potential solution for target tracking during hypofractionated radiotherapy for prostate cancer. *Radiat. Oncol*. 2018;13(151):1–7. Available from: https://doi.org/10.1186/s13014-018-1097-8

69. Decker G, Mürtz P, Gieseke J, Träber F, Block W, Sprinkart AM, et al. Intensity-modulated radiotherapy of the prostate: Dynamic ADC monitoring by DWI at 3.0T *Radiother Oncol* 2014;113(1):115–20. Available from: https://dx.doi.org/10.1016/j.radonc.2014.07.016 0167-8140

70. Azcona JD, Li R, Mok E, Hancock S, Xing L. Automatic prostate tracking and motion assessment in volumetric modulated arc therapy with an electronic portal imaging device. *Int. J. Radiat. Oncol. Biol. Phys.* 2013;86(4):762–8. Available from: http://dx.doi.org/10.1016/j.ijrobp.2013.03.007

71. CASP *Critical appraisal skills programme* https://casp-uk.net/ [accessed 14/11/20]

72. Al-Jundi A, Sakka S. Critical appraisal of clinical research. *J. Clin. Diagnostic Res*.2017;11(5):1–5 Available at https://doi.org/10.7860/JCDR/2017/26047.9942

73. The Academic and Clinical Central Office for Research and Development. *ACCORD*. http://www.accord.ed.ac.uk/ [Accessed 01/12/20]

74. McCusker K, Gunaydin S. Research using qualitative, quantitative or mixed methods and choice based on the research. *Perfusion* 2015;30(7):537–42. Available from: https://doi.org/10.1177/0267659114559116

75. Chasseray M, Dissaux G, Lucia F, Boussion N, Goasduff G, Pradier O, et al. Kilovoltage intrafraction monitoring during normofractionated prostate cancer radiotherapy.

Cancer Radiother. 2020;24(2):99–105. Available from: https://doi.org/10.1016/j.canrad.2019.11.001

76. Varian Medical Systems *Radiotherapy products* Available at: https://www.varian.com/en-gb/products/radiotherapy [accessed 06/11/20]

77. Kim KH, Chung JB, Suh TS, Kang SW, Kang SH, Eom KY, et al. Dosimetric and radiobiological comparison in different dose calculation grid sizes between Acuros XB and anisotropic analytical algorithm for prostate VMAT. *PLoS One*. 2018;13(11):1–18. Available from: https://dx.doi.org/10.1371/journal.pone.0207232

78. Koo T, Chung JB, Eom KY, Seok JY, Kim IA, Kim JS. Dosimetric effects of the acuros XB and anisotropic analytical algorithm on volumetric modulated arc therapy planning for prostate cancer using an endorectal balloon. *Radiat Oncol*. 2015;10(1):1–11. Available from https://dx.doi.org/10.1186/s13014-015-0346-3

79. Micropos. *Raypilot Hypocath.* https://micropos.se/micropos-introduces-raypilot-hypocath-electromagnetic-tumor-tracking-without-surgical-intervention-at-estro/ [Accessed 01/12/20]

80. Zilli T, Scorsetti M, Zwahlen D, Franzese C, Förster R, Giaj-Levra N, et al. single shot radiotherapy for localized prostate cancer: Study protocol of a single arm, multicenter phase I/II trial. *Radiother Oncol.* 2018;13(1):1–8. Available from: https://doi.org/10.1016/j.radonc.2019.07.018

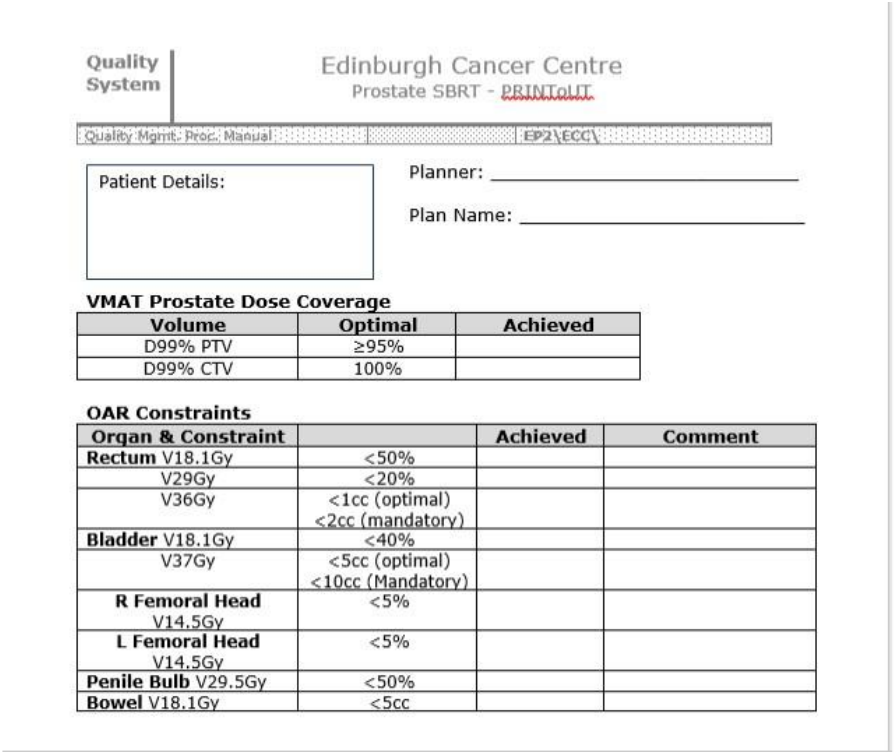
Appendix 1

DClinSci Appendix – List of AMBS A units and Medical Physics B units together with assignments – Michael Trainer

AMBS – A Units		
Unit title	**Credits**	**Assignment wordcount**
A1: Professionalism and professional development in the healthcare environment	30	Practice paper – 2000 words A1 – assignment 1 – 1500 words A1 – assignment 2 – 4000 words
A2: Theoretical foundations of leadership	20	A2 – assignment 1 – 3000 words A2 – assignment 2 – 3000 words
A3: Personal and professional development to enhance performance	30	A3 – assignment 1 – 1500 words A3 – assignment 2 – 4000 words
A4: Leadership and quality improvement in the clinical and scientific environment	20	A4 – assignment 1 – 3000 words A4 – assignment 2 – 3000 words
A5: Research and innovation in health and social care	20	A5 – assignment 1 – 3000 words A5 – assignment 2 – 3000 words
Medical Physics – B Units		
B1: Medical Equipment Management	10	3000 word assignment (plus Specification, Risk assessment, commissioning plan and quality assurance schedule)
B2: Clinical and Scientific Computing	10	3000 word assignment
B3: Dosimetry	10	3000 word assignment
B4: Optimisation in Radiotherapy and Imaging	10	Group presentation 1500 word assignment
B6: Medical statistics in medical physics	10	3000 word assignment
B8: Health technology assessment	10	3000 word assignment
B9: Clinical applications of medical imaging technologies in radiotherapy physics	20	Group presentation 2000 word assignment
B10a: Advanced Radiobiology	10	Virtual experiment + 1500 word report
B10c: Novel and Specialised External Beam Radiotherapy	10	1500 word report/piece of evidence for portfolio
B10f: Radiation Protection Advice	10	1500 word report/piece of evidence for portfolio
Generic B Units		
B5: Contemporary issues in healthcare science	20	1500 word assignment + creative project
B7: Teaching Learning Assessment	20	20 minute group presentation
Section C		
C1: Innovation Project	70	4000-5000 word Literature Review Lay Presentation

Appendix 2

Plan assessment form for the PRINToUT trial



Quality System

Edinburgh Cancer Centre

Prostate SBRT - PRINToUT

Quality Mgmt. Proc. Manual | EP2\ECC\

Patient Details:

Planner: _____

Plan Name: _____

VMAT Prostate Dose Coverage

Volume	Optimal	Achieved
D99% PTV	≥95%	
D99% CTV	100%	

OAR Constraints

Organ & Constraint		Achieved	Comment
Rectum V18.1Gy	<50%		
V29Gy	<20%		
V36Gy	<1cc (optimal) <2cc (mandatory)		
Bladder V18.1Gy	<40%		
V37Gy	<5cc (optimal) <10cc (Mandatory)		
R Femoral Head V14.5Gy	<5%		
L Femoral Head V14.5Gy	<5%		
Penile Bulb V29.5Gy	<50%		
Bowel V18.1Gy	<5cc		

Appendix 3

Poster presentation for ESTRO 2020

Investigating the use of RayPilot for motion management during prostate SBRT: initial experience

Michael Trainer[1], Linda Carruthers[1], Bill Nailon[1] Mike Kirby[2]
[1]Edinburgh Cancer Centre (ECC) UK, [2]Liverpool University Directorate of Radiotherapy UK

NHS Lothian

Introduction

Changes in the position of a target volume during treatment can impact the dosimetry of a radiotherapy treatment, especially for SBRT [1]. Real-time positional verification is therefore an important consideration in the safe delivery of SBRT. The purpose of this study was to assess the viability of the RayPilot system [2] for intra-fractional motion tracking of the prostate during SBRT and to benchmark this system against established local imaging methodologies such as using kV planar imaging and CBCT.

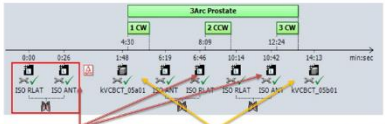
Methods & Materials

RayPilot real-time tracking system: A table-top array containing an antennae and a small EM transmitter that is inserted trans-perineally into the prostate

- 7 Patients in study
- SBRT Prostate
- 36.25Gy in 5 Fractions
- TPS – Eclipse v13.6
- 3 treatment arcs
- RayPilot tracking used alongside local imaging protocol (2DkV / CBCT)
- Treatment halted if RayPilot positional discrepancy >0.2cm

The x, y & z co-ordinates of the tip of the RayPilot transmitter and each of the 3 fiducial markers were recorded. This was carried out on the CT scan and each of the pre and post CBCT scans retrospectively for all 7 patients and for all fractions. The following comparisons were used for each positional displacement calculation:

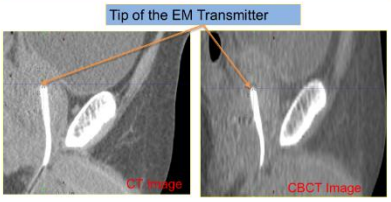
- ***CT Scan Vs CBCT Scans***
- ***Pre-treatment CBCT Vs Post-treatment CBCT***



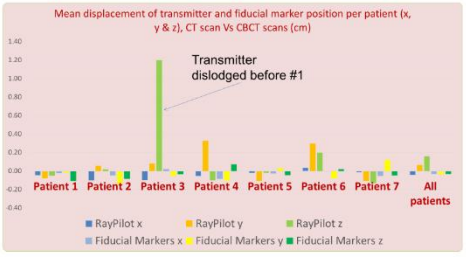
2DkV planar imaging used for patient positioning: pre-treatment and between arcs

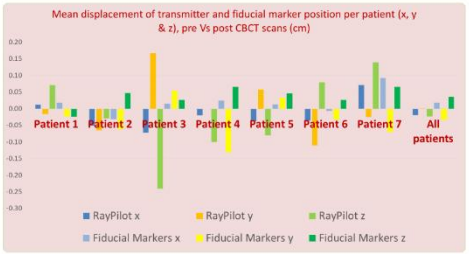
CBCT acquired pre and post treatment to assess anatomy

Tip of the EM Transmitter



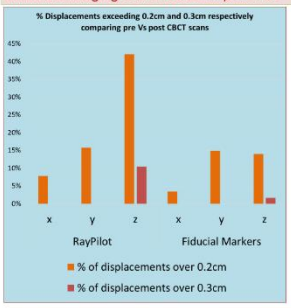
Results

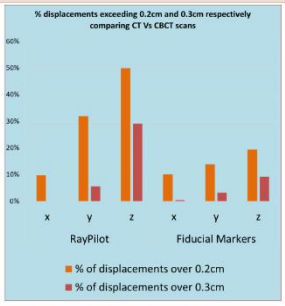




CT Vs CBCT: The position of the transmitter was within the local imaging threshold of 0.2cm for all but 3 parameters - Pt3 (z), Pt 4 (y) and Pt 6 (y). Pt 3 had an adverse event dislodging the transmitter before #1. The position of the fiducials remained within the imaging tolerance for all patients.

PreCBCT Vs PostCBCT: The position of the transmitter tip was within the local imaging threshold of 0.2cm for all but 1 parameter – P 3 (z). The position of the fiducials remained within the imaging tolerance for all patients.





CT Vs CBCT: The number of displacements >0.2cm observed was highest in the z direction for RayPilot. The fiducials had the most displacements >0.2cm in the z-direction. The most stable direction for both the RayPilot and fiducials was the x direction.

CBCT Vs CBCT: The number of observed displacements >0.2cm was highest in the z direction for the RayPilot transmitter and in the y-direction for the fiducials.

Conclusion

These initial results show that the RayPilot transmitter can be used as a viable method for tumour tracking during prostate SBRT alongside other imaging modalities. The positional differences recorded between the device and the CT and CBCT images requires further investigation before the RayPilot system could be used as the stand-alone modality for intra-fractional positional verification for SBRT in our department.

References:
[1] Lovelock, D. M. et al. (2015) 'Continuous Monitoring and Intrafraction Target Position Correction During Treatment Improves Target Coverage for Patients Undergoing SBRT Prostate Therapy', *Int J Radiat Oncol Biol Phys* 91(3), pp. 588–594.
[2] Micropos Medical (2019) 'RayPilot', http://www.micropos.se/products/.

Appendix 4

Poster presentation for ASTRO 2020