MONASH University

Margin Reduction in Prostate Radiation Therapy

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A thesis submitted for the degree of Doctor of Philosophy at

Monash University in 2017

Faculty of Medicine, Nursing and Health Sciences

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Abstract

External beam radiotherapy is one of the main treatment modalities for localised prostate cancer and is received by large numbers of men in Australia and globally. This thesis is focussed on improving prostate cancer external beam radiotherapy by safely reducing the treatment margin around the prostate which compensates for its movement within the pelvis during a course of treatment. The healthy tissues included within the treatment margin include organs such as the rectum and bladder, which receive radiation dose during treatment and cause treatment toxicity as a consequence. The main cause of prostate motion during treatment is due to changes in rectal filling from one treatment fraction to the next, but also within a treatment fraction. The approaches studied within this thesis are; reducing the variability in rectal volume by implementing a diet intervention and treating with a smaller treatment margin when the prostate is less likely to move.

The first two studies in this thesis focus on the implementation of a diet intervention comprised of an antiflatulent diet with psyllium husk laxative. This diet intervention reduces the number of foods which are likely to cause bowel gas, and therefore, change the rectal volume within a treatment fraction. Psyllium husk is a non-fermenting, bulking laxative which should enable patients to have regular bowel movements and present for treatment with an empty rectum. The first study successfully demonstrates feasibility of ten prostate cancer patients recording their diet over the eight week course of treatment. This diet diary was then used to measure dietary intake and compliance in the subsequent diet intervention study. The diet intervention study randomised 30 patients equally to either receive standard treatment or follow the diet intervention. The study indicated a trend to reduced rectal volume variability with diet intervention. It also allowed a sample size calculation for an adequately powered study, which would require 50 patients per arm to demonstrate efficacy in reducing rectal volume variability.

The last three studies focus on the appropriateness of our treatment margin and when during treatment we can reduce the treatment margin. The assessment of our current treatment margin indicated that some patients will have a geographic miss of the prostate, particularly those with large prostates, but other patients potentially could benefit from a reduced margin. The latter two studies demonstrate a method to reduce the treatment margin when the rectum is empty, which predicts reduced prostate motion within the treatment fraction. The study successfully determined a threshold of a full or empty rectum which can be measured on pre-treatment volumetric imaging. If the rectum is below the threshold, a smaller margin could be applied for the treatment fraction, sparing dose to the healthy tissues and reducing treatment complications.

Overall, the two approaches complement each other and are promising for reducing the treatment margin. The methods can work together, where diet intervention would allow the patient to present to treatment with an empty rectum more frequently, and therefore, use a reduced margin more frequently. This would reduce the toxicity of the treatment.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: 

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Publications during enrolment

Oates R, McPhee N, Lim Joon M, Schneider-Kolsky M & Kron T (2013). Recording a patient diet over the radical course of radiotherapy for prostate cancer using a diet diary: A feasibility study. Journal of Radiotherapy in Practice, 12 (1), 18-25.

Oates R, Schneider M, Lim Joon M, McPhee N, Jones D, Foroudi F, Collins M & Kron T (2014). A randomised study of a diet intervention to maintain consistent rectal volume for patients receiving radical radiotherapy to the prostate. Acta Oncologica. 53 (4), 569-71

Oates R**,** Gill S, Foroudi F, Lim Joon M, Schneider M, Bressel M & Kron, T (2015). What benefit could be derived from on-line adaptive prostate radiotherapy using rectal diameter as a predictor of motion? Journal of Medical Physics. 40 (1), 18-23.

Oates R, Jones D, Foroudi F, Gill S, Ramachandran P, Schneider M, Lim Joon M & Kron T (2016). Geographical miss of the prostate during image-guided radiotherapy with a 6-mm posterior expansion margin. Journal of Medical Radiation Sciences. *In Press*

Oates R, Brown A, Tan A, Foroudi F, Lim Joon M, Schneider M, Herschtal A & Kron T (2017). Real-time Image-guided Adaptive-predictive Prostate Radiotherapy using Rectal Diameter as a Predictor of Motion. Clinical Oncology. 29 (3), 180-7.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes five original papers published in peer reviewed journals. The core theme of the thesis is an investigation into how to reduce the planning target volume treatment margin applied during prostate radiotherapy and how it may improve treatment outcomes. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Medical Imaging and Radiation Sciences under the supervision of Associate Professor Michal Schneider.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 2, 3, 4, 5 and 6, my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** *(published, in press, accepted or returned for revision, submitted)*	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
3	Recording a patient diet over the radical course of radiotherapy for prostate cancer using a diet diary: A feasibility study.	Published	80%. Concept, study design, data collection, data analysis and writing manuscript	1) Narelle McPhee, study design and manuscript 5% 2) Michael Lim Joon, data interpretation and manuscript 5% 3) Michal Schneider, study design, data interpretation and manuscript 5% 4) Tomas Kron, study design, data interpretation and manuscript 5%	No No No No
4	A randomised study of a diet intervention to maintain consistent rectal volume for patients receiving radical radiotherapy to the prostate.	Published	70%. Concept, study design, data collection, data analysis and writing manuscript	1) Michal Schneider, study design, data interpretation and manuscript 5% 2) Michael Lim Joon, study design, data interpretation and manuscript 5% 3) Narelle McPhee, study design and manuscript 5% 4) Daryl Jones, data collection and manuscript 2.5% 5) Farshad Foroudi, data	No No No No

				interpretation and manuscript 2.5% 6) Marnie Collins, statistics advice and data analysis 5% 7) Tomas Kron, study design, data interpretation and manuscript 5%	No No No
5	Geographical miss of the prostate during image-guided radiotherapy with a 6mm posterior expansion margin.	In Press	70% Concept, study design, data collection, data analysis and writing manuscript	1) Daryl Jones, study design, data collection and manuscript 5% 2) Farshad Foroudi, study design, data interpretation and manuscript 5% 3) Suki Gill, study design and manuscript 2.5% 4) Prabhakar Ramachandran, study design, data analysis and manuscript 2.5% 5) Michal Schneider, study design, data interpretation and manuscript 5% 6) Michael Lim Joon, study design, data interpretation and manuscript 5% 7) Tomas Kron, study design, data interpretation and manuscript 5%	No No No No No No
6	What benefit could be derived from on-line adaptive prostate radiotherapy using rectal diameter as a predictor of motion?	Published	70% Concept, study design, data collection, data analysis and writing manuscript	1) Suki Gill, study design, data collection and manuscript 5% 2) Farshad Foroudi, study design, data interpretation and manuscript 5% 3) Michael Lim Joon, study design, data interpretation and manuscript 5% 4) Michal Schneider, study design, data interpretation and manuscript 5% 5) Mathias Bressel, statistics advice, data analysis and manuscript 5% 6) Tomas Kron, study	No No No No No

				design, data interpretation and manuscript 5%	No
7	Real time image-guided adaptive-predictive prostate radiotherapy using rectal diameter as a predictor of motion.	Published	65% Concept, study design, data collection, data analysis and writing manuscript	1) Amy Brown, study design, data collection and manuscript 5% 2) Alex Tan, study design, data interpretation and manuscript 5% 3) Farshad Foroudi, study design, data interpretation and manuscript 5% 4) Michael Lim Joon, study design, data interpretation and manuscript 5% 5) Michal Schneider, study design, data interpretation and manuscript 5% 6) Alan Herschtal, statistics advice, data analysis and manuscript 5% 7) Tomas Kron, study design, data interpretation and manuscript 5%	No No No No No No No

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 08/03/17

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: [redacted] **Date:** 08/03/17

Acknowledgements

Firstly, I would like to thank my supervisors, Associate Professor Michal Schneider, Professor Tomas Kron and Dr Michael Lim Joon. Your support, guidance, enthusiasm and dedication over the years have helped me enormously in completing my thesis. I appreciate your integrity and passion towards research, which fosters the skills of everyone who is lucky enough to work with you, and I feel lucky to be counted as one of those people. Thank you for sharing your wisdom and giving me the opportunity to learn from you.

To all the staff at the Peter MacCallum Cancer Centre who have supported my research activities, I offer the sincerest thanks. Aldo Rolfo, thank you for being an inspiration to pursue radiation therapy research, for providing the opportunity and culture of inquiry in our department. Judy Andrews, thank you for your encouragement, enthusiasm, endless support and resources. Without your support I would never have reached this point. Professor Gillian Duchesne, Claire Fitzpatrick, Associate Professor Trevor Leong and Nilgun Touma, thank you for providing the environment for radiation therapists to conduct research and supporting my endeavours.

To my colleagues who have offered so much help and support, thank you. Daryl Jones and Christina Finlason, thank you for all your contouring assistance and advice. Alan Herschtal, Mathias Bressel and Marnie Collins, thank you for all your statistics advice and analysis. My co-authors, Dr Farshad Foroudi, Dr Suki Gill, Dr Alex Tan, Dr Prabhakar Ramachandran, Narelle McPhee and Amy Brown, thank you for all your advice, guidance and encouragement. Chris Gehrke, Jim Cramb and Dr Deloar Hossain, thanks for helping me secure my data and for physics advice. Dr Sarah Everitt, Daniel Pham, Dr Rebecca Owen, Kristie Matthews, Dr Kellie Knight, Dr Caroline Wright, Rebecca Height, David Willis and Nigel Anderson, thanks for your encouragement and always being available to chat.
To the staff at Bendigo Radiotherapy Centre, thanks for being so accommodating of my research activities.

To those who participated in the studies conducted for this thesis, thank you for giving your time and diligence. Your enthusiastic participation in research helps expand our knowledge of prostate radiotherapy treatment and will benefit those requiring treatment in future.

Finally, to my family, thank you for your support during my candidature. To my amazing mum, Eileen, thank you for being an inspiration to persist and achieve. To my beautiful wife, Alethea, thank you for your unending love, support and understanding. To my wonderful children, Isabelle and Oliver, thank you for being so patient and for providing the best distractions I could ever wish for. I will be forever grateful for that you have all helped me through this journey.

Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
99mTc-MDP	99mTc-methylene diphosphonate
AP	Anterior-posterior
BMI	Body mass index
bRFS	Biochemical recurrence-free survival
Cine-MRI	Cine magnetic resonance imaging
CSA	Cross sectional area
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DI	Diet intervention
DRE	Digital rectal examination
DVH	Dose-volume histogram
DW-MRI	Diffusion-weighted magnetic resonance imaging
EBRT	External beam radiotherapy
ECE	Extra-capsular extension
ECOG	Eastern Cooperative Oncology Group
ESMO	European of Medical Oncology
ETS	Erythroblast transformation-specific
FFQ	Food frequency questionnaire
FM	Fiducial marker
FROGG	Faculty of Radiation Oncology Genitourinary Group
GI	Gastrointestinal
GU	Genitourinary
HDR	High dose-rate
HGPIN	High Grade Prostate Intraepithelial Neoplasia
IGRT	Image-guided radiotherapy
IMRT	Intensity modulated radiotherapy
ISUP	International Society of Urologic Pathology
KIM	Kilovoltage intrafraction monitoring
LDR	Low dose-rate
LR	Left-right
LRP	Laparoscopic radical prostatectomy
MIRP	Minimally invasive radical prostatectomy
MLC	Multileaf collimator
MRD	Maximum rectal diameter
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NHMRC	National Health and Medical Research Council
NTCP	Normal tissue complication probability
OAR	Organ at risk
ORP	Open radical prostatectomy
PET	Positron emission tomography
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PTV	Planning target volume

PVC_R	Percentage rectal volume change
QoL	Quality of life
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
RANZCR	Royal Australian and New Zealand College of Radiologists
RARP	Robot-assisted radical prostatectomy
RP	Radical prostatectomy
RT	Radiation Therapist
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic ablative radiotherapy
SD	Standard deviation
SI	Superior-inferior
SPECT	Single-photon emission CT
ST	Standard therapy
TD	Target dose
TNM	Tumour Node Metastasis
TRUS	Transrectal ultrasound
TURP	Transurethral resection of the prostate
VMAT	Volumetric modulated radiotherapy
WHO	World Health Organisation

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Chapter 1 Introduction

Prostate cancer was first described through histological examination by John Adams, a surgeon at The London Hospital, in 1853[1]. Adams reported that the condition was an "extremely rare disease", which is probably true given the average life expectancy at the time[2]. Since then, populations around the world have seen their life expectancy almost double, following a continuous trend upward toward the present day[3, 4]. The ageing population and widespread adoption of prostate-specific antigen (PSA) screening has resulted in the increased incidence of prostate cancer, which has now become a very common disease[5]. Internationally, the estimated incidence of prostate cancer in 2012 was 1,094,916[6]. This was the second most common cancer in men behind lung cancer, making up 14.8% of male cancer incidence, and the fourth most common of all cancers, representing 7.8% of the total cancer incidence[6].

1.1 Prostate Cancer in Australia

Prostate cancer in Australia is a disease that affects many older men. The risk of Australian men being diagnosed with prostate cancer is one in nine by 75 years of age and one in six by 85 years of age[7]. The mean age for prostate cancer diagnosis is 68.2 years[7]. In cancer survivorship terms, prostate cancer survivors make up one of the largest groups in Australia, therefore, to minimise the physical, emotional, social and financial burden on this group and their economic and resource burden on the health system for their continued care.

Prostate cancer was the most diagnosed of all cancers in Australia in 2014 (excluding basal and squamous cell carcinoma of the skin), with an estimated 17050 cases making up 13.8% of Australia's cancer burden[7]. In 2012, Australia had the highest incidence rate of prostate cancer when compared to all other international regions, at 115 cases per 100,000 people[7]. Trends in PSA

testing have caused the incidence of prostate cancer in Australia to fluctuate over time. The incidence grew after the introduction of PSA testing in the 1990s, peaked around 2008, and has been falling since. The incidence in 2011 was 19,993 cases[7], which was higher than the 2014 incidence due to the prevalence of PSA testing back then. Since 2012 the United States Preventive Services Task Force has recommended against routine PSA screening[8]

A large proportion of men survive prostate cancer, either having their disease cured or controlled. In 2007–2011, 5-year survival for men diagnosed with prostate cancer was 93%[7]. This has increased from 85% in the 1998-2004 period, demonstrating an improvement in early diagnosis and treatment[9]. The current 5-year survival rate represents the third highest survival of all cancers, indicating the importance of maintaining high quality of life (QoL) in men surviving prostate cancer. The Australian mortality of prostate cancer in 2012 was 3079 men. The mortality of prostate cancer is estimated to increase in the coming years[7] due to the growing population surviving prostate cancer.

The burden of prostate cancer on the hospital system in Australia is substantial. Males over 60 years of age are more likely to be hospitalised due to cancer than females and men over 85 year of age are 2.4 times more likely to be hospitalised due to cancer than females[7]. This is partly attributed to the number of Australian men with prostate cancer[7]. Preventative public health measures and improving treatments should be a focus of research efforts to help reduce this burden in the future.

1.2 Aetiology of prostate cancer

1.2.1 Non-modifiable factors

Despite being one of the largest cancer burdens globally, the exact causes and risks of prostate cancer have not been identified[10, 11]. Those that have been identified are outlined in Table 1-1. Of those, three are non-modifiable factors have been identified in prostate cancer risk: age, race and

genetics[12, 13]. Age is a strong determining factor in prostate cancer risk. Compared to all other cancer types, the incidence of prostate cancer increases more rapidly with age[12].

Race plays a role in prostate cancer risk. In the USA, Hispanic men have a 14% lower incidence of prostate cancer than the white population of European decent, while those of African ancestry have a 58% greater incidence[13]. Geographical variation may also be a contributing factor. The incidence of prostate cancer in Sweden is around twice as high as that of Spain and about 1.5 times that of Italy[13].

The only other established risk factor for prostate cancer is familial, where the risk factor among men with first degree relatives diagnosed with prostate cancer is twice as high than the risk factor among the general population[13-15]. Monozygotic twins have up to a 50% higher risk of prostate cancer than dizygotic twins, indicating that there is a genetic factor in prostate cancer risk[14, 15]. Along with the gene mutations outlined in Table 1-1, there have been 77 single-nucleotide polymorphisms associated with prostate cancer, where most of these are in non-coding regions near the *c-MYC* oncogene, and may affect its expression[14]. These identified genetic variants only account for 35% of familial risk, with the other 65% currently unexplained[13, 14].

1.2.2 Modifiable factors

Beyond the non-modifiable factors, there appear to be many modifiable factors associated with prostate cancer risk as outlined in Table 1-1. Prostate cancer is far more prevalent in countries with a high Human Development Index[16] and appears to be in some way related to the 'Western' lifestyle. In Asian populations, the incidence of prostate cancer is significantly lower when compared with Western populations, but the incidence has been demonstrated to increase in Asian men who have immigrated to Western nations[10, 11, 13, 17].

There are many environmental and lifestyle factors that have been identified as having a potential role in prostate cancer development. Diet appears to play a key role in prostate cancer risk, but despite dietary factors being widely researched, there are few consistent results to indicate clear risks. Chronic inflammation of the prostate due to infections, diet and corpora amylacea (small hyaline masses in the prostate) may increase the risk of prostate cancer[13, 18]. The role of hormones in prostate cancer development is not well understood, however, insulin-like growth factor 1 shows a significant positive association with prostate cancer risk[13, 15]. There is no clear evidence of an association with sex hormones[13], but a better understanding of hormone levels in early life and duration of hormone exposure may clarify this relationship[11].

Taken together, these studies demonstrate potential associations between environment, lifestyle (in particular diet) and an increased risk of developing prostate cancer. However, the evidence to date is not conclusive. Further research into dietary risks is needed with extensive exposure measurement of both dietary and non-dietary risk factors to eliminate potential confounding factors[19]. With further research, an understanding of these factors will help guide public health measures and reduce the incidence of prostate cancer. Until then, offering improved treatment approaches is important to those diagnosed with prostate cancer.

Table 1-1. Risk factors for prostate cancer and their association with prostate cancer development

Risk Factor	Association with prostate cancer risk		
	Inverse Association	**Some Association**	**Strong Association**
Non-Modifiable			
Age	Younger[12]		Older[12]
Race	Hispanic, Asian [11, 13]		African[13]
Genetic		*BRCA1*, *CHEK2*, *PALB2*, *BRIP1*, *NBS1*[14, 20]	*BRCA2, HOXB13*[13, 14]
Modifiable			
Environmental		Ionising radiation, ultraviolet radiation[13]	
Lifestyle	Increased ejaculation frequency[21]	Smoking, body mass index (BMI)*, sedentary lifestyle[13]	Smoking*[13]
Diet		Red meat, processed meat[13, 15, 19], white wine, fortified wine, schochu, abusers of alcohol[19], mono-unsaturated fats, polyunsaturated fats[13, 19], coffee[13], most dairy products and high calcium intake (>2000mg/day)[13, 19]	

* Associated with advanced or aggressive cancer

1.3 Biology and histopathology of prostate cancer

The developed prostate gland is comprised of luminal and basal epithelial cell layers, along with extremely rare neuroendocrine epithelial cells[22], surrounded by stroma[23]. Luminal epithelial cells are polarized, columnar cells that line prostate lumen, and basal cells are elongated cells that separate lumen from stroma[23]. The cell of origin for prostate cancer is controversial, primarily due to luminal cell markers being present in prostate cancer and the absence of basal cells in typical prostate tumours[14, 23]. However, there have been recent reports of prostate cancer deriving from both luminal and basal epithelial cells[14, 23]. There is also evidence of basal-cell-initiated cancer evolving to adenocarcinoma maintained by luminal-like cells[14].

To date, a comprehensive understanding of prostate cancer initiation is not known[23]. There is a suggestion that tumorigenesis may happen quite quickly in a few punctuated steps in prostate

cancer, rather than the textbook model where oncogenic aberrations accumulate in cancer genomes gradually[24]. Studies of the prostate cancer genome have shown it is characterised by relatively few chromosomal gains or losses and has an overall low mutation rate when compared to other cancers[14]. Early events in prostate carcinogenesis are believed to be erythroblast transformation-specific (ETS) gene fusions, or the loss of *NKX3-1* or *FOXP1*, or the mutation of *SPOP* or *FOX1A*[23, 24]. It has been suggested that events such as alterations of *CDKN1B* or *TP53* may lead to enhanced proliferation, genomic instability and/or evasion of apoptosis[24]. The loss of the tumour suppressor gene *PTEN* may provide a final gating event in the development of aggressive prostate cancers[24]. The exact sequence of events, the range in resulting genomes and the prognosis of different prostate cancer subtypes is still to be determined with further research.

1.3.1 Histology

The histology of prostate cancer is well understood, although still an area of development. In 2004 the World Health Organisation (WHO) developed histological classifications for prostate tumours which are still largely in use today (Table 1-2). The lowest classification is High Grade Prostate Intraepithelial Neoplasia (HGPIN), which represents *in situ* adenocarcinoma and is recognised to progress to prostate cancer[23]. Multiple histologically distinct foci of prostate cancer are common in one prostate; these can be genetically heterogeneous, suggesting independent clonal origins[14]. Lower-grade cancers are relatively homogeneous unlike aggressive prostate cancers, which are more likely to be heterogeneous[14].

Prostate cancer can largely be divided into two groups, histological variants of acinar adenocarcinoma and non-acinar carcinoma variants or types[25]. The usual acinar adenocarcinoma and its variants make up around 90-95% of all prostate cancers[25]. The non-acinar carcinoma group make up approximately 5-10% of prostate cancers[25]. All of the non-acinar carcinoma group tend to be more aggressive than acinar adenocarcinoma, except pure urothelial carcinoma *in situ* and most basal cell carcinomas[25].

Since the 2004 WHO classification, several new histological types have been identified. Microcystic adenocarcinoma is an acinar variant found in 11% of prostate specimens with known adenocarcinoma, but not in pure form, so the prognostic significance of it is unknown[26]. The appearance of it at low magnifications is benign-looking, so there is concern of under-diagnosis of this type[26]. PIN-Like adenocarcinoma or PIN-Like ductal adenocarcinoma is a carcinoma which resembles HGPIN and has an incidence of around 1.3% of cases[27]. Other extremely rare and aggressive histologies are large-cell neuroendocrine carcinoma and pleomorphic giant cell adenocarcinoma[25].

Table 1-2. WHO histological classification of tumours of the prostate

Epithelial tumours	
Glandular neoplasms	
Adenocarinoma (acinar)	8140/3[1]
Atrophic	
Pseudohyperplastic	
Foamy	
Colloid	8480/3
Signet ring	8490/3
Oncocytic	8290/3
Lymphoepithelioma-like	8082/3
Carcinoma with spindle cell differentiation (carcinosarcoma, sarcomatoid carcinoma)	8572/3
Prostatic intraepithelial neoplasia (PIN)	
Prostatic intraepithelial neoplasia, grade III (PIN III)	8148/2
Ductal adenocarcinoma	8500/3
Cribriform	8201/3
Papillary	8260/3
Solid	8230/3
Urothelial tumours	
Urothelial carcinoma	8120/3
Squamous tumours	
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Basal cell tumours	
Basal cell adenoma	8147/0
Basal cell carcinoma	8147/3
Neuroendocrine tumours	
Endocrine differentiation within adenocarcinoma	8574/3
Carcinoid tumour	8240/3
Small cell carcinoma	8041/3
Paraganglioma	8680/1
Neuroblastoma	9500/3
Prostatic stromal tumours	
Stromal tumour of uncertain malignant potential	8935/1
Stromal sarcoma	8935/3
Mesenchymal tumours	
Leiomyosarcoma	8890/3
Rhabdomyosarcoma	8900/3
Chondrosarcoma	9220/3
Angiosarcoma	9120/3
Malignant fibrous histiocytoma	8830/3
Malignant peripheral nerve sheath tumour	9540/3
Haemangioma	9120/0
Chondroma	9220/0
Leiomyoma	8890/0
Granular cell tumour	9580/0
Haemangiopericytoma	9150/1
Solitary fibrous tumour	8815/0
Hematolymphoid tumours	
Lymphoma	
Leukaemia	
Miscellaneous tumours	
Cystadenoma	8440/0
Nephroblastoma (Wilms tumour)	8960/3
Rhabdoid tumour	8963/3
Germ cell tumours	
Yolk sac tumour	9071/3
Seminoma	9061/3
Embryonal carcinoma & teratoma	9081/3
Choriocarcinoma	9100/3
Clear cell adenocarcinoma	0/3
Melanoma	8720/3
Metastatic tumours	
Tumours of the seminal vesicles	
Epithelial tumours	
Adenocarcinoma	8140/3
Cystadenoma	8440/0
Mixed epithelial and stromal tumours	
Malignant	
Benign	
Mesenchymal tumours	
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Liposarcoma	8850/3
Malignant fibrous histiocytoma	8830/3
Solitary fibrous tumour	8815/0
Haemangiopericytoma	9150/1
Leiomyoma	8890/0
Miscellaneous tumours	
Choriocarcinoma	
Male adnexal tumour of probable Wolffian origin	9100/3
Metastatic tumours	

[1]Morphology code of the International Classification of Diseases for Oncology (ICD-O) [808] and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade III intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

Reproduced from: Eble et al, World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs, International Agency for Research on Cancer, 2004[28].

1.4 Prostate cancer screening, diagnosis and staging

Screening for prostate cancer is currently controversial due to the question of efficacy of available methods and risk of overtreatment. PSA testing as a screening method has a low specificity of 21–40% when PSA levels fall in the range of the so-called grey area of 4.0–10.0 ng/ml, resulting in a high negative biopsy rate[14, 29]. Despite the fact that population-based PSA screening results in lower prostate cancer mortality, worldwide agreement has been reached that it is not an appropriate screening method because of a mismatch between harms and benefits[14]. However, individual PSA screening upon request to well-informed patients is a reasonable approach[14, 30].

Diagnosis of prostate cancer is traditionally via a combination of digital rectal examination (DRE), repeated PSA testing and transrectal ultrasound (TRUS) guided biopsy. Increasingly, however, multi-parametric MRI is being used in the initial diagnosis of prostate cancer as a triage procedure to avoid unnecessary TRUS biopsy[31]. DRE alone should not be used to make clinical decisions, as at least 40% of patients with prostate cancers judged to be clinically confined (T1 or T2) by DRE may later be found to have extraprostatic extension at surgery[32]. A TRUS-guided systematic biopsy of at least 10-12 cores is recommended and potentially more cores are recommended for prostate volumes over 40ml[30]. The cores should include sites as far posterior and lateral as possible, as well as suspect areas, so as to detect the most likely locations of cancer[30]. Rising and/or persistently elevated PSA, suspicious DRE, atypical small acinar proliferation, and multifocal HGPIN are all indications for repeat biopsy[30]. Multi-parametric MRI with MRI-guided biopsy or template-based biopsy with MRI data guidance may be indicated for suspicion of anteriorly located tumours[14, 30, 33].

The biopsy specimen will be graded according to the updated International Society of Urologic Pathology (ISUP) 2014 Gleason grading standard for grading adenocarcinoma of the prostate[34]. The reported Gleason scores range between 6 and 10, with 6 being the less aggressive than 10. The new Gleason Grade Group system now reports Grade Groups 1-5 and has been incorporated into staging

due to the fact that Gleason scores 2-5 have virtually disappeared from clinical practice[34]. A key reason for changing to the Grade Group system is to reduce the chance of patient anxiety involved with the reported score. Patients may fear having an aggressive cancer when told they have a Gleason score of 6 out of 10, despite it being the lowest score commonly assigned[34].

1.4.1 Local (T) staging

Clinical staging is the traditional pathway for locally staging prostate cancer and involves the methods of DRE, PSA serum level and biopsy[32]. The tumour will be locally staged according the Tumour Node Metastasis (TNM) staging system (Table 1-3). Treatment decision-making is performed with the assistance of decision aides such as nomograms and risk group stratification to guide clinicians and patients on the likely pathologic stage and risk of aggressive disease. There are many pre-treatment predictive models (probability graphs, nomograms, look-up tables, and neural networks) available that use the classical prognostic factors of clinical T stage, PSA and Gleason score to predict treatment outcomes, pathological stage or biochemical recurrence[35]. To assess risk of biochemical failure after treatment there are many, albeit similar, risk stratification versions which combine clinical data of the classical prognostic factors into three (or more) categories of low- to high-risk (Table 1-4)[36]. The current Royal Australian and New Zealand College of Radiologists (RANZCR) Faculty of Radiation Oncology Genitourinary Group (FROGG) guidelines most closely represent the National Comprehensive Cancer Network (NCCN) or European of Medical Oncology (ESMO) guidelines in Table 1-4[37].

Table 1-3. TNM Classification for Prostate Cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour not palpable or visible by imaging	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level
T2	Tumour confined within the prostate[1]	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than one half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule[2]	
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than the seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional lymph nodes[3]		
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant metastasis[4]		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

1 *Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging is classified as T1c*

2 *Invasion into the prostatic apex, or into (but not beyond) the prostate capsule is not classified as pT3, but as pT2*

3 *Metastasis no larger than 0.2cm can be designated pN1 mi.*

4 *When more than one site of metastasis is present, the most advanced category should be used*

Note: This classification applies to adenocarcinomas, and their variants, and squamous carcinomas, but not to sarcoma or transitional cell (urothelial) carcinoma of the prostate. Transitional cell (urothelial) carcinoma of the prostate is classified as a urethral tumour.

Reproduced from: Sobin LH, Gospodariwicz M, Wittekind C (Eds). TNM classification of malignant tumours. UICC International Union Against Cancer. 7th edn. 2009. [38]

Table 1-4. Organizational pre-treatment prostate cancer risk stratification systems.

Institution/organisation	Low risk	Intermediate risk	High risk
Harvard (D'Amico) AUA EAU	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10-20 not low risk	≥T2c or PSA >20 or GS 8-10
GUROC* NICE	T1-T2a and GS ≤6 and PSA ≤10	T1-T2 and/or GS ≤7 and/or PSA ≤20 not low risk	≥T3a or PSA >20 or GS 8-10
CAPSURE*	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10-20 not low risk	T3-4 or PSA >20 or GS 8-10
NCCN	T1-T2a and GS 2-6 and PSA ≤10 not very low-risk *AND* very low-risk category: T1c and GS ≤6 and PSA ≤10 and Fewer than 3 biopsy cores positive and ≤50% cancer in each core	T2b or T2c and/or GS =7 and/or PSA >10-20 not low risk	T3a or PSA >20 or GS 8-10 not very high-risk *AND* very high-risk category: T3b-4
ESMO	T1-T2a and GS ≤6 and PSA ≤10	Not high risk and not low risk (the remainder)	T3-4 or PSA >20 or GS 8-10

AUA: American Urological Association; EAU: European Association of Urology; GUROC: Genitourinary Radiation Oncologists of Canada; NICE: National Institute for Health and Clinical Excellence; CAPSURE: Cancer of the Prostate Strategic Urologic Research Endeavour; NCCN: National Comprehensive Cancer Network; ESMO: European Society of Medical Oncology; T: T stage; GS: Gleason score; PSA: prostate-specific antigen; *Use of the 1997 TNM staging system (T2a one lobe involvement, T2b two lobes involvement, no T2c category).

Reproduced from: Rodrigues et al, 2012[36].

The use of imaging can further, and potentially more accurately, guide local staging. Multi-parametric MRI is increasingly finding a role in local (T) staging for prostate cancer as it can identify the extent of intraprostatic disease burden and extra-capsular extension (ECE)[39]. European guidelines recommend local (T) staging via MRI over TRUS, as the latter is not recommended due to low sensitivity and tendency for understaging[30]. The sensitivity and specificity of prostate tumour localisation using 2D TRUS is 45% and 52%, and for 3D TRUS is 57% and 41%, respectively[40]. However, one study of 3D TRUS has demonstrated 84% sensitivity and 96% specificity in detecting ECE[41], but the results have not been repeated. A recent meta-analysis has also recommended caution with using MRI alone to assess T3 disease due to low sensitivity of 61% (88% specificity), therefore not providing enough information for prostatectomy planning[42]. However, combining MRI results with risk category data may improve the quality of information[42].

Positive diagnosis of prostate cancer and decisions about the patient's treatment path based on prostate cancer risk, patient performance and comorbidities will determine the further staging procedures required to detect metastatic spread. Prostate cancer metastatic spread is through the lymphatic and circulatory systems. The order of the most common sites of metastases are; lymph

nodes, bones, lungs and liver. Lymphatic spread is most commonly to the para-aortic and pelvic lymph nodes, followed by the mediastinal nodes and inguinal nodes[43]. Where patients first present with metastatic disease, haematogenous metastases are most commonly found in bone (90.1%), followed by lung (45.7%) and liver (25.0%)[43]. However, the adoption of widespread PSA screening has led to the proportion of patients who initially present with metastases to fall rapidly[44]. Currently, few patients present with metastatic disease, but the investigation of potential metastatic spread is an important part of working up new patient diagnoses. The most common sites of spread guide the procedures for nodal and metastatic staging of prostate cancer.

1.4.2 Nodal (N) staging

Currently, the treatment decision making is guided by risk categories and increasingly imaging is playing role in pre-treatment investigations. The most recent guidelines recommend intermediate- and high-risk patients should have CT or MRI cross-sectional abdominopelvic imaging to screen for metastases[45]. The gold standard for lymph node (N) staging intermediate- to high-risk patients is extended pelvic lymph node dissection, which can detect nodes less than 5 mm[30]. Unfortunately, this is a very invasive procedure and is only performed when radical surgery has been chosen as a treatment option. Less invasive dissection techniques such as limited pelvic lymph node dissection may be preferred, but risk missing 41% of metastatic lymph nodes[46]. Other nodal staging techniques will potentially guide treatment decisions in future, giving a clearer picture about treatment options. Intravenous lymphotropic ultrasmall superparamagnetic particles of iron oxide (ferumoxtran-10) called 'Nano-MRI', combined with diffusion-weighted MRI DW-MRI may play a role in N staging. This method is able to detect metastatic lymph nodes from as small as 2 mm[46, 47]. Positron Emission Tomography (PET) is another imaging modality which may play a role in N staging. Radiolabeled ligand targeted to prostate-specific membrane antigen (PSMA) PET has demonstrated the best performance of PET tracers for prostate cancer staging, particularly for identifying disease outside the prostate[48]. Nano-MRI and PSMA PET/CT are the most promising techniques for further

study in lymph node imaging, as these techniques, alone or in combination, may provide an option of non-invasive N staging over more traditional approaches[46].

1.4.3 Metastasis (M) staging

Distant metastases are most frequently to bone, making it the most common site of investigation. Skeletal metastases are best assessed via a bone scan[30], which is recommended in patients with more advanced prognostic factors[30, 32]. The radionuclide 99mTc-methylene diphosphonate (99mTc-MDP) using planar imaging or single-photon emission CT (SPECT) is the current standard of care[32]. The sensitivity and specificity of planar 99mTc-MDP for detecting bone malignancy is 79% and 82%, while SPECT is 87-92% and 91%[49], respectively. In future, 18F-fluoride PET/CT or PET alone may be the recommended method for assessing skeletal metastasis as they demonstrate an advantage over 99mTc-MDP[32, 50].

1.5 The treatment of prostate cancer

A patient's treatment path depends on their health, staging and the likelihood of aggressive disease. The current international and Australian recommendations for deciding on the optimal treatment approach is for a case discussion in the multidisciplinary setting and informed discussion with the patient about treatment choice, particularly in the case of high-risk prostate cancer[30, 51]. Unfortunately, in Australia there are suggestions that discussion of treatment options with patients and multidisciplinary discussion of patient cases does not always occur[52].

The topic of this thesis will focus on treatment options for localised disease. The mainstays of localised prostate cancer treatment are active surveillance, radical prostatectomy (RP), external beam radiotherapy (EBRT) with or without androgen deprivation, high-dose rate (HDR) brachytherapy as monotherapy or EBRT boost, or low-dose rate (LDR) seed brachytherapy as monotherapy or with EBRT boost[14, 30, 53, 54]. Experimental treatment options for localised prostate cancer such as cryosurgical ablation of the prostate, high-intensity focused ultrasound and

photodynamic therapy have emerged as alternative therapeutic options[14, 30], but will not be discussed at length.

To date the active local treatments of radical prostatectomy, external-beam radiotherapy, and brachytherapy have not been comprehensively compared in robust randomised trials[14]. Few randomised trials have been attempted, with most either providing underpowered results or closing early due to poor recruitment[55, 56]. Retrospective analyses usually produce controversial results, where different methods in reporting outcomes from retrospective studies makes comparing the techniques difficult and have a high risk of bias[53, 57-59].

In terms of randomised studies, the recently reported ProtecT study compared active surveillance, prostatectomy and EBRT in low-risk patients[54]. It did not detect a difference between the three approaches in prostate cancer specific survival, but lower rates of disease progression and metastases were seen in the active treatment arms[54]. The ProtecT study found little difference between the active treatment arms in terms of prostate cancer-specific survival, clinical disease progression or metastatic progression. However, there were more treatment complications in the prostatectomy arm, nine men had thromboembolic or cardiovascular events, 14 required transfusion of more than 3 units of blood, one had a rectal injury, and nine required intervention for anastomotic problems[54]. A key outcome from this study is that, despite using outdated techniques for RP and EBRT, there is very little difference in oncological outcomes between the two treatment methods for low-risk prostate cancer. This contradicts retrospective comparisons that have shown a large advantage of one approach over the other[56] and supports the notion that a large randomised trial would be required to detect a difference in terms of overall survival or prostate cancer-specific survival between the treatment approaches[59].

Another important aspect of the ProtecT study is that it measured patient-reported QoL impacts in terms of urinary, bowel and sexual function, as well as health-related QoL. The main QoL impacts of prostatectomy were on urinary continence and sexual function, in particular erectile function[60]. The impact was greatest at 6 months, and although there was some recovery, the effect was worse than in the other treatment groups over 6 years[60]. However, prostatectomy was not associated with changes in bowel function[60]. At 6 months, the negative impact of radiotherapy with neoadjuvant androgen deprivation therapy on sexual function, particularly erectile function, was only a little less than that of prostatectomy[60]. At the same time point bowel function, urinary voiding, and nocturia were worse in the radiotherapy group than in the other groups[60]. However, the radiotherapy group experienced considerable recovery for these measures, apart from more frequent bloody stools[60]. The active-monitoring group experienced a gradual worsening of sexual (including erectile) function and urinary continence and urinary function than the active treatment groups[60]. This was reportedly due to increasing numbers of men on the active-monitoring arm receiving radical treatments and age-related changes[60]. There was no significant difference in health-related QoL reported between the three arms[60].

A smaller randomised study comparing LDR brachytherapy and prostatectomy in low-risk patients detected no significant difference in biochemical disease-free survival at 5 years, 91% for prostatectomy and 91.7% for brachytherapy[61]. In that study the brachytherapy arm produced longer lasting urinary irritative disorders than prostatectomy, however the prostatectomy arm was worse for incontinence and erectile dysfunction. Both arms reported no significant urinary disorders at 5 years[61]. An older randomised controlled trial of EBRT with endocrine therapy vs RP with endocrine therapy in T2b-T3N0M0 patients indicated lower biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival for the radiotherapy arm, but all with non-significant results[62]. This study used very outdated techniques for

radiotherapy, however, the rate of urinary incontinence was significantly higher in the surgery arm ($p < 0.01$)[62].

Three randomised trials of EBRT alone versus EBRT plus a boost of either HDR or LDR brachytherapy have been published[63-65]. All three studies have demonstrated an increase in biochemical progression-free survival when brachytherapy boost is added to EBRT. The older studies demonstrated the greatest advantage of EBRT plus brachytherapy boost, however, they delivered outdated techniques to a lower total dose in the EBRT alone arms than used currently. The study by Morris et al, used dose-escalated EBRT to 78Gy compared to EBRT to 46Gy followed by permanent seed iodine 125 implants to 115Gy[65]. In that study EBRT plus LDR boost improved the 7-year biochemical progression-free survival by 11% (86% vs75%) and an estimated 21% by 9 years of follow-up (83% vs 62%)[65].

Ultimately, there is no clear published indication of which localised treatment method offers the best results. The lack of randomised data to support one method over another means that patients need to be aware of their treatment options, the risks involved and then given the choice to make an informed decision.

1.5.1 Active surveillance

Active surveillance is an increasingly recommended treatment path, as many low-grade (Gleason score of 6 or less) localised prostate cancers are harmless[14, 30]. Large studies have indicated that most men with low-risk disease can safely avoid treatment with a risk of death from prostate cancer of 1% at 10 years, but longer-term outcomes of active surveillance are not yet known[14]. This approach can spare many patients unnecessary and potentially harmful treatment[14], but a curative treatment approach will be offered if progression, or threat of progression occurs[30]. Some patients may not do well on active surveillance due to factors including the patient's perception that the physician is doing most of the decision-making, a poor physical health score, a high neuroticism

(anxiety) score, and a high PSA value[66]. These patients may choose to progress to active treatment to offer better health-related quality of life [66].

1.5.2 Radical Prostatectomy

Open radical prostatectomy (ORP) is the traditional surgical approach for patients with localized prostate cancer, however, the minimally invasive radical prostatectomy (MIRP) techniques of laparoscopic radical prostatectomy (LRP) and, more recently, robot-assisted radical prostatectomy (RARP) have been developed to reduce surgical morbidity[67]. Traditionally, RP procedures have been utilised in the low- to intermediate-risk setting due to the risk of positive surgical margins[68]. Broadly, the nerve-sparing RP procedures involve pelvic lymph node dissection in selected patients, the removal of the prostate and surrounding tissues for clear surgical margin, with/without partial or full seminal vesicle removal, while preserving some or all of the network of nerves surrounding the prostate, seminal vesicles and urethral sphincter, then anastomosis of the bladder neck with the urethra[67, 69, 70].

MIRPs are increasingly the most common methods of radical prostatectomy, having seen a rapid increase in use since the early 2000s[71-74]. The introduction of MIRP, however, has not necessarily resulted in better outcomes for patients. The overall complication rates between the RARP and ORP are similar[75, 76], but RARP demonstrates lower rates of intraoperative complications[76]. With RARP hospital stay is reduced and lower rates of blood transfusion are required for RARP[75, 76], the costs are not reduced[74, 75]. Studies have indicated that sexual function and continence outcomes for MIRP are not better than ORP[76, 77] and the outcomes for erectile dysfunction and voiding dysfunction may actually be worse with MIRP[78]. Some of these adverse effects of MIRP may be due to a learning curve with the introduction of new techniques[78].

It has been suggested that RARP does offer better outcomes in terms of positive surgical margins in intermediate- and high-risk patients over ORP and reduced use of other therapies such as androgen deprivation therapy (ADT) and radiotherapy after surgery[79]. However, other studies have indicated that the incidence of positive surgical margins may be higher in RARP (15% RARP vs 10% ORP)[76] or equal[80]. The suggested advantages of RP in the high-risk setting are accurate pathological staging to assist with an individualized approach to secondary therapies, durable local control, and excellent long-term cancer-specific control[68]. To date, a randomised comparison of RP and radiotherapy in the high-risk setting has not yet been reported[68]. RP followed by EBRT with or without ADT has been suggested as a multimodal treatment mix for patients with high-risk prostate cancer, similar to the approach used for breast and colorectal cancers[68].

Surgery has been shown to achieve a biochemical recurrence-free survival (bRFS) rate at 5 years of >80% in low-risk prostate cancer patients[81, 82], 80.2-93% in intermediate-risk patients[82, 83], and 43-84% in high-risk patients[58, 82, 83].

In terms of side effects, a recent non-randomised, controlled study between robotic and open radical prostatectomy reported that the urinary incontinence rate 12 months after surgery was 21.3% for robotic procedures and 20.2% for the open approach[80]. Erectile dysfunction rates were 70.4% for robotic and 74.7% for open procedures, (Odds ratio 0.80 (95% CI 0.64-1.00)), therefore slightly favouring RARP[80]. A meta-analysis of urinary incontinence after RARP reported that incontinence rates at 12 months after surgery ranged between 4-31%[84]. The analysis reported that the absolute risk of urinary incontinence at 12 months for RARP was lower than ORP at 7.5% and 11.3% respectively (OR 1.53, 95% CI 1.04-2.25; p = 0.03), and the recovery time to continence was quicker for RARP[84].

1.5.3 Radiotherapy treatment options

Radiotherapy treatment uses ionising radiation sources to damage normal and malignant tissue in the body. The preferential repair of normal tissues over malignant tissues is what creates the therapeutic window that allows the process to have a treatment effect[85]. The overall treatment dose is divided into treatment fractions to allow for normal tissues to repair and, therefore, improving the therapeutic window[85]. For prostate cancer the alpha-beta ratio is believed to be quite low, which means it is a late responding tissue and either needs a high overall dose or large doses per fraction to eradicate the tumour[85, 86]. This understanding of prostate cancer radiobiology is what underpins the radiation treatment options of LDR brachytherapy, HDR brachytherapy and EBRT as discussed below.

1.5.4 Low-dose rate seed brachytherapy

Low-dose rate brachytherapy is the implantation of small radioactive seeds into the prostate to deliver a tumorcidal dose of radiation. LDR brachytherapy may involve preplanning the seed insertion either prior to the procedure based on TRUS, CT or MR imaging, or on the day in a preoperative or intraoperative approach[87]. Needles are then inserted under TRUS and template guidance, and loose or stranded seeds of required strength are deposited in the prostate at planned locations[87]. Iodine 125 seeds have been in clinical use the longest and are implanted to a dose of 140-160 Gy, while palladium 103 seeds were introduced in the 1980s and are implanted to a dose of 110-125 Gy[87]. Caesium 131 seeds are relatively new and were only introduced in 2004[87], the recently reported dose with these seeds is 115 Gy[88-90]. After the implant procedure and resolution of oedema, post-implant dosimetry is performed to assess the delivered dosimetry to the prostate, urethra and rectum[87]. LDR brachytherapy is mostly delivered as a monotherapy, but can be in combination with EBRT and is primarily used in low- to intermediate-risk patients.

Recent studies have reported 5 year bRFS for low-risk prostate cancer as 85-95.2%[58, 81, 91]. In terms of toxicity, LDR brachytherapy as a monotherapy is well tolerated, but the inclusion of EBRT with LDR

brachytherapy has mostly shown an increase in toxicity over EBRT alone or LDR brachytherapy alone[92]. Acute urinary retention is a common toxicity and will develop in 6-36% of patients. Radiation Therapy Oncology Group (RTOG) acute Grade 3 urinary toxicities will occur in around 16% of patients[93]. Late RTOG Grade 3 urinary toxicities will occur in around 6.5% of patients[93], with the incidence of late urethral stricture development after implantation reported at 1.3-4%[93, 94]. Around 1% of patients develop late Grade 3 rectal bleeding[94]. The erectile dysfunction rate is around 50%[81].

1.5.5 High-dose rate brachytherapy

High-dose rate brachytherapy can be delivered as a monotherapy or in combination with EBRT as a boost. Any risk category is appropriate for HDR brachytherapy, however, mostly low- to intermediate-risk patients are treated with HDR brachytherapy, especially via monotherapy[53, 95]. A wide range of doses and fractionations are used, but mostly the fractionations exploit the radiobiological advantage of large doses per fraction[86, 95]. The most common HDR brachytherapy is iridium 192 using a stepping source through transperineal catheters[95]. A treatment plan is created based on 3D imaging, and then evaluated in the patient before the dose is delivered[95]. The sources dwell at various points for planned durations, to allow for the desired dose to be delivered, but concurrently limiting dose to organs at risk[95].

The reported five-year biochemical control rates for HDR brachytherapy boost are 85-100%, 80-100% and 43-96% for low-, intermediate- and high-risk prostate cancers respectively[86, 95].

The toxicity profile of HDR boost treatment is good, acute urinary toxicities usually resolve with time and late Grade 3 urinary toxicities are reported in 3-9% of patients treated[95]. Urethral stricture is the most significant late toxicity, which has been reported to occur in up to 8% of patients[86]. Serious late rectal complications are seen in less than 1% of patients[95]. 40% of potent patients

experience erectile dysfunction after HDR, but 80% of those respond to pharmacological treatment[95].

1.6 External Beam Radiation Therapy

External beam radiation therapy utilises high energy x-ray (photon) or proton beams to deliver a tumouricidal radiation dose to the prostate. The use of photon radiotherapy is far more prevalent than proton radiotherapy due to the much lower cost for photon facilities[85]. Currently there are no proton facilities in Australia so they will not be discussed at length. The interventions described in this thesis would apply equally to proton therapy, but due to the rarity of proton therapy, it has not been considered in the studies conducted.

The aim of EBRT is to deliver a homogeneous dose of radiation to a planning target volume (PTV). This PTV includes the clinical target volume (CTV) incorporating the whole prostate with or without the seminal vesicles. Typical dose-escalated EBRT monotherapy treats the PTV to a dose of 74 to 81 Gy at 1.8-2 Gy per fraction delivered on weekdays[96, 97], and doses of up to 86.4 Gy have also been safely delivered[98]. EBRT is usually given with 6 months of neo-adjuvant hormone therapy for intermediate- and high-risk prostate cancer and for up to 3 years after EBRT in high-risk patients[30, 37]. If prostate cancer has been identified to have spread to local pelvic lymph nodes, these may also be included in the treatment fields. However, the role of lymph node radiotherapy remains uncertain[85]. This thesis is primarily focussed on localised disease to the prostate and seminal vesicles.

Contemporary EBRT works on the principle of taking a planning CT scan with the patient in the treatment position and then attempting to reproduce, as accurately as possible, the patient position, organ locations and organ shape for each treatment fraction. The treatment dose is calculated on the planning CT scan to deliver the prescribed dose to the PTV while maintaining dose to the critical organs within predefined constraints to minimise toxicities.

1.6.1 PTV Margin Theory

The concept of the PTV was introduced in International Commission of Radiation Units and Measurements (ICRU) Report 50, "Prescribing, Recording, and Reporting Photon Beam Therapy"[99]. The concept has been restated in Report 62, which was a supplement to Report 50 that builds on some of the concepts of the volumes, and Report 83, which deals with photon IMRT[100, 101]. The ICRU state: "The PTV is a geometrical concept introduced for treatment planning and evaluation. It is the recommended tool to shape absorbed-dose distributions to ensure that the prescribed absorbed dose will actually be delivered to all parts of the CTV with a clinically acceptable probability, despite geometrical uncertainties such as organ motion and setup variations. It is also used for absorbed-dose prescription and reporting. It surrounds the representation of the CTV with a margin such that the planned absorbed dose is delivered to the CTV. This margin takes into account both the internal and the setup uncertainties. The setup margin accounts specifically for uncertainties in patient positioning and alignment of the therapeutic beams during the treatment planning, and through all treatment sessions"[101].

The ICRU suggest using internal components (e.g. the position, size and shape of the CTV) and external components (e.g. patient positioning, mechanical uncertainty of the equipment, dosimetric uncertainties, transfer errors from CT and simulator to the treatment unit, and human factors) to determine the required PTV margin[101]. Whereas many margin recipes use systematic and random errors to define components of the margin. The systematic errors occur during treatment preparation (e.g. delineation error, some components of organ motion, mechanical uncertainty of the equipment, transfer errors from CT to the treatment unit, and human factors)[102, 103]. Random errors can occur during treatment execution (e.g. patient setup errors and organ motion)[102, 103]. The margin recipes define these terms because the random errors lead to a blurring of the dose distribution, while systematic errors lead to a displacement of the dose distribution with respect to

the CTV[102]. The typical PTV expansion for prostate radiotherapy is 5-10mm to account for these errors[104-106].

1.6.2 Three-dimensional conformal radiotherapy

At the start of the three-dimensional conformal radiotherapy (3DCRT) era, prostate radiotherapy typically used four field box techniques which used anterior, posterior and lateral beams[57]. The rectum sparing 3DCRT techniques were later introduced, where the posterior beam was avoided to limit the amount of dose delivered to the rectum and instead wedged lateral or lateral oblique beams along with anterior oblique beams were used to shape the dose within the treated volume[85]. However the rectum was still the key dose limiting structure that determined how high the total treatment dose could go.

1.6.3 Modern external beam radiotherapy

EBRT has seen a number of recent advancements which have improved the treatment quality and outcomes. Dose escalation has largely been achieved safely through the introduction of new technologies. CT-MRI fusion for treatment planning has improved delineation of target structures and organ at risk (OAR) structures[107-109]. Pre-treatment image-guided radiotherapy (IGRT) with implanted fiducial markers has improved the accuracy of treatment delivery[104, 110-112]. While intensity-modulation with intensity-modulated radiotherapy (IMRT) and volumetric modulated arc radiotherapy (VMAT) has improved target dose distributions and sparing of healthy tissues[57, 113-115]. Additionally, there have been new developments in the way radiotherapy is delivered, with moderate and extreme hypofractionation, intrafraction target monitoring and rectal separation methods. Hypofractionation, intrafraction guidance and rectal separation will be discussed later in the thesis.

Intensity-modulation during IMRT is achieved by moving the multileaf collimators (MLCs) to alter the intensity of treatment over small areas within the beam, called beamlets. Using 5-7 non-opposed beams allows for highly conformal dosimetry and the ability to 'sculpt' the dose around complex shapes such as the rectum[85]. One of the main disadvantages to IMRT is the increased delivery time and number of monitor units delivered. VMAT is a form of IMRT that delivers the radiotherapy in one or more arcs, while modulating the gantry speed, dose rate and MLC positions. VMAT largely produces comparable dosimetry to IMRT, but with fewer monitor units and faster delivery times[116, 117]. IMRT and VMAT use inverse planning where plan parameters are specified as objectives and the treatment planning system performs a series of iterations to aim to meet these objectives.

In terms of disease control outcomes, the inclusion of IMRT, IGRT and dose escalation appear to demonstrate improvement, particularly in bRFS. The Princess Margaret Hospital treated prostate cancer with 3DCRT and IMRT to 79.8 Gy and demonstrated bRFS at 5 years of 88.4%, 76.5% and 77.9% for low-, intermediate- and high-risk patients respectively[118]. Both treatment modalities in that study included IGRT, but the inclusion of 3DCRT may have lowered the overall bRFS rates. The Memorial Sloan-Kettering Cancer Centre's experience with IMRT with and without IGRT to a dose of 86.4Gy demonstrated bRFS at 7 years of 98.8%, 85.6%, and 67.9% respectively[98]. The inclusion of IGRT with IMRT appears to improve the outcomes in terms of bRFS for high-risk patients with Memorial Sloan-Kettering Cancer Centre finding the 3 year bRFS rate improves to 97% with IGRT versus 77.7% without IGRT[104]. A recent Australian series which reported the five year bRFS outcomes for modern prostate radiotherapy including image-guided IMRT to 73.8-81 Gy found that the intermediate risk disease rate was 95.5% and 91.3% for high risk disease[58].

Despite the excellent results reported, prostate EBRT is still a challenging treatment with room for improvement in terms of survival outcomes and QoL after treatment. In an environment where other treatment modalities are favoured, developing the best treatment protocols is important to

offering the most competitive outcomes for this modality. The next sections will give a background to the importance of the pelvic anatomy in prostate EBRT and the impact of organ motion on treatment dose delivered, which form part of the ongoing challenge in delivering the best outcomes through EBRT.

1.7 The critical role of pelvic anatomy in prostate radiotherapy

Within the pelvis are many organs which receive radiation dose when patients undergo EBRT for prostate cancer. The PTV margin typically includes part of organs immediately adjacent to the prostate and seminal vesicles which may be dose limiting OARs, such as rectum and bladder. Radiation to these organs potentially results in toxicities that limit the dose that can be delivered to the PTV. The organs at risk for prostate radiotherapy may include the rectum, urinary bladder, anus, penile bulb, the femurs and potentially the large and small bowel.

1.7.1 OAR: Rectum

Historically, rectal toxicities were the most frequently observed toxicities in prostate EBRT and are the most comprehensively studied and understood. However, many of these toxicities were mostly due to now outdated treatment techniques and are now becoming less frequent with newer techniques. In the rectum, acute radiation injury is largely due to epithelial injury where the rapidly replacing epithelial cells are poorly replaced, resulting in the breakdown of the mucosal barrier and intestinal mucositis (inflammation of the mucosa)[119]. Acute anorectal radiation injury, generally termed radiation proctopathy, presents with symptoms of diarrhoea, tenesmus, haematochezia (bloody stools), cramping and frequency[119, 120]. Upper abdomen symptoms, such as nausea and abdominal pain, will present in many patients even in the absence of small bowel irradiation suggesting secondary effects[119] or possibly the movement of small bowel into the treatment fields.

Long-term radiation rectal injuries are complex and involve changes in most parts of the rectal wall, often displaying mucosal atrophy, fibrosis and vascular sclerosis[119]. Common mucosal changes are often telangiectasia (dilation of the capillaries) which commonly cause rectal bleeding, and congestion of the mucosa[121]. Ulceration, stricture, fistula and necrosis are rare but potentially life-threatening chronic changes of the rectum[119-121]. Late radiation proctopathy may include symptoms of frequent or clustered bowel movements, anal discharge, rectal pain, urgency, tenesmus, incontinence, and haematochezia[119, 120]. Fibrosis is likely to cause urgency and ulcers can cause rectal pain[119]. Fortunately, it appears that the incidence of late toxicity may reduce over time with longer follow up[122].

Several studies that have reported dose escalated radiotherapy with IMRT report low rates of gastrointestinal (GI) toxicity. An Australian study of 78 Gy IMRT has demonstrated that Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher GI toxicity during treatment, at 3 months and at 2 years were, respectively, 6.9%, 1% and 2%[123]. Another Australian study of 78 Gy image-guided IMRT demonstrated CTCAE grade 2 or higher GI toxicity at 5 years of 1.6%[58]. RTOG Grade ≥2 acute and late rectal toxicity for patients treated with IMRT to 74-78Gy were 2.3% and 2.4% respectively[124]. For patients treated with IMRT to 81 Gy CTCAE Grade ≥2 acute rectal toxicity was seen in 3% of patients and the Grade ≥2 10 year actuarial incidence of rectal toxicity was 5%[115]. Patients treated with 86.4 Gy using IMRT the actuarial incidence of late CTCAE Grade ≥2 GI toxicity was 4.4% at 7 years[98]. Overall this demonstrates that dose escalated IMRT treatment is well tolerated in terms of GI toxicities. While the acute toxicity rate may be high during treatment, it quickly resolves in the short term, although a slightly higher number may experience late toxicity. By far the most common late toxicities are rectal bleeding, followed by mucous discharge/leakage[115].

Although the ProtecT study used radiotherapy techniques that are now outdated it provided patient-reported outcomes for bowel related QoL after radiotherapy. Bowel function and bowel bother

scores and the effect of bowel habits on QoL were worse in the radiotherapy arm than those reported for prostatectomy and active-monitoring at six months, but returned to be similar to the other arms over the next two years[60]. The effect of radiotherapy on loose stools and fecal incontinence was small compared to the other arms, however more patients who had received radiotherapy reported bloody stools after two years[60].

An important part of radiation treatment planning is to understand how much of the rectum is receiving dose and what impact that is likely to have on treatment toxicity. To measure this, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) and FROGG guidelines recommend contouring the rectum as a solid structure from the anal verge to the sigmoid flexure[37, 120]. The QUANTEC paper for rectal dose constraints recommends that a conservative starting point for 3D treatment planning are to limit the volume of rectum receiving 50Gy (V50) < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15%[120]. The FROGG guidelines recommend V50 < 55%, V60 < 40%, V70 < 25%, and V75 < 15%[37]. Memorial Sloan-Kettering IMRT experience suggests that doses in the intermediate range of 40–60 Gy may become important in patients who are receiving radiation prescriptions in excess of 78 Gy[120]. Eade et al, recommend limiting 40 Gy < 35%, suggesting that the lower doses are indeed important to limit toxicity[123]. Over time the understanding of the dose-response relationship will improve with further data, however, it is understood that lowering the dose received by the rectum at all dose levels will reduce the rectal toxicity.

1.7.2 OAR: Urinary Bladder

The QUANTEC guidance paper regarding bladder toxicity suggests that for prostate cancer treatment there is no clear part of the bladder or prostatic urethra that cause urinary toxicity for this treatment[125]. Irradiation of different bladder tissues, including the urothelium, smooth muscle, and vasculature may cause acute and late genitourinary (GU) toxicity and potentially nerve activation

changes may cause late toxicity[126]. While there are conflicting results, limiting dose to the bladder neck and trigone may improve late GU toxicity after high-dose IMRT, as well as patient QoL[126]. Late symptoms include dysuria, frequency, urgency, contracture, spasm, reduced flow, and incontinence[125]. Symptoms of haematuria, fistula, obstruction, ulceration, and necrosis are thought to arise from focal injury[125]. Acute symptoms usually resolve within a few months[125], however, a relationship between acute and late GU toxicity is demonstrated by some authors[98].

The reported frequency of toxicities is somewhat higher for genitourinary toxicities than for GI toxicities. The RTOG Grade ≥2 acute and late urinary toxicity for patients treated to 74-78 Gy with IMRT were 6.9% and 3.5% respectively[124]. An Australian study of 78 Gy IMRT demonstrated CTCAE grade 2 or higher GU toxicity during treatment, at 3 months and at 2 years were, respectively, 39%, 6.9% and 3%[123]. Another Australian study of 78 Gy image-guided IMRT demonstrated CTCAE grade 2 GU toxicity at 5 years of 1.3% and 0.3% grade 3 GU toxicity[58]. For patients treated with IMRT to 81 Gy CTCAE the Grade ≥2 10 year actuarial incidence of GU toxicity was 20%[115]. While treating to a higher dose, the Grade ≥2 late actuarial GU toxicity at 7 years for patients treated with 86.4 Gy IMRT was 21.1%[98]. The inclusion of IGRT significantly reduces the rates of urinary toxicity where 3 year Grade ≥2 late actuarial GU toxicity reduced from ~20% to 10% with the inclusion of IGRT to 86.4 Gy[104].

In the ProtecT study, radiotherapy had little impact on QoL in terms of urinary incontinence and use of absorbent pads when compared to the active-monitoring group[60]. Radiotherapy patients did report increased rates of urinary voiding and nocturia problems at 6 months, but recovered quickly[60]. The radiotherapy arm also reported worse impacts of urinary symptoms on QoL at 6 months than the active-monitoring arm, but better than the prostatectomy arm[60]. The impacts on the radiotherapy reduced over time to be better than the other arms, but not significantly so[60].

To understand the dose/volume relationship, the QUANTEC and FROGG guidelines both recommend contouring the bladder as a solid organ from the base to the dome[37, 125]. The lack of reliable data lead the QUANTEC guidelines to recommend bladder constraints of V80 < 15%, V75 < 25%, V70 < 35%, and V65 < 50%[125]. The FROGG guidelines recommend similar dose constraints to the rectum[37].

1.7.3 OAR: Penile Bulb

The QUANTEC guideline for the penile bulb as an organ at risk and its dose relationship to erectile dysfunction has found conflicting evidence, with some papers supporting a relationship and others not. The QUANTEC guideline recommends a prudent approach is to keep the mean dose to 95% of the penile bulb volume to <50 Gy[127]. The paper also suggests that it may be prudent to limit the V70 < 70% and V50 < 90% Their recommendation is to not compromise coverage of the planning target volume as the penile bulb itself may not be the structure that relates to erectile dysfunction. A subsequent paper reviewed the quality of studies that have assessed the relationship between dose delivered to the penile bulb and erectile dysfunction[128]. That investigation found that the highest quality studies supported limiting dose to the penile bulb, whereas lower quality studies did not support the relationship. This paper restated that the penile bulb is not likely to be the structure related to erectile dysfunction, but can be used as a surrogate[128].

A recently reported single-institution study has identified likely structures that may be best defined as OARs instead of using the penile bulb as a surrogate[129]. The study demonstrated that vessel-sparing radiotherapy which limits dose to the critical erectile vascular elements results in high rates of erectile function preservation (87%) in baseline-potent men[129]. The vessel-sparing technique uses MRI to accurately outline the internal pudendal artery, the erectile tissue of the corpus cavernosum, the penile bulb and the apex of the prostate to achieve maximum sparing of the critical structures[129].

In the ProtecT study radiotherapy group, the men reporting erections firm enough for intercourse fell sharply at 6 months, then returned to being slightly worse than those in the active-monitoring group until three years where they remained falling at a similar rate[60]. The sexual function, sexual bother and sexual QoL scores for the radiotherapy arm followed a similar trend with a sharp spike to being worse at 6 months, but then returning to be similar to the active-monitoring group at two years[60].

1.7.4 OAR: Large bowel

Radiation-induced large bowel symptoms are similar to rectal symptoms, but may include abdominal pain, changing bowel habits, intermittent diarrhoea, constipation due to fibrosis and stricture formation, and increased risk of obstruction[130]. The large bowel contour included in the radiation treatment fields is usually the sigmoid colon as it extends superior away from the rectum, but also sometimes if it continues over the bladder dome and falls inferior again toward the treated volume. There are few published records for dose constraints to the large bowel for prostate radiotherapy beyond those for the rectum. The Memorial Sloan-Kettering use a 60Gy point dose constraint[98].

1.7.5 OAR: Small bowel

The acute radiation-induced small bowel complications can include nausea and vomiting, diarrhoea, obstruction or constriction, fistula or perforation, and ulceration[130, 131]. Late small bowel injury most commonly include ulceration, fistula, perforation, and bleeding[131]. The risks of small bowel injury are predominantly taken from the treatment of other cancers and the dose constraints are applied to prostate cancer. However, some studies have suggested specific dose constraints for prostate cancer treatment, such as limiting a small bowel point dose to 53 Gy[98] or 68 Gy[132]. This type of constraint makes sense for localised prostate treatment were the amount of small bowel in the treated volume is usually individual loops which may be found in the treatment fields at the time of the planning CT scan, but may not always be present during treatment due to organ mobility. On

the other hand, when the pelvic lymph nodes are irradiated more of the peritoneum will be included in the treatment fields. The QUANTEC recommendation is to limit a dose of 45Gy to <195cc if the peritoneum within which the small bowel can move can be contoured, Eade et al, recommended limiting the same dose to <150cc[123].

1.7.6 OAR: Femurs

Femoral head irradiation is associated with the risk of femoral head necrosis or femoral neck fracture[133]. The original Emami paper recommended to keep the volume of 52 Gy to less than 100% of the contoured femur[133]. The FROGG guidelines suggest there is insufficient evidence correlating late toxicity with femoral head DVH parameters to recommend specific dose constraints, but suggests V35 < 100%, V45 < 60%, V60 < 30%[37]. The contouring recommendation is for the femoral head and neck from 1 cm below the PTV to roof of acetabulum[37]. Modern IMRT techniques easily allow the femur dose constraints to be achieved in most patients, therefore, the principle of aiming for doses which are as low as reasonably achievable is an appropriate approach for the planning team to take. This principle applies to all organs at risk to achieve the best treatment outcomes possible for the patient.

1.8 Localisation of Prostate Cancer for Radiation Therapy

When treating cancers using EBRT, many systematic and random errors can cause geographic misses of the CTV. Missing the CTV can underdose the tumour and overdose the organs at risk. Errors leading to inadequate prostate treatment can occur at two time points, inter- and intrafraction.

Interfraction motion is primarily due to variations in patient positioning and location of the prostate from one treatment to the next. Prostate interfraction motion is mainly in the anterior-posterior (AP) and superior-inferior (SI) directions, with smaller translations in the left-right (LR) direction and is usually responsible for the greatest amount of error in prostate treatments[134]. The seminal

vesicles also move independently of the prostate and are subject to larger movements[135, 136]. Both organ motions are strongly correlated to rectal filling[134, 137].

The introduction of online image-guided radiation therapy (IGRT) for prostate EBRT has greatly reduced interfraction errors by allowing accurate targeting of the prostate prior to each fraction[138, 139]. This reduces many large systematic and random errors particularly in relation to organ location and patient setup errors, but also some potential errors in relation to laser alignment, transfer, transcription and human errors. With IGRT there remain some systematic errors such as delineation errors and mechanical uncertainties. The delineation errors potentially comprise a substantial proportion of the required PTV, with error in the LR, SI and AP planes being 1.7mm, 2-3.5mm and 2mm respectively[103]. However, minimisation of interfraction error through the almost universal use of IGRT has led to intrafraction error being the focus for more recent studies.

Intrafraction motion occurs during a single treatment session, from the time of patient positioning and localisation of the target volume to the time the treatment delivery is completed at each session. It is responsible for small but significant deviations in prostate position[140, 141]. The most authoritative studies of intrafraction motion used cine magnetic resonance imaging (Cine-MRI) to assess prostate motion where the impact of organ volume changes can be observed[140, 142-144]. Intrafraction prostate motion is correlated with rectal filling of either gas or faeces, where movement of rectal gas is the major cause of sudden motion[144]. Prostate displacements of <3 mm can be expected in a 20 minute time period for patients with an empty rectum, however there is a 10% probability of having a displacement of >3 mm in just over a minute for patients with a full rectum[144]. These studies highlight the importance of intrafraction motion in relation to rectal filling.

1.9 Rationale for Margin Reduction

If the PTV margin around the CTV can be safely reduced there will be less radiation delivered to the dose-limiting organs such as the rectum and bladder. This will reduce the toxicity of prostate radiation treatment and/or potentially allow for higher doses to be delivered to the prostate. It has been demonstrated that for every 1 Gy increase in dose delivered to the prostate there is a 1.8% reduction in the risk of biochemical failure of prostate radiotherapy[96], clearly indicating the benefit of dose escalation. There are now several options for PTV margin reduction or reducing treatment toxicity in prostate radiotherapy. These include intrafraction monitoring of the prostate location, adaptive radiotherapy, diet or pharmacological interventions to reproduce rectal volumes, and rectal separation methods which will be discussed later in the thesis. The studies included in this thesis will look at potential methods of margin reduction for prostate radiotherapy, namely, diet intervention and adaptive margins. With regard to diet intervention, the thesis aims to explore the use of diet modification, specifically introducing an anti-flatulent diet and psyllium husk as a bulking laxative, to reduce prostate motion during radiotherapy by reproducing the planned rectal volume. The second theme will look at a potential method of adaptive margins for prostate radiotherapy where a reduced PTV margin would be applied when intrafraction prostate motion is likely to be small.

Chapter 2 Review of relevant research

2.1 Diet intervention studies

2.1.1 Dietary influence on prostate motion

Previous studies have demonstrated the impact of bowel gas on prostate motion[140, 142-144]. Many dietary fibres that promote laxation are comprised of complex carbohydrates which are responsible for hydrogen and methane production in the bowel[145]. Reducing these gas-producing fibres to limit prostate motion and supplementing with a laxative may be an effective way of reducing treatment error, yet there is limited and conflicting research into antiflatulent dietary interventions in prostate radiotherapy. Several studies of dietary interventions have been published, the methods of those studies are summarised in Table 2-1.

The study of Smitsmans et al, demonstrated a significant reduction in faeces, gas and moving gas through implementation of their dietary intervention[146]. Their data suggested trends of reduced interfraction and intrafraction motion, however these were not significant, most likely due to the small sample size. This study was replicated in the Australian study by Dixon and colleagues, demonstrating feasibility of diet intervention in the Australian setting[147]. Nichol et al, utilised a similar antiflatulent diet and milk of magnesia (magnesium hydroxide) but used MRI to investigate the effect of the diet on intrafraction motion and rectal area[148]. The study found no significant difference between the pre-intervention and post-intervention scans, most likely due to their requirement to vacate the bowel before any scan and possibly due to a lack of dietary compliance as recognised by the authors. Darud et al, used another similar to compare interfraction displacements of fiducial markers with no diet instructions[149]. The authors did not find any useful trend in reduced interfraction displacement of the prostate or changing of bowel habits[149]. The measurement of prostate interfraction displacement is likely to be influenced by gross displacements of the patient's anatomy, so the results of this study cannot reliably assess the impact of diet.

McNair et al, used a baseline assessment of dietary intake followed by a fibre and fluids prescription based on diet analysis[150]. They also scheduled radiotherapy appointments within two hours of the planning CT appointment time. Their results found that a modification of fibre intake resulted in no improvement in rectal volume consistency[150]. The non-randomised study by Lips et al, investigated if there was a reduction in intrafraction prostate motion assess by implanted fiducial markers after an antiflatulent diet was implemented[151]. The study found statistically significant increase in prostate motion of >3 mm for 50% of fractions in those who received the diet, the opposite of the intended outcome[151]. Their double-blind, placebo-controlled randomized trial investigated whether adding magnesium oxide laxative reduces intrafraction prostate motion assessed by implanted fiducial markers[152]. There was no significant difference in >2mm intrafraction prostate motion for 50% of fractions between the treatment arms[152]. A further analysis of that study found no clinically significant difference in rotation of the prostate or gas in the rectum[153]. There was no assessment of dietary compliance.

The lack of convincing evidence for diet interventions to reduce prostate motion or reproduce planning rectal volumes from large, adequately powered studies means this is an area still in need of investigation. Most studies have used retrospective datasets and have not assessed compliance with the interventions, which makes the rigour of the reported outcomes questionable.

Table 2-1. Summary of study methods for dietary interventions for prostate radiotherapy.

Author	Study type	Sample size per arm	Intervention	Imaging
Smitsmans et al,	Prospective with retrospective comparator	26 Prospective	Antiflatulent Diet & Magnesium oxide 2x 500 mg Treatment scheduling	CBCT for a mean of 12 Fx per patient
		23 Retrospective	None	
Dixon et al,	Prospective with retrospective comparator	20 Prospective	Antiflatulent Diet & Magnesium oxide	EPI daily during RT
		15 Retrospective	None	
Nichol et al,	Prospective, intra-patient control	42 Prospective	Antiflatulent Diet & Milk of Magnesia 30 ml	MRI before intervention, at planning and randomly during RT.
Darud et al,	Non-randomised prospective	17 Prospective	Low Fibre Diet & Milk of Magnesia 2 Tbsp	EPI daily during RT
		15 Prospective	None	
McNair et al,	Prospective, intra-patient control	22 Prospective	Individualised High Fibre Diet Treatment scheduling	CT before intervention. 2 CT after intervention and CBCT Fx 1-3, then weekly.
Lips et al,	Prospective with retrospective comparator	105 Prospective	Antiflatulent diet	EPI daily during RT
		739 Retrospective	None	
Lips et al,	Randomise, double blind	46 Prospective	Antiflatulent Diet & Magnesium oxide 4x 250 mg	EPI daily during RT
		46 Prospective	Antiflatulent Diet & Placebo 4x 250 mg	

Note: EPI = electronic portal imaging, Fx = fractions, RT = radiotherapy

2.1.2 Dietary Intervention Rationale

Our study was the first identified to implement an antiflatulent diet for patients undergoing prostate EBRT using psyllium to promote laxation. The diet was similar to those which had previously demonstrated feasibility and successful implementation[146-148]. The diet potentially would be a relatively low-cost, non-invasive way to enable patients to present for planning and treatment

appointments with an empty rectum, allowing the accurate reproduction of organ position, reduced intrafraction motion and improved radiation dose distributions.

2.1.3 Diet Intervention Description

The hypothesis was that an antiflatulent diet, supplemented with psyllium would reduce bowel gas production to levels absorbable within the intestine. The diet would restrict foods containing fermentable carbohydrates which include many fruits, vegetables, legumes, nuts, seeds and wholegrains[146, 154]. Lipids were also limited, which delay gas transit[155]. The intervention gave instructions to reduce aerophagia which should reduce bowel gas and increase exercise to promote frequent bowel motions[146]. Precise instructions for bowel and bladder preparation were given to aid in presentation for planning and treatment with an empty rectum. The intervention advised to avoid caffeine intake in the two hours prior to presentation as caffeine is a bowel motility stimulant[156] which may cause intrafraction organ motion.

The diet used psyllium husk (psyllium) as a bulk-forming laxative to increase bowel frequency. Psyllium is a partially fermented fibre that does not promote gas generation by gut microflora[145]. Psyllium husk is digested in humans into 15-20% insoluble material, 55-60% gel-forming largely unfermented material and 10-15% viscous, not gel-forming mostly fermented material[157]. High doses of psyllium have been safely implemented in cholesterol-lowering studies and chronic constipation studies[158, 159].

2.1.4 Recording a Diet Diary

For our diet intervention study we required a tool to record participant diets to measure compliance. It has been demonstrated in nutrition studies that compliance with diet recording is high for short periods of time[160]. It has also been shown that diet diaries are a well-accepted form of diet recording by participants[161]. Using diet diaries over a short period of time has been

suggested to show a better correlation to measured nutrient intake when compared to other methods of diet recording[162]. At the time of investigation, a review of the literature did not reveal studies showing the use of diet diaries to record food intake for extended periods of time such as in a seven to eight week course of daily radiation therapy treatment. Therefore we initially tested the feasibility of using a diary to record dietary intake over the course of radical external beam radiotherapy (EBRT) for prostate cancer.

2.2 Adaptive Studies

2.2.1 Rationale assessing the potential for margin reduction based on rectal diameter

Prostate displacements of <3 mm can be expected in a 20 minute time period for patients with an empty rectum, however, there is a 10% probability of having a displacement of >3mm in just over a minute for patients with a full rectum [144]. These data are supported by a Calypso study where prostate displacements of >3 mm and >5 mm were identified for 13.6% and 3.3% of the treatment time respectively [163]. A local study of Cine-MRI in 10 patients indicated that prostate displacements of >4mm and >5mm were identified for 18% and 12% respectively during a 6 minute imaging duration, which supports these data (unpublished data).

The current PTV margins applied during prostate radiotherapy are calculated based on historic data of interfraction and intrafraction motion of the prostate. These data take into account random treatment errors for all treatment fractions, many of which will not be present at each fraction. We hypothesized that patients who present with an empty rectum will be at much lower risk of intrafraction prostate motion compared to patients who present with a full rectum as supported by the Cine-MRI data [140, 144]. This is further supported by data which demonstrated intrafraction motion of greater than 5 mm in only 4.7% of fractions [164].

Kupelian et al [165] have reported on monitoring prostate motion during radiotherapy using the Calypso implanted electromagnetic transponder system. They found that 59% of fractions display

less than 3 mm of motion for an interval greater than 30 seconds. However, the more conservative estimate by Langen et al [163] report that 34% (188 of 550) of all fractions will demonstrate less than 3 mm of prostate motion and therefore a reduced margin could be applied on these fractions.

2.2.2 Adaptive Radiotherapy Background

Previous studies have outlined offline, hybrid and online protocols for adaptive prostate radiotherapy. The most experience with these protocols are the offline methods [166-168]. Typically, these methods involve a series of repeat CTs or CBCTs, an adapted plan is created based on the organ positions within these datasets and used for the remaining fractions in the course. These methods have been demonstrated to reduce biochemical failure in this population [169]. The hybrid methods involve a combination of offline adaptive replanning with a grouping according to a subpopulation of patients with small, medium or large prostate motion, or offline replanning with online image guidance [170, 171]. Online methods involve aperture modification for CRT, segment modification for IMRT using MLC, or online inverse planning [172-176]. None of the adaptive methods previously identified have taken advantage of the possibility of predicting the prostate motion daily based on the appearance of the rectum which, if demonstrated to be effective, could be implemented from the first fraction.

2.3 Purpose of this thesis

The purpose of this thesis is to investigate methods to improve prostate cancer radiotherapy outcomes by reducing the treatment margin required for adequate radiation dose delivery. The central theme of research is that methods of diet intervention and adaptive application of treatment margins may reduce the overall radiation dose delivered to healthy tissue surrounding the prostate, while delivering an adequate dose to the prostate itself. The manuscripts follow two themed approaches of diet intervention and adaptive margins, linked by their application to reducing the treatment margin applied. The two approaches have the potential to work in synergy, where the

application of a diet intervention will reproduce the planning prostate and rectum positions more frequently for treatment and therefore an adaptive margin can be applied more often. The implementation of these two methods together are likely to lead to improved tumour control and reduced treatment toxicity, however to demonstrate this will require further research which is beyond the scope of this thesis.

The aims of this thesis are to:

- Record the diet of patients with prostate cancer over the course of radical prostate radiotherapy for the purpose of assessing compliance with a diet intervention (Chapter 3).
- Investigate the impact of a diet intervention on the reproducibility of rectal volumes over the course of radical prostate radiotherapy (Chapter 4).
- Assess the current margin applied for prostate radiotherapy when considering the anatomical variations of prostate displacement, rotation and deformation on CBCT (Chapter 5).
- Investigate a potential method of adaptive margins radiotherapy based on the presentation of the rectum on post-treatment CBCT (Chapter 6).
- Investigate a relationship between maximum rectal diameter (MRD) on pre-treatment CBCT and intrafraction prostate motion, in the context of an adaptive margins IGRT method (Chapter 7).

Chapter 3 Recording a patient diet over the radical course of radiotherapy for prostate cancer using a diet diary: A feasibility study.

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Journal of Radiotherapy in Practice, 2013, 12 pp18-25

Our initial review of the literature in **chapter 2** has indicated that there is only limited evidence available about recording a diet diary for an eight week duration. There was no evidence available for prostate cancer patients recording their diet for this duration. We hypothesised that patients would be able to record their diet during the course of prostate radiotherapy to provide a reliable estimate of food intake. At the time of our investigation, earlier studies had not monitored compliance with their diet intervention (Smitsmans et al, 2008), which is important to determine efficacy of the intervention. Therefore, the aim of this study was to test the feasibility of recording a patient diet for the radical course of prostate radiotherapy. The secondary aim was to measure the amount of fibre and fluid in an 'ordinary' diet in this population.

Abstract

Aims: To obtain an estimate of dietary fibre and fluid intake in Australian men undergoing prostate radiotherapy and to establish feasibility and patient compliance with recording normal diet without intervention during the radical course of radiotherapy.

Methods: Eleven participants were enrolled and treated with 74-78 Gray (Gy) to the prostate over eight weeks. Participants were instructed to record a diary of their food and fluid intake and bowel motions for the duration of treatment. Treating radiation therapists were instructed to initial the diet diary daily. Diet diaries were assessed for compliance by analysing the number of days over the treatment period and the number of diary pages submitted. The diet diaries were analysed for nutrient intake of fibre and fluids.

Results: Ten of 11 participants submitted a diet record for the full duration of treatment with a median compliance of 100 % (range 90.4-100%) of days recorded. The mean (standard deviation) of fibre and fluids recorded in the diets were 21.5 grams (g) (5.5) and 2227.1 g (733.1) respectively.

Conclusions: It is feasible for patients to record a diet diary over a radical course of prostate radiotherapy. In this study most patients were highly compliant with submitting a diet record for each day during treatment.

3.1 Introduction

In 2005, prostate cancer diagnosis was the most common of all cancers diagnosed in men in Australia[9]. Many of these men undergo external beam radiotherapy (EBRT) for their treatment. Prostate motion during EBRT is known to be influenced by the filling of the bowel and bladder[134], with changes in rectal filling being the major cause of motion[142, 144]. This has led to studies of dietary interventions aiming to reduce prostate motion by reducing the frequency of gas and faeces present in the bowel[146, 148]. These studies have implemented antiflatulent diets with a magnesium-based laxative, which in the study by Smitsmans et al demonstrated a significant reduction in gas, faeces and moving gas[146]. Smitsmans et al, hypothesized that this reduction should correlate with a reduction in intrafraction prostate motion, a result that was not supported by Nichol et al, who found an antiflatulent diet with milk of magnesia did not significantly reduce intrafraction prostate motion on Cine-Magnetic Resonance Imaging (Cine-MRI)[148]. Neither study did, however, assess compliance with the diet intervention. Compliance with a diet during radiation therapy may impact on the presence of moving gas which in turn may impact on intrafraction prostate motion as recognised by Nichol et al[148].

Diet diaries have demonstrated relatively good correlation to weighed food records when compared to other recording methods[177]. This may make them useful in capturing compliance with diet interventions. However, most diet records are usually applied over a short term such as in diet intervention and diet recording studies, capturing diet information for a few days to a week[178-181]. No previous studies were identified which assess the feasibility of utilizing a diet diary to record diet intake in patients receiving radical prostate radiotherapy for the full course of treatment which usually takes eight weeks. Some weight loss studies have utilized diaries over a longer periods which may limit their relevance to the present studies' population[182, 183]. This study was conducted to establish feasibility and patient compliance with recording a normal diet without intervention for the

full course of radical radiotherapy. The study also aimed to obtain an estimate of fibre and fluids intake of Australian men undergoing radiation therapy to the prostate.

3.2 Method

3.2.1 Participant recruitment

Eleven participants were recruited consecutively between February 2009 and May 2009. Informed consent was obtained verbally after detailed information provision about the purpose and requirements of the study. This study was approved by the Peter MacCallum Cancer Centre (PMCC) Expedited Ethics Review committee.

Eligible participants had biopsy proven adenocarcinoma of the prostate and were eligible for radical radiotherapy to the intact organ. All participants were required to be implanted with gold seed fiducial markers and have no other prostheses in the pelvic region. Patients who had a history of irritable bowel syndrome, recent history of constipation or receiving opioid analgesics were deemed ineligible.

3.2.2 Radiation therapy

Participants were treated to 74-78 Gy in 37-39 fractions over eight weeks in the supine position using a Combifix (Sinmed, Civco Medical Solutions, Reeuwijk, Netherlands) for pelvis immobilisation without the use of a thermoplastic drape. All participants had kilovoltage (kV) paired images at the beginning of treatment with an online correction protocol of matching to fiducial gold seeds with a 0 millimetre (mm) tolerance. All participants followed the standard instructions for bladder and bowel preparation of 750 millilitres (ml) of water 30 minutes prior to treatment for a comfortably full bladder and to empty their bowel before treatment. Participants were advised to take Fybogel (Reckitt Benckiser, West Ryde, Australia) if needed to promote regular bowel motion.

3.2.3 **Recording and assessment of the diet diary**

Participants met with the dietitian and/or principle investigator prior to the treatment planning appointment for instructions on recording the diet diary and provision of materials. The diet diary provided was a folder with instructions and pro-forma A4 loose-leaf diary pages to be completed. Participants were instructed to complete a new page each day, recording the time and place that food or drink was consumed. Each ingredient of food or drink item, if known, was to be listed separately with the cooking method and brand, as well as the estimate of weight or volume. Each diary page also had a space to list the times a participant had a bowel motion in the day.

A subjective global nutritional assessment[184, 185] was performed at either the pre-study meeting or first week of treatment, and again in the last week of treatment to assess any changes in nutritional health. The participants were encouraged to maintain and record their normal dietary intake and bowel motions. None required additional dietary education due to special nutritional needs.

Patients were instructed to present their diet diary at each of the daily treatments where a treating radiation therapist initialled the record to assess compliance. The participants also met with investigators weekly throughout the course of treatment for systematic questioning about their progress with recording their diet, to discuss any issues with the diet diary and to record their weight. During the final meeting participants were given the chance to offer suggestions for improvement of the diet diary as a consumer.

The diet diary was assessed for missing data points to evaluate compliance. The data points assessed were the number of diary pages compared to total days over the treatment period, the number of days bowel motions were recorded and the number of days RT initials were recorded. Dietary records were de-identified and entered by the principal investigator into Foodworks 2007, Version 5, SP1 (Xyris Software, Highgate Hill, Australia) to assess the diet for intake of fibre and fluids. For

foods where the quantity was not estimated the 'unspecified serve' amount in Foodworks was entered. The water content was reported according to the calculation by Foodworks as the total water in the diet from foods and fluids consumed.

3.2.4 **Statistical analyses**

Frequency analyses were carried out to obtain the median (ranges) number of days recorded in the diet diary. Mean (± Standard Deviation (SD)) of the daily intake of fibre and fluids were assessed. All statistical analyses were carried out using Microsoft Excel 2003 (Microsoft Corporation, Redmond, USA).

3.3 Results

Thirteen patients were approached for this study during the recruitment period. One patient declined due to personal reasons and availability. One patient was approached but later deemed ineligible due to receiving radiotherapy following prostatectomy. The demographics for the 11 participants who successfully enrolled in the study are shown in Table 3-1. Ten of the 11 recruited participants submitted a diet diary which spanned the duration of their treatment. One participant withdrew from the study due to personal reasons. Another patient became ineligible while on study due to requiring opioid analgesics for an extended period for sciatica pain. However, he was keen to continue his participation and the investigators considered it would only impact his bowel motion frequency, so he was allowed to continue on study.

Table 3-1. Demographic characteristics of prostate cancer patients participating in a diet diary and bowel motion compliance study (total N = 11).

	n/N (%)
Age (years) (mean 71.8, SD 7.25)	
50-59	1/11 (9)
60-69	3/11 (27)
70-79	5/11 (46)
80+	2/11 (18)
Stage (TNM)	
T2	6/11 (55)
T3	5/11 (45)
PSA (ng/ml)	
0-10	1/11 (9)
10.1-20	10/11 (91)

Note: n = number of participants; N= total number of participants; TNM = TNM Classification of Malignant Tumours, 6th Ed; SD = standard deviation; PSA = prostate-specific antigen.

With ten of eleven enrolled participants completing the study requirements the feasibility of recording a diet diary for the full course of radiotherapy in prostate cancer patients was 90.9 %. When all eligible patients approached for the study are accounted for the feasibility was 83.3 % (10/12). Seven out of the ten participants who completed the study requirements submitted a fully compliant diet record. However, only three of those had daily entries in the bowel motion section of the record for their full duration of treatment. The participants' compliance with the diet diary, recording bowel motions and for the treating RTs who initialled the diary pages is reported in Table 3-2. The median compliance for recording bowel motions and for RTs initialling the diary pages is reported both for the number of submitted diary pages and for the total number of treatment days which includes days were participants failed to submit a diary page.

Table 3-2. Compliance with recording diet diary, bowel motions and for radiation therapists initialling diet diaries. Submitted pages indicating the recording frequency on pages submitted to investigators, total treatment days indicating recording frequency over the total treatment duration. (Total N = 10)

	Median (%)	Range (%)
Compliance for submitting daily page	100	90.4-100
Bowel motions (submitted pages)	97.3	42-100
Bowel motions (total treatment days)	95.5	39.6-100
RT initial (submitted pages)	79.3	20-100
RT initial (total treatment days)	77.2	18.9-100

Note: N = total number of participants

The mean of the recorded averages for the total number of daily dietary fibre and water intake is reported in Table 3-3. The dietary water content is reported in grams as per the report from Foodworks. Each gram of water equates to approximately one millilitre[186]. The duration of the diet diary recording varied by a small number of days amongst participants (mean 53.9 and SD 3.6). Since the average fibre and fluids of participants was only minimally affected by the duration of recording, each participant was given an equal 'weight' when calculating the group mean.

Table 3-3. The weight, (mean ± SD) and range of fibre and water recorded in participant diets during RT for prostate cancer.

	Mean (±SD)	Range
Fibre (g)	21.5 (±5.5)	15-32.4
Water (g)	2227.1 (±733.1)	1409-3462

Note: SD = standard deviation; g,= grams.

Only three participants submitted a complete record of bowel motions. There were five other participants who had sufficient data (above 90% compliance) to perform a frequency analysis of bowel motions (total of 14 missing data points) after the poor recording participant, the withdrawn participant and the participant who received opioid analgesics were excluded. This offered 378 of 392 possible data points for analysis. These eight participants saw an increase of their mean daily bowel motions from 1.72 per day in week one to 2.39 per day in week seven. Figure 3-1.

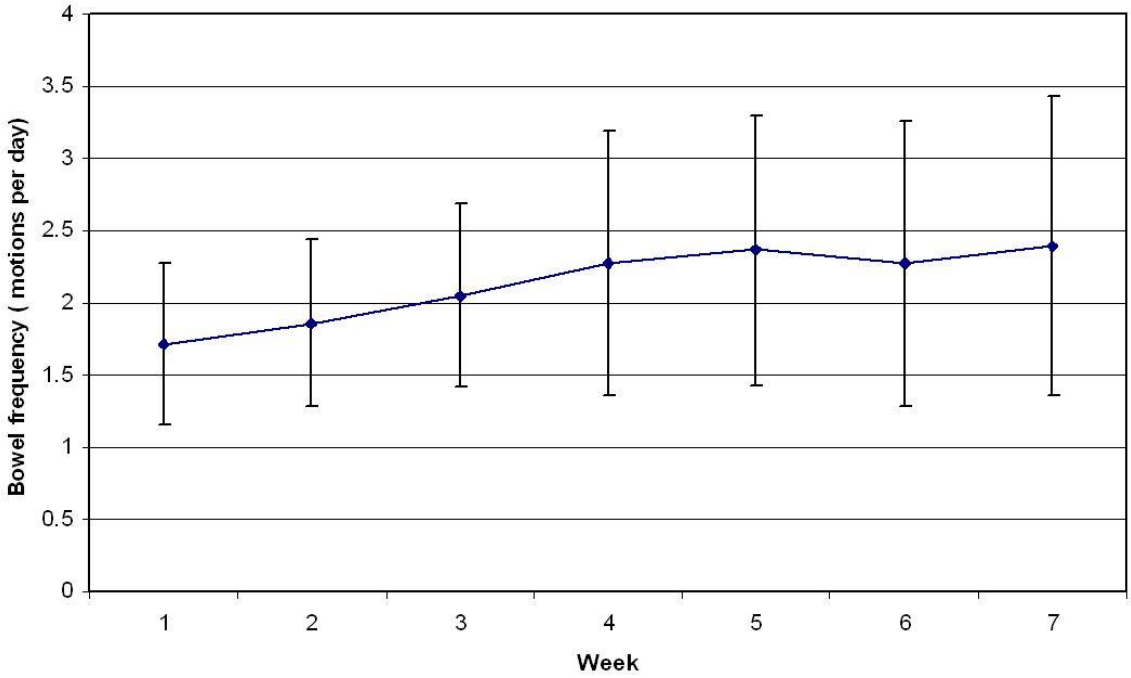

Figure 3-1. Average frequency of bowel motions per day over radical radiotherapy for eight participants. Error bars represent the standard deviations (1 SD), i.e. the variation in bowel motion frequency in these participants.

Participant weight was recorded fortnightly with assessable results available for ten participants. All had a stable weight over the seven-to-eight weeks of treatment. The mean weight change was a 0.53 kilogram (kg) gain, median 0.55 kg gain (range -1.2-2 kg). This represented a mean weight gain of 0.6 % bodyweight (range -1.7-2.3 %).

3.4 Discussion

This study demonstrates that patient initiated recording of a diet diary for the complete duration of radical prostate radiotherapy is feasible. Compliance with recording the diet diary was very high with a median of 100 % (range 90.4-100 %) of days recorded during the treatment period. One participant who returned the least number of sheets did not realise he needed to record his diet diary over the weekend for the first week, which explained some of his missing pages. Participants generally responded at weekly review that it was not much of a burden to record their diary. Most recorded it at each meal, or caught up at the following meal if they had skipped recording the diary at the time of a meal. A subjective assessment would suggest the submitted pages were almost entirely complete with only two pages potentially missing a meal at the end of the day. This was indicated by only two main meals being recorded for the day, however, on those days the participant may not have had a meal at the end of the day. This was not questioned during weekly review and is a weakness in the diary recording.

One participant in this study withdrew because he felt the diet recording was too onerous given his personal circumstances. Due to the small number of participants in this study it is hard to suggest how many participants may typically be unable to comply with recording diet records over several weeks. In the breast cancer nutrition adjuvant study, a study investigating the feasibility of reducing dietary fat intake as a component of treatment regimens for patients with resected breast cancer, two of 59 participants were excluded from the study due to inability to complete the four day food records which were to be completed at baseline in the 'run in' period[178]. The reasons for inability were not discussed. In a diet intervention and exercise study among healthy male participants with risk factors for coronary heart disease by Naslund et al [179], 88 % (104 of 118) of participants returned completed seven day diet records. Those result are similar to ours with an approximately 10 % dropout rate.

In weight loss programs where diet diaries are used for self-monitoring over even longer periods the reported levels of compliance with completing the diet diaries are lower. In a study comparing hardcopy diet diaries versus Personal Digital Assistant (PDA) entered diaries the rates of compliance were around 57 % (n = 93) and 52 % (n = 57) respectively over a period of 24 weeks[182]. Other authors have reported comparable rates of compliance using an internet self-monitoring system[183]. In the present study the far greater level of compliance could be due to shorter recording periods, the diet records being signed off by treatment staff frequently during treatment and repeated, regular contact with clinical and research staff. The higher rate of compliance may also be due to the fact that participants had cancer and were more likely to participate in trials than people participating in weight loss or less traumatic studies.

In their study comparing a 3-day food record to a food frequency questionnaire (FFQ) in a similar aged cohort, Schaefer and colleagues[180] found only 17/57 (29.8 %) of participants submitted completed food records. In contrast, 7/10 (70 %) of those who completed the present study submitted entire food records over the whole period. However, when using the same definitions of what constitutes a complete record, our study would likely fall below 50 % as many records had some foods where the type or portion was not specifically entered. For example participants may have recorded the measurement of a serving of soup as 'bowl' rather than an estimate in millilitres or may have failed to estimate the size of a piece of fruit. In the study by Schaefer[180] the participants were eating known portions of prescribed diets, whereas in our study the diet was unrestricted and estimates of portions were allowed. In reporting dietary intake over a long period it is not unreasonable to suggest that the occasional omission of specific food weight still offers a complete record.

In assessing the completeness of dietary records Thorogood et al[181] used a formula of 1.2 basal metabolic rate as the minimum energy required to be healthy. They found that 147/186 (79 %) of

the dietary records in their study had sufficient energy recorded to be considered complete. In this study using the same formula we found that 7/10 (70 %) of the dietary records were complete, indicating that three participants underreported their dietary intake. This formula does not take in to account the level of daily activity for each participant though, which means that some will require more or less energy each day. Therefore, it would be reasonable to suggest that there was underreporting of diet intake in the present study. This suggestion is supported by the fact that all patients had a stable weight over the course of treatment.

The mean fibre and fluid intakes reported in this study are below the National Health and Medical Research Council (NHMRC) Australian guidelines for recommended dietary intake[187]. The NHMRC recommends 30 grams of fibre per day for males in this age category[187]. The figures reported in this study may be below their true value due to the underreporting by some participants. However, the 1995 National Nutrition Survey found the average fibre intake in this age category to be around 24-26.3 grams of fibre per day[188] indicating that most males will not achieve the recommended daily intake of fibre.

The NHMRC recommendation for total water intake is 3.4 litres, including 2.6 litres drinking fluids[187]. Most in this study did not achieve the recommended total water intake, however some drinking fluids were likely to be omitted. It appears the most frequent omission of fluid intake was water consumed on treatment days for bladder preparation. It is also possible that males undergoing prostate radiotherapy may reduce fluid intake due to urinary frequency and retention toxicities, which may explain this observation.

It is possible that participant compliance with bowel motion recording was higher than the result presented here due to inadequate recording instructions. The recording space may have been left blank if no motion was passed in a day. Some participants were diligent in recording days when they

had no motion, however others may not have been. It was also observed in this study that daily bowel motions increased over the course of treatment, however, the exact increase cannot be confirmed due to some missing data points.

The requirement for treating radiation therapists to initial the diet diary each day achieved the lowest score of compliance. The rotation of staff to and from the treatment machine may have been responsible for periods of low compliance with initialling diet records. The study, with information about staff requirements, was initially presented at voluntary staff inservice and infrequently during the treatment team meetings throughout the study so staff may not have clearly understood their role. It is not clear if initialling the diet diary by RT staff impacts on participant compliance with recording the diary, although it may benefit some participants to have frequent reminders.

This study had several limitations which potentially could be remedied. The diet diary was not sensitive to participants skipping a meal at the end of the day and this was not part of the weekly review questioning. The diary format and instructions to participants were also not sensitive to days when patients did not have a bowel motion. A recommendation for future applications is for patients to record 'nil' when a bowel motion is not passed during the day and any blank records for bowel motions or meals are questioned at weekly review. Improved information provision to the staff involved through more frequent presentations and electing staff members to 'champion' the requirements to other staff may be a method of improving compliance with staff initialling the diet diaries. Importantly, the sample size was small and the application of the diet diary in a larger population could yield different outcomes.

This study indicates that a diet diary may be a useful tool for recording dietary intake over a course of radical prostate radiotherapy. Such a tool may be useful for recording compliance with diet interventions, which a lack of compliance has potentially impacted the results of previous studies[146,

[148]. We intend to use this tool for future diet intervention studies which will aim to tests if dietary intake can reduce organ motion during radical prostate cancer radiotherapy. Measuring compliance with an intervention will strengthen the study design, establish rates of compliance and improve the applicability of results. The validation of this tool to monitor dietary intake for use in clinical practice is beyond the scope of the present study and will require further studies using larger patient populations.

In conclusion, based on our small sample it is feasible for prostate cancer patients to record a diet diary over the full course of radical radiotherapy to the prostate of approximately eight weeks. In our study most patients were highly compliant with submitting a record of their diet and bowel motions for each day during that time period. To further improve compliance the treating radiation therapists could undergo further education to ensure they check the record daily. The results suggest that diet diaries can be implemented to investigate the effects of gas and faeces on prostate motion during radiation therapy studies. Such practices may support the development of improved treatment protocols for patients with prostate cancer.

Chapter 4 A randomised study of a diet intervention to maintain consistent rectal volume for patients receiving radical radiotherapy to the prostate.

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Acta Oncologica, 2014, 53 (4) pp569-71

At the time of investigation, there were very few publications of diet interventions for prostate radiotherapy. The only published investigations had used antiflatulent diets and magnesium laxatives[146-148]. Our study chose to combine an antiflatulent diet with psyllium husks as a natural alternative to the magnesium laxatives previously studied. Using the diet diary which had demonstrated feasibility in **chapter 3**, we would also be able to gather information regarding compliance with the intervention. We implemented the recommendations from **chapter 3**, including asking patients to score 'nil' for days with no bowel motion, questioning any empty records at weekly review and increasing staff training for initialling dietary records daily at treatment.

The hypothesis for this study is that the antiflatulent diet, supplemented with psyllium should minimise bowel gas production to levels absorbable within the intestine and allow patients to present for treatment with an empty rectum. The anti-flatulent diet, developed in-house by the study dietitian and incorporating the recommendations by Smitsmans et al[146], aims to restrict the intake of fermentable carbohydrates which result in the production of bowel gas. The psyllium in the diet is a bulk-forming laxative which aims to promote regular bowel motions, while undergoing minimal fermentation to produce bowel gas. The reduction in bowel gas aims to reduce intrafraction prostate motion and reproducing the empty rectal volume aims to reproduce the prostate position as at CT planning.

The pilot study was conducted to assess feasibility and to calculate the sample size required for a definitively powered study to investigate if a diet intervention would reduce rectal volume variation when compared to standard radiotherapy for prostate cancer.

4.1 Introduction

Treatment outcomes for prostate cancer radiotherapy improve with increased dose delivered to the prostate[96]. To enable dose escalation to the prostate without increasing treatment toxicity requires reducing the planning target volume (PTV) margins which allow for prostate movement within the pelvis. A major cause of intrafraction prostate motion is due to changes in the rectal volume which lies adjacent to the prostate[142, 144]. A potential method to reduce prostate motion within the pelvis is to alter the dietary intake by reducing fibre and gas producing foods of patients who receive radiotherapy.

Previously reported studies provide inconclusive evidence regarding the effectiveness of diet interventions. A study using magnesium oxide laxative with an antiflatulent diet reported a trend of reduced prostate motion[146], while other work using a similar intervention reported no impact on prostate motion[148, 151].

The current study investigated an antiflatulent diet combined with psyllium husk (psyllium) during radiotherapy. The study hypothesis was that the diet intervention can minimise bowel gas production to levels absorbable within the intestine and allow patients to present for treatment with an empty rectum. This pilot study was conducted to assess feasibility and inform the sample size for a definitively powered study to investigate if a diet intervention would reduce rectal volume variation when compared to standard radiotherapy for prostate cancer.

4.2 Materials and Methods

This study was a randomised, controlled pilot study with a pragmatic sample of 15 participants in each arm to generate activity data. Following Human Ethical Review approval, thirty participants were enrolled at Peter MacCallum Cancer Centre Bendigo, Australia between February 2010 and July 2011. Eligible participants were 50 years of age or older receiving external beam radiotherapy (EBRT) to the intact prostate, TNM stages T1-T3b. All participants received implanted prostate fiducials

with daily imaging as part of our standard care[189], had ECOG performance status 0-2 and provided written informed consent. Those who gave consent were randomised by telephone using a computer-generated varied-size block randomisation. The participants and investigators were not blinded to their randomisation assignment, although blinding did occur during organ contouring as described below.

4.2.1 Treatment Delivery and Interventions

All participants were prescribed radiotherapy of 74-78 Gy in 2 Gy fractions. Planning and treatment was in the supine position with immobilisation using a Combifix (CIVCO Medical Solutions, Kalona, USA). Pre-treatment kilovoltage (kV) paired images were acquired with a 0 mm tolerance online correction to gold fiducials applied each day before treatment. Cone-beam CT (CBCT) images were acquired at the end of treatment for fractions 1-5 and then every second fraction. Missed CBCT acquisition due to mechanical or system failure were not repeated, however, CBCTs not acquired due to micturition urge were repeated at the next fraction.

Standard therapy (ST) bladder and bowel preparation instructions were to consume 750 ml of water 30 minutes before treatment and to take 5 g/d Fybogel (Reckitt Benckiser, Slough, UK) if required to promote regular bowel motions.

The diet intervention (DI) involved the consumption of psyllium as a bulk-forming laxative. Psyllium dose was 20 g/d and instructions to consume at least two litres of water per day to avoid dehydration or constipation. The antiflatulent diet developed for this project is outlined in Supplementary Table 4-3. Recommendations were to avoid excessive dairy intake, hot and spicy foods, the stems and skins of fruits and vegetables, and to eat cooked vegetables warm. Reducing lipid intake, which delays gas transit, was recommended[155]. Instructions were given to reduce aerophagia and increase exercise to promote frequent bowel motions[146]. Patients were asked to

empty bowel and bladder 50 minutes before treatment, to consume 750mls of water from 45 until 30 minutes before treatment and to maintain bladder filling until the end of treatment. If feeling of gas present in bowel, patients were to expel the gas if possible. The intervention also advised to avoid caffeine intake in the two hours prior to treatment.

All participants completed a daily diet diary from two weeks prior to their CT planning appointment until the end of treatment following the recommendations outlined in a previous study[190]. The DI followed the intervention for the same duration. DI participants were provided with psyllium and diet intervention guidelines.

4.2.2 Contouring

De-identified datasets were contoured on FOCAL 4.62 (Elekta, Stockholm, Sweden) by one investigator (DJ) who was blinded to the randomisation assignment. The rectum was contoured as the external surface of the rectum from the nearest slice to 9 mm inferior to the top (superior border) and to the nearest slice to 9 mm superior to the bottom (inferior border) of the treatment field. Contouring this way minimised including the sigmoid colon and anal canal with prostate motion. The prostate was contoured as the external surface of the prostate from the base to the apex. Seminal vesicles were not contoured for the study.

4.2.3 Data Collection and Statistical Methods

Rectal volumes were recorded from all CBCTs contours using XiO 4.62 (Elekta, Stockholm, Sweden). The CBCT intra-patient rectal volume standard deviation for each patient was calculated as a measure of their rectal volume variability. On each scan at the centre and superior slices of the prostate, the rectal filling was assessed by the principal investigator and was given a score of empty, gas, moving gas and/or faeces using a similar criteria to Smitsmans et al[146]. 'Empty' was defined as a

measurable lumen diameter of less than 1 cm in the axial plane or outer rectal surface of less than 3 cm in diameter.

Per-protocol analysis was performed, withdrawn patients were excluded from the analysis. All analyses were performed using R software version 2.15.1 (www.r-project.org/). All tests were two-tailed with an alpha of 0.05. The Welch's T-test was used to assess the difference between arms in within patient rectal volume variability due to larger between-patient variation in the standard therapy arm. Pearson's chi-square test was used to assess the difference between arms in terms of rectal filling. The assumption was made that each participant's rectal filling at a given fraction was independent to their rectal filling at subsequent fractions.

4.3 Results

Over 16 months, 56 patients were approached for participation, demographics for the 30 participants are in Table 4-1. Eight patients withdrew during the study. While the overall attrition was 26.6%, only three patients withdrew potentially related to the diet intervention. One was due to dehydration, one due to diabetes diagnosis before starting the diet, which was not stabilised with medication and the last due to constipation issues which was complicated by his hypothyroidism.

Table 4-1. Demographic characteristics of prostate cancer patients participating in a diet intervention and bowel motion compliance study (total N = 30).

	Standard Therapy n/N (%)	Diet Intervention n/N (%)
Age (years)		
Mean (±SD)	**69 (±8.5)**	**70.4 (±5.8)**
Risk Group (MD Anderson)		
Low	1/15 (7)	2/15 (13)
Intermediate	6/15 (40)	5/15 (33)
High	8/15 (53)	8/15 (53)
Previous TURP		
	5/15 (33)	3/15 (20)
Hormone Therapy		
	11/15 (73)	12/15 (80)

TURP = transurethral resection of the prostate.

4.3.1 Rectal Volume Variability

Usable CBCT datasets were available for 435 fractions (ST = 238, DI = 197) with a median (range) of 20 (16-22) CBCT per patient. The mean intra-patient rectal volume variability for ST was 15.8cc (95% CI: 10.9 - 20.7) and for DI it was 11.8cc (95% CI: 9.1 - 14.5). This difference did not reach statistical significance with an estimate of the mean difference 4.0 (95% CI: -1.4 - 9.3, p = 0.133). Significance was not reached due to the small sample, however, there appears to be activity with the intervention, (Figure 4-1).

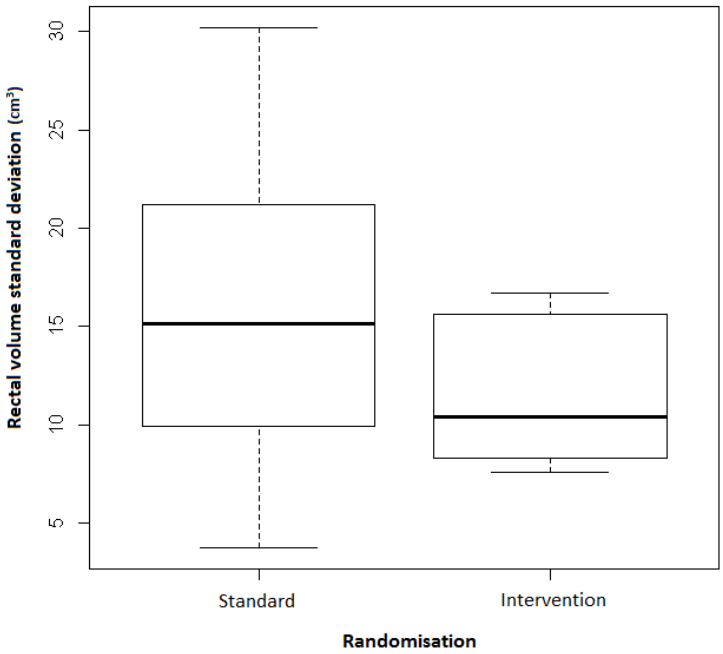

Figure 4-1. Boxplot displaying the per-patient rectal volume standard deviation – a measure of rectal volume variability, grouped per randomisation. The bar represents the median rectal volume standard deviation per randomisation; the box represents the inter-quartile range and the whiskers represent the 95 percentile.

Using the data available, a conservative sample size requires 40 patients in each arm to detect a difference of 4cc in the average rectal standard deviation between the two study arms. This sample gives a power of >0.80 at the significance level of 0.05. A sample size of approximately 50 patients per arm would be required to allow for a 20% withdrawal rate.

4.3.2 Rectal filling

Overall, no relationship between diet and superior rectal filling was demonstrated (Table 4-2). At the centre rectal filling a relationship was found between diet intake and a rectum that was empty, filled with gas or faeces, with patients in the DI arm more likely to have an empty rectum, absent of gas and faeces. No relationship was demonstrated between diet intervention and moving gas.

Table 4-2. Relationship between rectal filling at superior and centre slices of the rectum to randomisation of standard therapy or diet intervention.

		Treatment Arm				
		Standard		Intervention		
Rectal Filling		Y	N	Y	N	p-value
Superior	Empty	89	161	88	119	0.13
	Gas	59	191	38	169	0.17
	Moving Gas	10	240	10	197	0.67
	Faeces	119	131	94	113	0.64
Centre	Empty	108	142	130	77	<0.001
	Gas	62	188	28	179	0.003
	Moving Gas	5	245	6	201	0.58
	Faeces	95	155	53	154	0.004

4.4 Discussion and Conclusion

Our results demonstrate that a diet intervention appears to reduce rectal volume variability when compared with standard therapy. These results provide preliminary data for a sample size of 100 participants for a future study.

A previous diet intervention study of an antiflatulent diet with magnesium oxide was published by Smitsmans and colleagues[146]. Their study of CBCT from 26 patients who followed the intervention compared to 23 historic datasets suggested a trend of reduced prostate motion, indicating activity, however their results were not statistically significant. At the prostate level they found a significant reduction of gas, moving gas and faeces in the intervention arm, which agreed with our results for gas and faeces for the centre of the prostate. However, our study also assessed superior prostate level which did not demonstrate any significant changes in rectal filling, potentially due to greater variation in rectal filling at that level.

A subsequent study by Lips et al[151] compared the intrafraction motion of 105 patients following the antiflatulent intervention described by Smitsmans and colleagues to 739 patients without intervention and did not find reduced intrafraction prostate motion. A critical difference between the two studies was that Lips did not include a laxative in their intervention, which may have impacted on their results.

In another study using antiflatulent diet and milk of magnesia as the DI they used 42 patients with intra-patient controls to test the intervention[148]. A pre-intervention Cine-MRI was taken to observe prostate motion and rectal filling, followed by a Cine-MRI with diet intervention at the time of planning CT and one during the course of treatment. They found that moving gas was the main cause of prostate intrafraction motion. However, because they asked their participants to void their bowel immediately before each scan, they did not detect a decrease in intrafraction prostate motion with the intervention.

A different intervention approach was taken by McNair and colleagues[150]. Their protocol required a baseline assessment of dietary intake followed by a fibre and fluids prescription based on diet analysis. They also scheduled radiotherapy appointments within two hours of the planning CT appointment time. Their results, from 22 patients found that a small modification of fibre intake resulted in no improvement in rectal volume consistency, potentially due to the small change in diet and the inclusion of fibre which may cause bowel gas.

In conclusion a diet intervention of an antiflatulent diet supplemented with psyllium husk appears to offer a more consistent rectal volume when compared to no intervention. The findings reported here support further investigation of efficacy of a DI in a larger cohort.

Table 4-3. Supplementary Table: List of food recommendations

Foods To Avoid	Foods To Include
Carbonated Beverages	
Sparkling wine	Water
Beer	Cordial
Soda water	Weak Tea
Mineral water	
Soft drinks	
Fruit	
Raisins	Stewed Apple
Sultanas	Stewed Pear
Bananas	Stewed Peaches
Oranges	Stewed Apricot
Pineapple	Watermelon
Prunes	Cantelope
Prune Juice	Grapes
Dates	Nectarines
Strawberries	Plum
Tomato	Cherry
All Dried Fruits	Mandarins
All Berries	Mango
	Tinned tomato
	Tinned fruit
	Other Stewed fruits
Vegetables	
Onions	Potato
Garlic	Pumpkin
Green Peas	Sweet potato
Cabbage	Spinach
Capsicum & Peppers	Silverbeet
Asparagus	Beetroot
Celery	Cauliflower
Brussel Sprouts	Snow peas
Beans	Swede
Broccoli	Turnip
Leeks	
Minimise all raw vegetables & salads	
Nuts and seeds	
Avoid all.	
Legumes	
Baked Beans	
Split peas	
Chick peas	
Lentils	
Cereals	
Wholegrain bread	White bread
Wholegrain cereals	Porridge
Wholemeal pasta	Plain biscuits & crackers
Brown rice	Rice bubbles
Muesli	Cornflakes
Wheat germ	Special K
Bagels	Weeties
Pretzels	White pasta
	White rice

Chapter 5 Geographical miss of the prostate during image-guided radiotherapy with a 6mm posterior expansion margin.

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Journal of Medical Radiation Sciences, 2016, *IN PRESS*. DOI: 10.1002/jmrs.186

The theme of this thesis focuses on ways to safely reduce the PTV margin for prostate radiotherapy. Before reducing PTV margins, it is important to understand the currently applied PTV margin in the light of new information available. Our department had previously conducted an investigation into the intrafraction displacement of the prostate based on pre-treatment and post-treatment orthogonal kV imaging[164]. This investigation had used the fiducial marker translations as a surrogate of prostate location, but had not determined the impact of prostate rotations and deformations. With volumetric imaging available in the form of post-treatment CBCT from **chapter 4,** we should be able to gather more information about the effectiveness of the PTV margin to cover the target volume at the end of treatment. We could determine if the fiducial marker translations were an accurate representation of the translations rotation and deformation of the prostate, and therefore, were reliable for setting margins. We could also look for reasons as to why there may be a geometric miss with our current PTV margins and evaluate which patients are more likely to have geometric misses during treatment.

Abstract

Introduction

Our department commonly uses a planning target volume (PTV) expansion of 6 mm posterior and 1 cm in all other directions when treating prostate cancer patients with image guided radiotherapy (IGRT). This study aimed to test the adequacy of this PTV expansion by assessing geographical miss of the prostate on post-treatment cone-beam CT (CBCT) and identify those at risk of geographical miss.

Methods

Twenty-two prostate cancer patients receiving IGRT with implanted fiducial markers underwent daily pre-treatment orthogonal kV imaging followed by a post-treatment CBCT for a total of 432 fractions. The prostate was outlined on all CBCTs. For each imaging set, the volume of geographic miss was measured by subtracting the PTV from the planning CT and prostate volume on the post-treatment CBCT.

Results

The prostate volume moved outside the PTV by >0.01 cc in 9% of fractions (39/432). This occurred in 13 of 22 patients (59%). Large prostates >40 cc and >50 cc had significantly more geographical miss events (both $p<0.001$). Changes in rectal filling appear to be responsible for prostate motion/deformation in 82% (32/39) of fractions.

Conclusions

Our analysis suggests that, despite IGRT, prostate PTV margins are not adequate in some patients, particularly those with large prostates. PTV margins may be reduced in some other patients. Prostate rotation and deformation play an important role in setting margins and may not always be

represented accurately by fiducial marker displacements. Individualised and adaptive margins for prostate cancer patients should be a priority for future research.

5.1 Introduction

One challenging technical aspect of prostate cancer radiotherapy is prostate motion. Interfraction motion that occurs between fractions is responsible for the greatest amount of error in prostate treatments due to systematic errors and anatomical variations[134]. Meanwhile, intrafraction motion, motion which occurs during the treatment fraction, is responsible for short-duration, small, but significant deviations in prostate position[140, 141]. The greatest cause of intrafraction prostate motion during external beam radiotherapy is changes in the rectal volume[140, 142, 144].

The introduction of image-guided radiotherapy (IGRT) has reduced the impact of interfraction prostate motion, while improving treatment accuracy and reducing treatment side-effects[191]. However, in many centres the margins used during IGRT are still largely based on historic practice from pre-IGRT era. Our departmental clinical protocols currently recommend a clinical target volume (CTV) to PTV expansion of 0.5-0.7cm posterior and 1cm in all other directions. The posterior expansion has traditionally been reduced as a compromise between covering prostate motion and limiting treatment toxicity[101]. These PTV expansions have been used in large clinical studies[104-106], but need reviewing in the IGRT setting.

With the move to treatment alignment using electromagnetic transponders, further reduction in PTV expansions have been proposed[141, 192, 193]. However, the use of electromagnetic transponders without imaging information and correcting the treatment alignment using only translational information may not account for the effect of prostate rotation and deformation[138, 194].

This study had multiple aims. First, to use post-treatment cone-beam CTs (CBCT) to test the adequacy of our most commonly used CTV to PTV expansion of 0.6 cm posterior and 1 cm in all directions for prostate cancer patients. Second, to investigate the relationship between fiducial marker motion and the rotation/deformation of prostate contoured on CBCT. Third, to determine

the cause of prostate displacements, rotations and deformation, and to determine which sub-group of patients were at risk of geographical miss.

5.2 Method

5.2.1 Treatment Protocol

This prospective study was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee. Twenty-two prostate cancer patients were treated between February 2010 and July 2011. Some participants followed an antiflatulent diet intervention with psyllium as a bulk forming laxative, a full description of the diet intervention has been reported previously[195]. Eligible participants were ≥50 years of age, ECOG performance status of 0-2, and had biopsy proven prostate adenocarcinoma, stage T1-T3b. All participants had three gold seed fiducials implanted for IGRT.

All participants were prescribed radiotherapy of 74-78 Gy in 2 Gy fractions. Planning and treatment was in the supine position with a Combifix (CIVCO Medical Solutions, Kalona, USA) for pelvis immobilisation. Kilovoltage (kV) orthogonal images were acquired at the beginning of each fraction and an online correction protocol was applied matching to the gold seed fiducial markers with a 0 mm tolerance[189]. CBCT images were acquired at the end of treatment for fractions 1-5 and then every second fraction.

5.2.2 Contouring

De-identified datasets were contoured by one investigator (DJ). All contouring was performed using FOCAL v4.62 (Elekta, Stockholm, Sweden). The external surface of the rectum was contoured from 9 mm inferior to the superior border of the treatment field to 9 mm superior to the inferior border of the treatment field. The prostate (i.e. CTV) was contoured on the planning CT and CBCTs as the external surface of the prostate from the base to the apex. The seminal vesicles were not contoured for this study. Prostate rotation was measured using the contours as outlined in Owen et al[196].

5.2.3 Adequacy of PTV margin

A priori, we considered a margin to be adequate if the PTV expansion covered all CBCT prostate displacements for 90% of patients, which follows a simple interpretation of van Herk's recommendation that "for 90% of the patient population, the minimum dose to the CTV must be 95% of the nominal dose (i.e., the dose at the specification point) or higher"[102]. We assessed the number of times where the prostate (CBCT-CTV) displaced beyond the PTV as seen on post-treatment CBCT and defined this as a geographical miss. Where the standard margin was inadequate we created a new CTV to PTV expansion, increasing the margins in 1 mm steps in the required direction (posterior or all other directions) until the PTV covered the CTV for all CBCTs.

5.2.4 Volume of prostate geographical miss

The volume of the prostate outside the PTV at the end of each treatment fraction was measured by creating a structure subtracting the CBCT-CTV from the PTV using FOCAL. Only volumes of 0.01 cc or greater were measurable with FOCAL.

5.2.5 Direction of excursion

The direction of the CBCT-CTV outside of the PTV was recorded by identifying the location of the geographical miss. For each fraction, this was compared to the greatest direction of intrafraction prostate motion, recorded as the displacement of the fiducial markers on post-treatment CBCT imaging from online correction at the start of the treatment fraction by one investigator (RO).

5.2.6 Cause of excursion

One investigator (RO) assessed the cause of prostate displacement. The CBCT rectum contour was compared to the planning rectum contour to determine if rectal distortion, (i.e. changes in rectal volume or shape from the planning rectum) may account for prostate motion. The volume and

location of the bladder was also visually compared to the planning volume to determine if prostate displacement was impacted by bladder filling.

5.2.7 Predictors of patients "at risk" of geographical miss

To identify potential predictors of patients at risk of geographical miss we followed the suggestions by Hatton et al[194]. We aimed to identify a large prostate volume and large rectal cross sectional area (CSA) at planning which may put patients in an "at risk" sub-group.

5.2.8 Statistical Methods

Descriptive statistics were used for all data assessed. To test for "at risk" sub-groups a Chi-squared test of independence was used to compare the proportion of prostates above or below the large prostate threshold, grouped with a geographical miss or no miss. The other sub-group compared the proportion of those above or below the large CSA threshold, and grouped with a geographical miss or no miss. This assumes each fraction and prostate size is independent of all others and there is no patient effect. All tests were performed at $\alpha = 0.05$, using R software v2.15.1 (www.r-project.org/).

5.3 Results

CBCT datasets were available for 432 fractions from 22 patients with a median (range) of 20 (16-22) CBCT per patient. Fifty of the 482 (10%) planned CBCT scans were unusable due to image quality or data capture failure (e.g. pre-treatment alignment offsets), or were missed due to equipment failures (primarily a CBCT reconstructor failure). Eleven patients received 3D conformal radiotherapy (3DCRT), the remaining eleven received intensity-modulated radiotherapy (IMRT). The mean (± standard deviation) treatment time from kV imaging to CBCT capture was 7 min (± 2 min).

5.3.1 Adequacy of PTV margin

The prostate displaced outside the PTV by >0.01 cc in 39/432 (9%) of fractions (Table 5-1). This occurred in 13 of 22 patients (59%). Only five geographical miss fractions were longer than nine minutes (mean plus standard deviation fraction duration) and all were less than 12 minutes, indicating a small impact of fraction duration. When the posterior margin was expanded to 7 mm, 15 of 22 patients (68%) received adequate coverage. Expanding the posterior margin to 8 mm covered the remaining posterior prostate displacements in all patients. Three patients required expansions in other directions to cover anterior and superior excursions, with two patients requiring 12 mm expansions to cover the prostate displacement (Table 5-2). Overall, for the PTV to cover displacements, rotations and deformations for 90% of patients, an expansion of 11 mm in all directions except 8 mm posterior would be required.

Table 5-1. Details of prostate geographical miss for 432 fractions in 22 patients receiving radical prostate radiotherapy.

Patient	CBCT #	Volume outside PTV (cc)	Direction	Intrafraction displacement			Rotation	Agree with fiducial displacement?
				LR	SI	AP	(^{o})	
1	18	0.04	Post	0	0	0	-22	YES
2	17	0.03	Post-Inf	0.1	-0.3	-0.1	-3	YES
2	18	0.11	Post-Inf	0	-0.2	-0.4	9	YES
2	19	0.09	Post	0.1	-0.4	-0.6	4	YES
3	09	0.02	Post-Sup-Lat	-0.3	0	0.2	30	YES
3	10	0.02	Post	0.1	0	-0.2	20	YES
7	07	0.06	Ant	0.2	0	0.1	12	YES
7	08	0.18	Ant	0.1	0	0	1	YES
9	22	0.15	Post	0	-0.2	-0.3	9	YES
11	03	0.02	Post	-0.1	0.1	-0.1	7	YES
11	05	0.03	Post	0	0	0	-6	YES
11	06	0.07	Post	-0.2	-0.1	0	-10	YES
11	09	0.04	Post	0.1	0	0.1	3	NO
11	17	0.01	Post	0.1	0	0	7	YES
12	15	0.02	Post	0.1	0.1	-0.1	0	YES
12	19	0.08	Post	-0.1	0	-0.3	-5	YES
15	18	0.61	Ant-Sup	-0.1	0.6	0.5	-10	YES
15	19	0.06	Post-Sup-Lat	-0.1	0.3	0.2	-16	NO
17	02	0.07	Post	-0.2	-0.4	-0.5	1	YES
17	03	0.10	Post-Inf	-0.2	-0.3	-0.2	12	YES
17	07	0.02	Post-Inf	-0.3	-0.3	-0.4	3	YES
18	02	0.08	Post	-0.1	-0.2	-0.3	3	YES
18	04	0.03	Post	0.1	-0.1	-0.3	3	YES
19	03	0.17	Post-Sup	0	0	-0.2	-1	YES
19	10	0.05	Post-Sup	-0.1	0.5	0.3	30	YES
19	14	0.03	Post	-0.2	0	-0.2	13	YES
19	15	0.06	Post	-0.1	0	-0.2	31	YES
19	17	0.02	Post-Sup-Lat	-0.2	-0.1	-0.4	9	YES
19	19	0.79	Post	0	0	-0.3	18	YES
21	02	0.63	Post-Inf	0	-0.2	0.1	7	YES
21	03	0.63	Post-Inf	0	0.1	0.3	14	NO
21	05	0.47	Post-Inf	0	0.1	0.3	26	NO
21	07	0.05	Post-Inf	0	0	-0.2	9	YES
21	08	0.09	Post-Inf	0.2	0	0.2	10	NO
21	10	0.04	Post	0.1	0	0.1	18	NO
21	16	0.20	Post	0.1	0	0	8	YES
22	09	0.02	Post	-0.1	-0.3	-0.4	-3	YES
22	14	0.04	Ant-Sup	0.2	0.5	0.6	8	YES
22	16	0.25	Ant-Sup	0.2	0.9	0.9	7	YES

Abbreviations: CBCT = Cone-beam CT, PTV = Planning Target Volume, cc = cubic centimetres, Ant = anterior, Post = posterior, Sup = superior, Inf = inferior, Lat = lateral.

Displacements: L = +ve, S= +ve, A= +ve

Rotations: +ve represents the base of the prostate rotating anteriorly from the planned angle.

Table 5-2. PTV expansion required to cover all prostate displacements on post-treatment CBCT for 22 patients.

Patient	Diet Intervention	Prostate Volume (cc)	Planning Rectum CSA (cm^2)	Margin Required for 95% TD	
				All directions (except posterior) (mm)	Posterior (mm)
1	NO	14.8	5.5	10	**7**
2	YES	27	9.5	10	**8**
3	YES	20.7	6.8	10	**7**
4	NO	25.5	6.3	10	6
5	NO	32	7.4	10	6
6	YES	11.8	6.3	10	6
7	YES	36.8	5.6	**11**	6
8	NO	31.1	9.6	10	6
9	NO	22	6.8	10	**8**
10	YES	26.3	3.5	10	6
11	YES	51.2	7.5	10	**8**
12	NO	39.1	8.9	10	**8**
13	YES	22	6.2	10	6
14	YES	26.8	4.3	10	6
15	NO	40.2	6.1	**12**	**8**
16	YES	27.5	6.7	10	6
17	NO	32.9	6	10	**8**
18	NO	54.3	3.9	10	**8**
19	NO	41.1	6.1	10	**8**
20	NO	33.3	6.3	10	6
21	NO	50.1	4.1	10	**8**
22	YES	30.6	6.5	**12**	**7**

Note: Bold indicate cases where the margin was changed from standard due to geographic miss on CBCT..
Abbreviations: CSA = cross sectional area, TD = target dose, cc = cubic centimetres, CBCT = Cone-beam CT, PTV = Planning Target Volume.

5.3.2 Volume of prostate geographical miss

The median (range) of prostate volume displaced beyond the PTV was 0.06 cc (0.01-0.79). The median (range) prostate volume in our patient cohort was 30.85 cc (11.8 – 54.3), indicating the proportion of prostate geographical miss was relatively small. In 90% (35/39) of cases the geographical miss volume was less than 1%. Only one fraction saw the volume of geographical miss greater than 2%. Table 5-3 indicates that within patients there may be a trend for prostate intrafraction displacement and, therefore, a variation in the margin required to cover this motion. However, the incidence of geographical miss varied during the course of treatment in each patient.

Using early fractions to predict displacement later in treatment would be ineffective for most patients. This indicates that daily margin assessment is required and a daily adaptive treatment approach would be best suited to modifying margins according to individual patient needs.

Table 5-3. Patients with the same prostate geographic miss location in multiple fractions, leading to a risk of inadequate treatment dose.

Patient	Prostate location	Number of fractions
2	Posterior apex	3
11	Posterior base	5
17	Posterior apex	3
19	Posterior apex	3
19	Posterior base	4
21	Posterior apex	7

5.3.3 Direction of excursion

The direction of prostate geographical miss agreed with the fiducial marker shift in 85% (33/39) of fractions. The direction of fiducial marker displacement contradicted the prostate geographical miss direction four times in one patient. This was due to the posterior prostate apex moving beyond the PTV while the superior aspect of the prostate had rotated forwards. In another case, prostate rotation was also responsible for geographical miss where the prostate base rotated posteriorly while the apex was displaced anterior. The last case appeared to be due to prostate deformation where the posterior edge of the prostate displaced outside the PTV, while there was a 1mm anterior displacement of the seeds. In this case, the rectal contents had 'flattened' the prostate.

5.3.4 Cause of excursion

Rectal changes appeared to be responsible for geographical misses in 82% (32/39) of fractions, with the remaining potentially impacted by the bladder. The changes in the rectum appeared to rotate and/or deform the prostate volume in most cases, with prostate rotations of ≥10 degrees evident in

41% (16/39) of geographical misses. All geographical misses due to bladder impacts were apparent in patient 21 (Table 5-1). His very large bladder at treatment compared to a small bladder at planning CT appeared to displace the prostate inferiorly in conjunction with a large expansion of the superior rectum (Figure 5-1). His seed placement was also not ideal with the seeds clustered at the prostate base, poorly representing the apex.

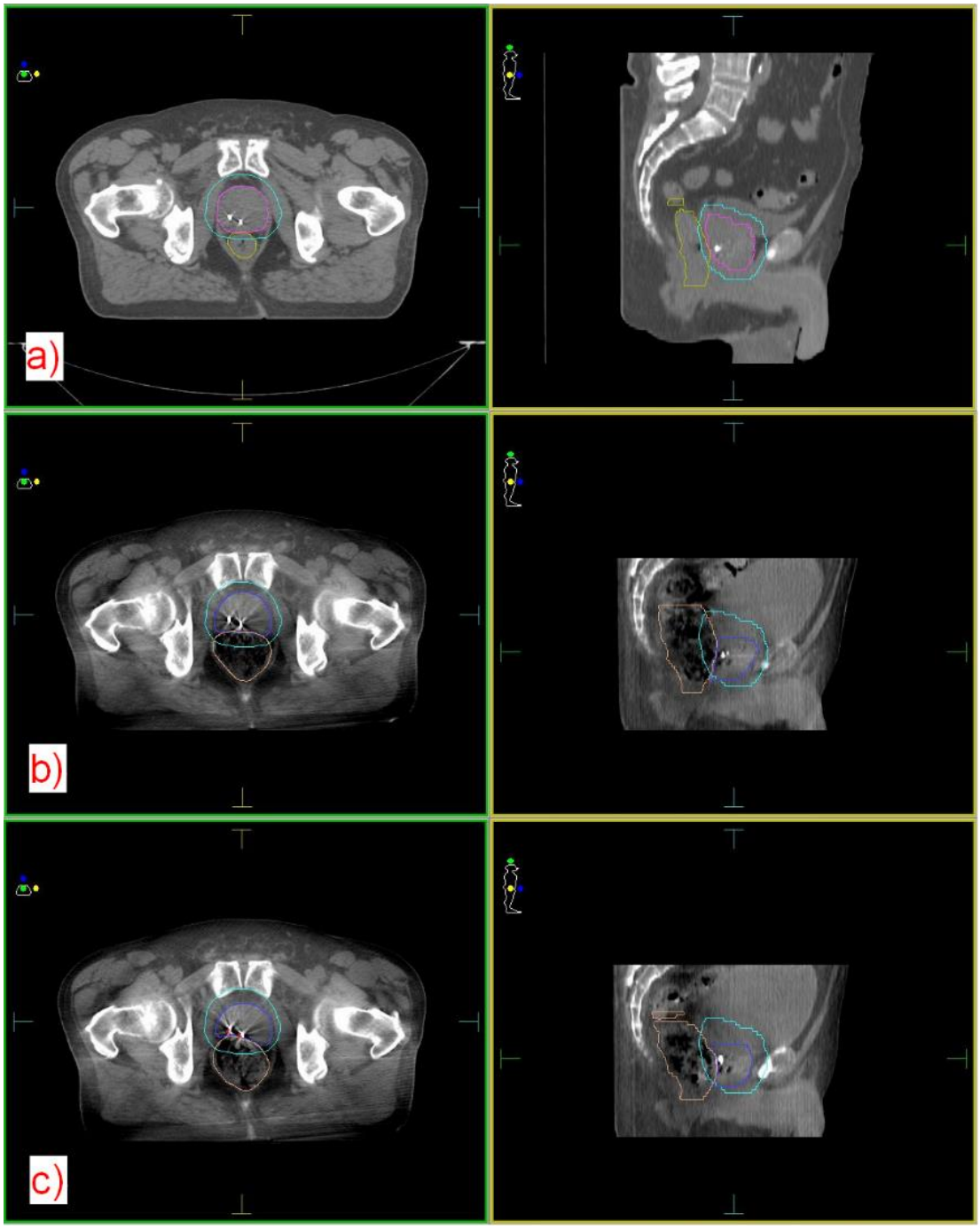

Figure 5-1. Pelvic anatomy for patient 21; 1a) at planning with the CTV (including seminal vesicles) outlined in magenta, the PTV in cyan and the rectum in gold, 1b) fraction five showing the change to the prostate location in indigo and the rectal volume in pale brown, 1c) fraction eight showing the change to the prostate location in blue and the rectal volume in brown with the anterior displacement of the gold seeds demonstrated relative to the planned location in red.

5.3.5 Predictors of patients "at risk" of geographical miss

Hatton et al. suggested that patients with a prostate of >50 cc were more likely to see the prostate dose compromised[194]. Three patients in our study were above this large prostate threshold and these three patients comprised 36% (14/39) of all geographical miss events. The proportion of geographic miss in patients with > 50 cc prostate volumes (14 of 59) was significantly different to those with small prostate volumes (25 of 373) ($p < 0.001$). If a threshold of >40 cc was used to define a large prostate, five patients were above the threshold. In this case the proportion of geographic miss in patients with large (>40cc) prostate volumes (22 of 59) was significantly different to those with small prostate volumes (17 of 373) ($p < 0.001$). These five patients represented 56% (22/39) of all geographical miss events.

No "at risk" relationship was found with planning rectal CSA. All patients had a rectal CSA below 10 cm^2 at planning due to our simulation protocol[197].

5.4 Discussion

This study uses anatomical data from CBCT to suggest that a PTV expansion margin of 0.6 cm posterior and 1 cm in all other directions from the prostate may not be adequate for all patients in the current IGRT application. Our data suggest that there is variation in prostate motion in a typical population and that individualised margins with an adaptive treatment approach may be beneficial. Our data also suggest that prostate deformation and rotation play a role in at least 41% of geographical miss events. Patients with a large prostate may be "at risk" of geographical miss and may require a larger PTV margin. Prostate rotation and deformation may not be accurately represented by fiducial marker translations, particularly if the markers are not optimally placed.

Our findings are supported by an investigation using a series of three Cine-MRI scans on six patients[144]. The authors found that prostate motion was well characterised by rotation and deformation, with the prostate apex more likely to be stable and rotation of the prostate base

common. This indicates the importance of accurate fiducial marker placement, with a marker close to each of the prostate base and apex to demonstrate rotation.

A study of repeated MRI scans in 25 patients assessed prostate deformation and rotation relative to fiducial markers, suggesting that these events were not insignificant, with the difference in prostate surface and fiducial marker location showing a standard deviation of 1.5 mm[138]. That study demonstrated deformations of the prostate surface of up to 13 mm from the planned prostate surface when only translational alignment of the fiducial markers were used[138]. MRI imaging offers improved prostate delineation and demonstrated substantial prostate deformation, particularly in patients who had undergone a trans-urethral resection of the prostate (TURP) and in the event of uncharacteristic rectal and/or bladder filling. Our data, with a greater number of fractions, suggests there is substantial prostate deformation/rotation which appears to be dependent on bladder and rectal filling. However, due to lower image quality, our prostate delineation is less accurate than those obtained on MRI.

Similar to our study, Hatton et al, used a series of repeat post-treatment CBCTs on twelve patients to assess prostate displacement during a treatment fraction and the impact on target coverage with a 7mm uniform margin[194]. They found four of 12 patients (33%) had compromised target dose coverage, partly due to intrafraction prostate displacement and mostly due to deformation. Similar to our findings, they found that patients with larger prostates are more likely to have compromised prostate dose.

While Hatton et al[194] and our study suggested changes in the prostate location on post-treatment CBCT were due to intrafraction motion, neither study assessed the impact of prostate rotation/deformation on PTV coverage with pre-treatment kV fiducial alignment. Nichol et al[138] suggest that some fractions may have a prostate geographical miss at treatment commencement.

Our study highlighted the importance of bladder filling at planning being representative of bladder filling during treatment. Our simulation protocol requires a rectum diameter of approximately 4 cm or less, and the absence of excessive gas or faeces at planning CT[197]. We use the same rectal filling assessment on treatment and will ask patients to empty their bowels if a large amount of gas or faeces is evident on pre-treatment kV imaging. We do not have a policy for prostate rotation, which is often evident on lateral pre-treatment images.

Methods should be developed to determine the impact of prostate rotation on PTV coverage and to define individualised thresholds of rotation before intervention. Planning software image fusion functions could be utilised to determine how much rotation of the fiducial centre of mass around the right-left direction could occur before the patient's CTV breaches the PTV contour (assuming the prostate rotates as a solid structure). Pre-treatment lateral imaging could use seed segmentation to estimate prostate rotation around the right-left direction. Alternatively, rotation could be more accurately estimated using pre-treatment CBCT imaging with fiducial tracking[198], radiofrequency transponder fiducials or by kilovoltage monitoring during treatment[199]. If prostate rotation was larger than the patient determined threshold, then the patient could be asked to empty their rectum, or repositioned on a six degrees of freedom couch. If a trend of prostate rotation was identified, a repeat planning CT could check for seed migration and/or for replanning if the prostate is consistently rotated relative to the original plan.

Our most commonly used CTV to PTV expansion is 0.6 cm posterior and 1 cm in all other directions. This study suggests that larger margins may be more appropriate in some patients, i.e. patients with large prostates, and that an individualised approach to setting margins may be beneficial. While the volume of prostate geographical miss is small, the location of geographical miss was consistent in some patients. This could lead to under-dosing part of the prostate. Historically, with 3DCRT, posterior geographical miss would result in a relatively small reduction of the dose received.

However, with current rectal-sparing IMRT and VMAT techniques the impact on prostate dose may be greater and could be of great concern for stereotactic ablative radiotherapy (SABR) techniques with small margins and high conformity index.

Several papers have proposed small treatment margins with online correction protocols based on translations of electromagnetic transponder fiducials. Liztenberg et al, suggested margins of 1.4, 2.3, and 1.8 mm using interbeam adjustment with a zero threshold and 1.3, 1.5, and 1.5 mm using intrabeam adjustment with a 3-mm threshold, in the LR, AP and SI planes respectively[141]. Su et al, suggested 1.1, 2.3 and 1.8 mm margins with a 3-mm threshold correction and 0.5, 1.5, and 1.0 mm margins with a 2-minutely correction, in the LR, AP and SI planes respectively[192]. Sandler et al implemented PTV margins of 3-5 mm in 64 patients in their study[193]. The margins suggested in these papers may not be adequate to account for prostate rotations and deformations, as recognised by some authors[200]. One paper which accounts for rotations and translations proposed a uniform margin of 5 mm when used with a 3 mm online correction protocol and <10 degree rotation allowance[201]. This is in agreement with our findings that prostate geographical miss may not be represented by all fiducial translations (Table 5-1).

When IGRT to implanted fiducial markers is used, tight margins of 3 mm, 5 mm and 4 mm (LR, AP and SI planes respectively) and a distended rectum at planning have a significant negative impact on biochemical control of prostate cancer[202]. Clinical data indicated that a uniform 6mm margin offers superior biochemical control to the previously used tight margins (25 patients in each group)[202]. Our study did not investigate the possibility of margin reduction, which for many patients may be suitable in the LR, SI and anterior expansions.

Our study has several limitations. We considered the prostate only and did not include seminal vesicles which are more prone to movement[135]. We only captured the prostate location at the end

of treatment, not the full intrafraction excursion of the prostate. As noted by Hatton et al, the impact on dose delivered to the prostate could be considered 'worst case'[194] as all motions of the prostate were not considered. It is likely that the location of post-treatment prostate geographical miss will have dwelled in a high-dose region before moving to a low dose region, except where the prostate is grossly rotated from the start of the treatment fraction or where intrafraction motion was a large, long-lasting prostate displacement early in the fraction. These considerations are supported by Engels et al, whose clinical data suggests a 6 mm uniform margin would be suitable[202] and by Li et al, who have demonstrated a small impact of intrafraction displacement on dose delivered to the prostate[203].

There may be some contouring error due CBCT image quality, particularly with contouring the prostate base and apex, which can be difficult to identify[204]. Due to this difficulty and reliance on surrounding anatomy, some contours may over-estimate the prostate boundaries, which again indicates worst case scenario. We minimised contouring uncertainty by having one contouring investigator and all CBCT-CTVs were similar to the planned volume. This study relates intrafraction displacements between kV/kV imaging and CBCT imaging, where CBCT 'best fit' matching offers greater error as not all fiducials can be visualised simultaneously. This study did not consider all treatment geographical miss events from all treatment fractions, which may overestimate/underestimate the impact on margins for some patients. Finally, some patients in this study underwent a diet intervention[195], although the data suggests any impact will be small (see Table 5-2).

From this study we recommend a larger study to clearly identify if a large prostate is an "at-risk" subgroup, or if the geographical miss events we observed for large prostate patients were simply due to patient effects. We recommend further investigation using Cine-MRI imaging to confirm our results. If confirmed, hormone therapy could reduce the prostate volume for patients with large

prostates. Alternatively, individualised margins and thresholds for prostate rotations could be determined at planning, with larger margins potentially required for larger prostates. For future studies, pre-treatment CBCT imaging would allow soft tissue assessment of rotation and deformation of the prostate, bladder and rectum. An adaptive approach could select appropriate fractions needing larger PTV margins, but also a smaller margin when the pre-treatment CBCTs indicate small prostates, stable bladders and rectums. Finally, while VMAT may reduce the fraction duration and risk of intrafraction motion, it will not preclude the risk of geographical miss from the start of the treatment fraction due to rotations/deformations.

5.5 Conclusion

Our study suggests that prostate CTV to PTV margins of 0.6cm posterior and 1cm in all other directions may not be adequate for all patients. Individualised margins would benefit some patients, with a larger margin potentially being more suitable for patients with a large prostate. The posterior margin was breached most frequently, therefore there is potential to reduce other margins. Prostate rotation and deformation play an important role in setting margins and further investigation using cine-MRI imaging should quantify the impact. To assess prostate rotation, seed placement is critical to represent the prostate base and apex, and soft tissue assessment may play a role. Adaptive margins could potentially be implemented to account for fractions where the prostate is likely to have smaller or larger motions and/or large rotations.

5.6 Addendum

As an addendum to this published paper, we briefly clarify the generation of contours to measure the volume of prostate geographic miss and how the location of geographic miss was identified. The volumetric information was obtained, as described, by creating the new structure using the Boolean subtract function to subtract the CBCT-CTV from the PTV. In most cases, as the PTV encompassed the CBCT-CTV there was no residual volume. In the case of a geographic miss there was a residual volume which indicated how much of the prostate had moved beyond the PTV. The limitation of volumetric measurement was, found to be small (0.01 cc). The location of geographic miss was identified visually as the location of the new structure after performing the subtraction.

Chapter 6 What benefit could be derived from on-line adaptive prostate radiotherapy using rectal diameter as a predictor of motion?

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Journal of Medical Physics, 2015, 40 (1) pp18-23

While the diet intervention in **chapter 4** may demonstrate efficacy in a larger study, the resulting margin reduction on a population basis is likely to be small. And, despite the effectiveness of the intervention, patients will still present with rectal filling at some fractions. While this can be detected with pre-treatment CBCT imaging, during a fully fractionated course of treatment only extreme events of rectal filling will usually be corrected and followed by repeat CBCT imaging due to concerns surrounding the imaging dose. The impact on department workflows of repeatedly correcting patients' bowel and bladder preparation can also be substantial.

Patients without diet intervention will present to around 40% of treatment fractions with an empty rectum[195], but a successful diet intervention would allow patients to present with an empty rectum even more frequently. The literature has demonstrated that patients with an empty rectum are at a lower risk of having a large displacement of the prostate within a treatment fraction[144]. To achieve further reductions in the treatment margin, we hypothesised that a patient who presented for treatment with an empty rectum could receive treatment for that fraction with a reduced PTV margin. However, we needed to define a threshold for an empty rectum in a way that is easily measured and with little subjectivity. A subjective grading system had previously been defined[142], however, interobserver variability of grading could likely be high thus reducing the reliability of this approach. Measuring the rectal diameter in the axial plane was also considered, but during our diet intervention study we observed that measuring rectal diameter this way may over-estimate the true filling of the rectum. So we devised a way to objectively measure rectal filling and aimed to determine the relationship of rectal filling to intrafraction displacement of the prostate. We also investigated the potential benefit of using an adapted margin.

Abstract:

This study investigated a relationship between rectum diameter and prostate motion during treatment with a view to reducing planning target volume (PTV) margins for an adaptive protocol. One hundred and ninety four cone-beam CT (CBCT) images of 10 patients were used to relate rectum diameter on CBCT to prostate intra-fraction displacement. A threshold rectum diameter was used to model the impact of an adaptive PTV margin on rectum and bladder dose. Potential dose escalation with a 6mm uniform margin adaptive protocol was compared to a PTV margin of 10mm expansion of the CTV except 6mm posterior. Of 194 fractions, 104 had a maximum rectal diameter of ≤3.5 cm. The prostate displaced ≤4mm in 102 of those fractions. Changing from a standard to an adaptive PTV margin reduced the volume of rectum receiving 25Gy, 50Gy, 60Gy and 70Gy by around 12, 9, 10 and 16% respectively and bladder by approximately 21, 27, 29 and 35% respectively. An average dose escalation of 4.2Gy may be possible with an adaptive prostate radiotherapy protocol. In conclusion, a relationship between the prostate motion and the diameter of the rectum on CBCT potentially could enable daily adaptive radiotherapy which can be implemented from the first fraction.

6.1 Introduction

Increasing the dose delivered to the prostate improves treatment outcomes for prostate cancer radiotherapy[96]. To enable dose escalation to the prostate without increasing treatment toxicity requires reducing the planning target volume (PTV) margins which allow for prostate movement within the pelvis. A major cause of intrafraction prostate motion is due to changes in the rectal volume which lies adjacent to the prostate[142, 144]. It has been demonstrated in Cine-Magnetic Resonance Imaging (Cine-MRI) studies that patients who present for treatment with a large rectum correlates with increased prostate motion during a treatment fraction[144]. Therefore there is the potential to modify the PTV margin based on the rectum presentation at each daily treatment.

Many current PTV margins applied during prostate radiotherapy are based on historical practice or historical interfraction margin formula[103]. These data take into account random treatment errors for all treatment fractions, many of which will not be present at each fraction. This is supported by our previous work which demonstrated intrafraction motion of greater than 5mm in only 4.7% of fractions[164]. That data showed that intrafraction motion was correlated with treatment fraction duration, although modifying margins based on fraction duration is difficult as it often varies from day to day[164]. Kupelian et al[165] monitored prostate motion during radiotherapy using the Calypso implanted electromagnetic transponder system and reported that 59% of fractions display less than 3mm of motion for more than a 30s interval. However, the more conservative estimate by Langen et al[163] report 34% (188 of 550) of all fractions demonstrated less than 3mm of prostate motion and therefore a reduced margin could be potentially applied on these fractions. We hypothesize that patients who present with an empty rectum will be at much lower risk of intrafraction prostate motion compared to patients who present with a full rectum as supported by the cine-MRI data[140, 144]. This relationship may form the basis of a daily adaptive treatment protocol where a smaller PTV margin is used when the prostate is at a lower risk of motion.

The primary aim for this study was to investigate a method for describing a relationship between prostate motion and rectum diameter by measuring the diameter of the rectum on cone beam CT (CBCT). The second aim was to model the dose to the organs at risk (rectum and bladder) for an adaptive margin compared to the dose received using standard technique. The third aim was to investigate the potential for dose escalation with adaptive margin reduction.

6.2 Materials and Methods

6.2.1 Participant selection

The study was approved by our institutional human research ethics committee. We used a pragmatic sample of ten consecutive patient datasets from patients who had received radical prostate radiotherapy between the 2nd February 2010 and 31st December 2010 and had CBCT imaging. The patients received 3DCRT or IMRT to a dose of 78 Gy. Image guidance for patient positioning was done matching to fiducial markers with kV/kV imaging prior to treatment. A CBCT image was acquired post treatment fractions 1-5 and every second fraction. All patients were contoured by a single observer to eliminate interobserver variation.

6.2.2 Data Acquisition

Pre-treatment kV/kV images and post-treatment CBCT datasets were available for 194 fractions in total. Intrafraction displacement was measured using the displacement of fiducial markers on the post-treatment CBCT relative to position of fiducials at the start of each fraction after online correction to gold fiducial markers. The fraction time was taken as the time stamp from the first kV image to the time stamp on the post-treatment CBCT.

The maximum true rectal diameter was measured on the coronal and sagittal sliced planes for the entire length of the prostate, and within 1.2 cm (4 x 3 mm slices) superior and inferior to the prostate on all CBCTs. The maximum true rectal diameter was determined to be the largest

diameter measured on the coronal and sagittal planes with the diameter measured from the outer rectal walls perpendicular to the path of the rectum. Measuring in this way avoids overestimating the rectal diameter which is likely when it is measured only in the axial plane (Figure 6-1).

The maximum rectal diameter and prostate displacement were plotted for each CBCT acquired (Figure 6-2). The authors used this data to select a rectal diameter which was associated with reduced intrafraction motion; this was subsequently used in planning for modeling an adaptive technique.

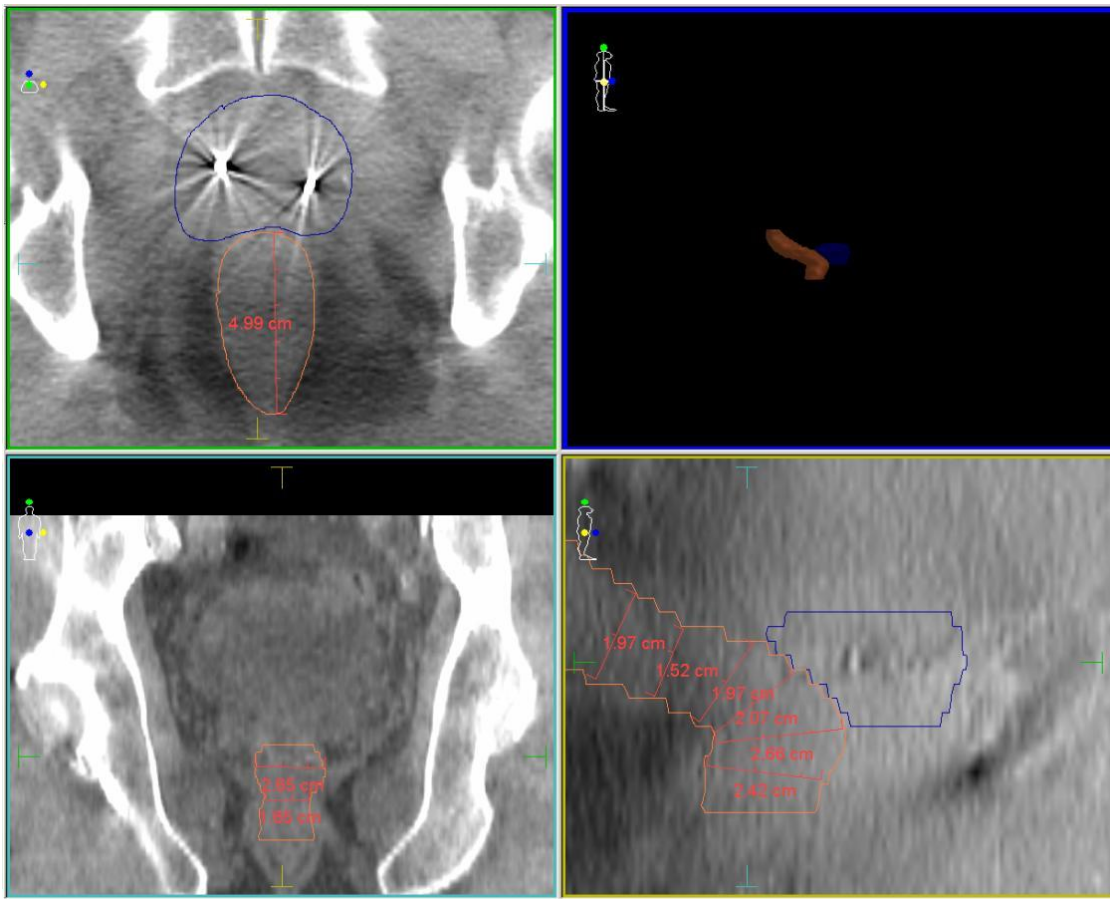

Figure 6-1. Sample patient showing maximum rectal diameter measured in axial plane as 4.99 cm, whereas on the sagittal and coronal planes it can be seen that the 'true' maximum rectal diameter is 2.66 cm.

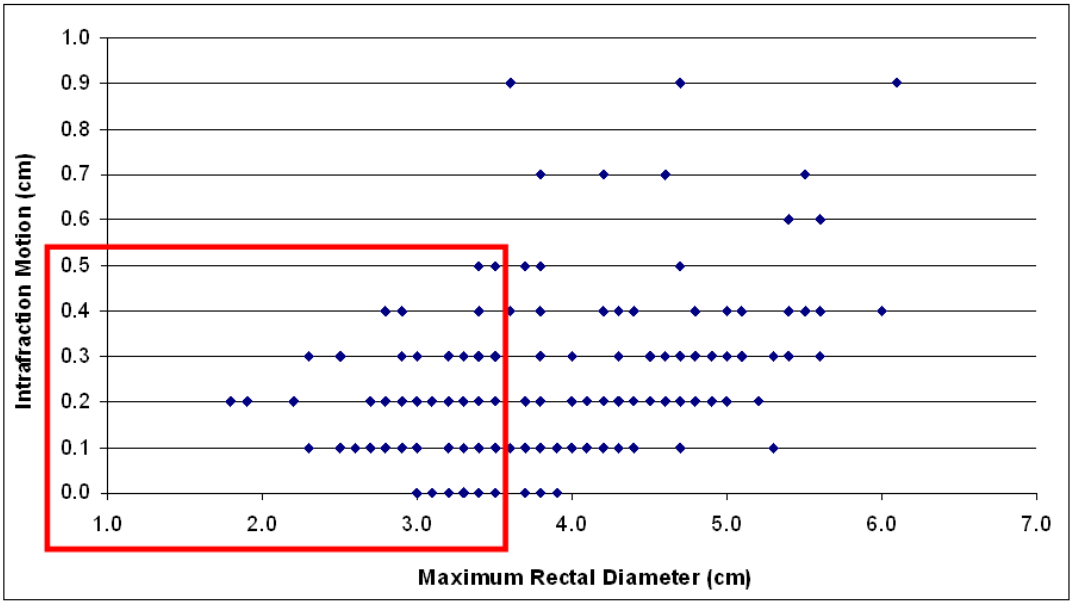

Figure 6-2. Scatter plot of maximum rectal diameter versus intrafraction displacement for 194 fractions.

6.2.3 **Planning Technique**

For study purposes the clinical target volume (CTV) was the prostate gland without seminal vesicles. The bladder was contoured as the external bladder wall to include the whole bladder. The rectum was contoured as the external rectal wall for the length of the PTV including an added length of 1.2 cm superior and 1.2 cm inferior to the PTV. The standard PTV margin was a 10 mm expansion of the CTV in all directions except 6 mm in the posterior direction. This is the standard margin used clinically in our department and a common margin which has been employed in large dose escalation trials[104]. The adaptive PTV margin was a 6 mm expansion in all directions, which allowed for 4 mm translocations of the prostate and a further 2mm for prostate rotation/deformation. This margin has been demonstrated to safely allow for intrafraction rotations and deformations[201], and has been demonstrated to have increased freedom from biochemical failure[202].

Four plans per patient were created for the study: a standard margin 78 Gy plan (StanPlan78Gy), a 6 mm margin 78 Gy plan (6mmPlan78Gy), a total adaptive dose escalation plan (AdapPlanDoseEsc) and an adaptive margin 78 Gy plan (AdapPlan78Gy). All plans were 3D conformal radiotherapy (3DCRT) plans with five fields comprised of two lateral fields, two anterior oblique fields and an anterior field. Minimum planning dose constraints were to be achieved for each plan. The PTV was to receive ≥74.1Gy to 99% of the volume. The rectal dose volume histogram (DVH) constraints were V50 Gy, V60 Gy and V70 Gy less than 50%, 30% and 20% respectively. The femoral head DVH constraints were V35 Gy, V45 Gy and V60 Gy less than 100%, 60% and 30% respectively. Lastly the bladder DVH constraint was V50 Gy < 50%.

The StanPlan78Gy was created to a dose of 78 Gy in 39 fractions using the study PTV (expansion of CTV which excluded seminal vesicles) and the standard planning contours. This plan was created to estimate the dose received by organs at risk using a standard margin alone. The 6mmPlan78Gy was also created using standard planning contours and a 6 mm CTV to PTV margin, which would simulate the dose to organs at risk if a 6 mm margin was used. These plans were used to calculate the volume of bladder and rectum receiving doses of 70 Gy, 60 Gy, 50 Gy and 25 Gy. The dose data was used to calculate the reduction in dose to the rectum and bladder using a 6 mm PTV margin when compared to a standard margin.

The AdapPlanDoseEsc was created based on the proportion of fractions where an adaptive margin and standard margins could be used for dose escalated radiotherapy (Table 6-1). The AdapPlanDoseEsc plan was dose escalated by two Gray fractions until the rectal V60 was nearest to the rectal V60 achieved in the StanPlan78Gy to estimate the dose escalation possible with an adaptive plan while maintaining the same toxicity profile. The contours used for AdapPlanDoseEsc were the planning rectum and bladder, and an adaptive 6mm PTV and standard PTV expansion from the planning CTV.

To check the validity of dose reduction to the organs at risk, the first CBCT for each patient was selected for planning where the maximum rectal diameter was less than the threshold set by the authors. The CBCT was fused as per the pre-treatment alignment to gold fiducial markers. The dosimetry was performed on the planning CT scan using CTV, 6mm PTV, rectum and bladder contours from the post-treatment CBCT. The StanPlan78Gy was used as the starting point for the AdapPlan78Gy which generally required only modification of the port size and weightings. The AdapPlan78Gy was used to calculate the volume of bladder and rectum which would receive doses of 70 Gy, 60 Gy, 50 Gy and 25 Gy during a treatment fraction, this was compared to the doses calculated from the StanPlan78Gy.

Descriptive statistics were used to report all data. The mean ± one standard deviation was used to report the fraction time, OAR dose volume reductions and dose escalation.

Table 6-1. The reduction in treated volume of organs at risk (OAR) if 6 mm uniform PTV margin (6mmPlan78Gy) or adaptive margins (AdapPlan78Gy) were used when compared to a standard PTV margin of 10mm expansion of the CTV except 6 mm posterior.

Plan	OAR	OAR Volume reduction at dose level (% ± SD)			
		25Gy	50Gy	60Gy	70Gy
6mmPlan78Gy	Rectum	12 ± 3	9 ± 5	10 ± 5	16 ± 7
	Bladder	28 ± 5	32 ± 5	36 ± 6	43 ± 8
AdapPlan78Gy	Rectum	4 ± 20	4 ± 27	8 ± 29	16 ± 36
	Bladder	43 ± 19	43 ± 19	45 ± 20	48 ± 21

6.3 Results

Of 194 fractions, 104 had a true maximum rectal diameter of 3.5 cm or less (Figure 6-2). The prostate displaced 4mm or less in 102 of those fractions. This indicates that potentially the rectum diameter may be a predictor of prostate displacement during a radiotherapy fraction and the authors therefore used a ≤ 3.5 cm rectum diameter threshold to determine adaptive fractions in the planning technique. The mean (±SD) fraction time was 11.1 (±3.9) minutes.

Estimated by the 6mmPlan78Gy, if a 6 mm PTV margin was used when compared to the StanPlan78Gy the reduction of the volume of rectum and bladder receiving 25Gy, 50Gy, 60Gy and 70Gy are outlined in Table 6-1.

The AdapPlanDoseEsc figures indicate that an average dose escalation of 4.2 (± 3.3) Gy would be possible for this patient group while maintaining the current rectal toxicity profile at the V60 dose constraint. The dose escalation achievable is largely dependent on the shape of the posterior edge of the CTV as illustrated in Figure 6-3. If the posterior CTV slopes superoposterior to inferoanterior then the 1cm inferior expansion of the irregular standard margin will cause a greater proportion of the rectum to be included in the standard PTV (Figure 6-3A). On the other hand, if the posterior CTV is more directly superior to inferior then there is a smaller difference between rectal volume included within the standard PTV and the adaptive PTV (Figure 6-3B). This is demonstrated by three patients who only achieved a dose escalation of 2 Gy despite having greater than 10 adaptive fractions in the modeled treatment (Table 6-2).

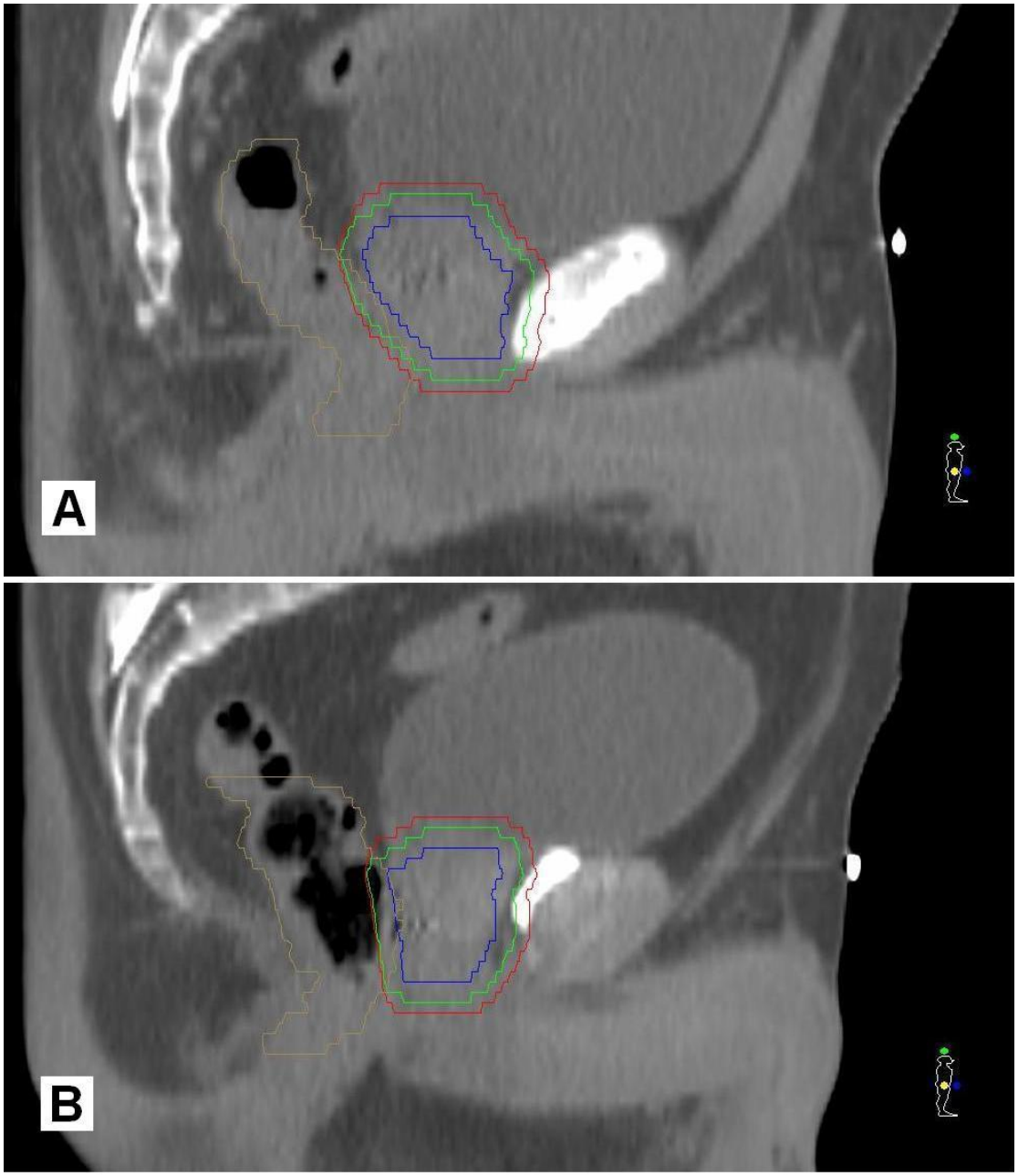

Figure 6-3. Two patient representing differences in PTV margin expansion due to the posterior CTV angle. The CTV is represented in blue, the 6mm PTV expansion in green, standard PTV expansion in red and rectum in brown.

Compared to the StanPlan78Gy, the AdapPlan78Gy dosimetry estimated reductions in the volume of rectum and bladder receiving 25 Gy, 50 Gy, 60 Gy and 70 Gy as outlined in Table 6-1. The figures are similar to those modeled on the planning scan contours, particularly for the rectum at 60 Gy and 70 Gy doses. The variation in bladder and rectum doses can be attributed to variations in the bladder and particularly the rectum volumes during the course of treatment which may change the volumes of OARs in high dose regions (Prabhakar et al., 2014). This supports the planning data that treatment fractions where a reduced margin is used there will mostly be a reduction in the dose to organs at risk.

Table 6-2. Estimated dose escalation achieved in ten patients using an adaptive protocol while maintaining equivalent rectal constraints. Adap # and Standard # represent the number of fractions where an adaptive and a standard margin would be used for each patient.

Patient	Dose	Adap #	Standard #	RecV60DoseEsc	RecV60StanPlan
01	90	36	9	29	28.85
02	80	2	38	17.6	16.9
03	80	19	21	20.4	20.6
04	80	11	29	30.5	30.1
05	80	4	36	26.61	26.22
06	86	33	10	17.9	17.5
07	82	30	11	20.9	20.7
08	80	21	19	20.54	20.23
09	82	27	14	14.75	14.7
10	82	37	4	26.71	26.72
Mean	82.2	22.1	19.0	22.5	22.3

6.4 Discussion

This study has described a relationship between the maximum rectal diameter and the displacement of the prostate during a radiotherapy treatment fraction. We observed that a rectum diameter of 3.5 cm or less appears to result in prostate displacement of 4 mm or less. The ability to predict prostate motion based on rectal diameter may allow for an adaptive margin to be applied for all treatment fractions where the pre-treatment CBCT anatomy may predict that prostate motion will be small, however, a larger study is needed to confirm this. Our modeling indicates that there may be a reduction in the volume of organs at risk treated when an adaptive margin is used. Further, an adaptive margin may allow dose escalation while maintaining the current treatment toxicity profiles.

Previous studies have outlined offline, hybrid and online protocols for adaptive prostate radiotherapy. The largest number of reports have used the offline methods[166-168]. Typically, these methods involve a series of repeat CTs or CBCTs being acquired early in the treatment course. An adapted plan is created based on the organ positions on the scans taken during the first four to six treatment fractions and used for the remaining fractions in the treatment course. The hybrid methods involve a combination of offline adaptive re-planning with a grouping according to subpopulation of small, medium or large prostate motion, or offline re-planning with online image guidance[170, 171]. None of these methods offer an adaptive margin from the first fraction which is a key point of difference from our approach.

Online methods involve aperture modification for CRT, segment modification for IMRT using MLC, or online inverse planning[172-176]. The online methods described allow for modification of the dosimetry based on deformations and rotations of the prostate at the time of pre-treatment imaging. These methods do not alter the treatment margin on a fraction to fraction basis, using a standard PTV margin to account for intrafraction motion. Our data highlights the importance of intrafraction prostate motion in setting PTV margins and the impact of rectal filling on the margin

required. This is supported by Cine-MRI data which has shown that patients with a full rectum have a 10% probability of >3 mm of motion in ~1 min[144]. Additionally, data from 184 patients has shown that around 25% of fractions will have a displacement of ≥3 mm if the fraction time is >9 min[164], which is expected for online adaptive methods where re-optimization is used[175]. This suggests that the 2 mm uniform PTV margin recommended by Ahunbay et al, for use in their adaptive methods may be inadequate[173]. In contrast, the 5 mm margin used by Li et al, in their modeling study is more likely to be adequate[174]. This is further supported by a study which demonstrated that margin reductions below 5 mm is associated with increased risk of biochemical failure in the image-guided radiotherapy setting[205]. Our study used a 6 mm adaptive margin which accounted for 4 mm intrafraction displacement of the prostate and 2 mm to account for rotations and deformations. We used a 2 mm expansion for prostate rotation and deformation based on the data from Olsen et al, who demonstrated that expanding their 3 mm margin to 5 mm provided adequate prostate coverage for all sample patients when using Calypso with an online correction protocol of 3 mm[201]. The 6 mm margin should safely account for posterior prostate motion which has been shown to be critical to increased risk of biochemical failure, particularly in the case of rectal distension at planning[205, 206].

While this study suggests an average dose escalation of 4.2 Gy may occur while maintaining the existing toxicity profile, we would not aim to extend the fractionated treatment. Potential approaches for dose escalation would be hypofractionated treatment or dose adaptive treatments where an escalated dose per fraction would be treated at fractions where margin reduction was permitted.

The fraction time for online adaptive prostate radiotherapy would be similar to that required for online adaptive radiotherapy to the bladder where CBCT acquisition, decision making, plan scheduling and treatment delivery is required. Online adaptive bladder radiotherapy required

around 10.7 minutes for CBCT acquisition and decision making during a pilot study[207], which is similar to the fraction time of around 11 minutes seen in the present study. Subsequent to that pilot study the fraction time for 50 online adaptive bladder patients was 13.9 minutes when beam delivery and a post-treatment CBCT QA scan was included, indicating a learning curve in decision making time after the pilot[208]. We estimate a fraction time of 15 minutes for the prostate adaptive method we have described when IMRT is used. Shorter times may be achieved for modulated arc therapy delivery and when newer record and verify processes for adaptive therapy become available.

A limitation of this study is that it relates post-treatment CBCT rectal diameter measurements to intrafraction displacement, which does not follow the workflow required for online adaptive prostate radiotherapy. The intrafraction displacement in this study is also only taken from two time points, which may not represent the full excursion of the prostate during treatment. The authors are currently investigating a larger sample of patients using pre-treatment CBCT and more comprehensive intrafraction prostate motion data to confirm the relationship seen in this study. We will also investigate the effect of bowel gas on predicting prostate motion as gas has been shown to impact on prostate motion[140, 144]. Another possible limitation is that we purposely used 3DCRT for the planning study. While many centres would use IMRT, a 3DCRT solution provides more consistency between plans and eliminates the potential impact of the optimizer settings. Further studies will also be required to quantify the ability and consistency of radiation therapists measuring the maximum rectal diameter on CBCT.

6.5 Conclusions

Our study proposes a method of daily adaptive prostate radiotherapy by describing a relationship between the prostate motion and the diameter of the rectum on CBCT. This method can implement an adaptive margin from the first fraction. Our sample demonstrated a uniform PTV margin of around 6 mm would be required to account for intrafraction prostate motion in an adaptive protocol. Further study is required to confirm the relationship between maximum rectal diameter on pre-treatment CBCT and prostate motion for use in an adaptive protocol.

Chapter 7 Real time image-guided adaptive-predictive prostate radiotherapy using rectal diameter as a predictor of motion.

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Clinical Oncology, 2017, 29 (3) pp180-187

Our study in **chapter 6** has demonstrated a relationship between MRD and intrafraction displacement of the prostate which may be suitable for use in the proposed adaptive method. However, the study measured the MRD on post-treatment CBCT, so captured the endpoint of rectal changes that may take place during the treatment fraction. During a fraction it is expected that the rectal filling may change due to movements of gas and faeces, but patients with a full rectum may also experience peristaltic motion. We needed to determine if the relationship held when MRD was measured on pre-treatment CBCT. In **chapter 7** we were able to utilise a larger dataset that had pre-treatment CBCT and intrafraction prostate displacement information to test this relationship. We also investigated the impact of CBCT image quality on the adaptive method and the potential impact of the adaptive method on normal tissue toxicity.

Abstract

Aims: To investigate a relationship between maximum rectal diameter (MRD) on pre-treatment cone-beam computed tomography (CBCT) and intrafraction prostate motion, in the context of an adaptive image-guided radiotherapy (IGRT) method.

Materials and Methods: The MRD was measured on 2125 CBCTs from 55 retrospective patient datasets and related to prostate displacement from intrafraction imaging. A linear regression model was developed to determine a threshold MRD associated with a high probability of small prostate displacement. Standard and reduced adaptive margin plans were created to compare rectum and bladder normal tissue complication probability (NTCP) with each method.

Results: Per-protocol analysis performed on 1910 fractions from 51 patients demonstrated with 90% confidence that for a MRD of ≤3 cm prostate displacement will be ≤5 mm, and that, for a MRD of ≤3.5 cm prostate displacement will be ≤5.5 mm. In the first scenario, if adaptive therapy was used instead of standard therapy, median reductions of NTCP for rectum and bladder were 0.5% (from 9.5% to 9%), and 1.3% (from 6.6% to 5.3%) respectively. In the second scenario, the NTCP for rectum and bladder would have median reductions of 1.1%, and 2.6% respectively.

Conclusions: We have identified a potential method for adaptive prostate IGRT based upon predicting small prostate intrafraction motion by measuring MRD on pre-treatment CBCT.

7.1 Introduction

Radiotherapy dose escalation for prostate cancer offers improved biochemical control, but may also lead to increasing toxicity which is concerning for patients with long-term survival prospects[209]. Prostate cancer radiotherapy clinical target volumes (CTV) most commonly include the prostate with or without the seminal vesicles. The rectum, bladder and penile bulb are organs at risk (OAR) in immediate proximity to the prostate and are partially included in the planning target volume (PTV). Minimising PTV margins where possible would reduce the risk of toxicity and potentially allow safe dose escalation.

Historic interfraction and intrafraction prostate motion data are commonly used to calculate PTV margins. These data take into account random treatment errors for all treatment fractions, many of which will not be present for each fraction. Two key components of prostate intrafraction motion are the filling of the rectum and the duration of the treatment. Cine-MRI has shown that patients who present with an empty rectum may be at much lower risk of intrafraction prostate motion compared to patients who present with a full rectum[140, 144]. Several studies have also demonstrated that the longer the fraction duration, the greater the risk of prostate motion[144, 164, 210].

To reduce the effect of random errors during prostate radiotherapy, intrafraction monitoring such as radiofrequency transponders, stereoscopic KV systems and intrafraction monitoring with on-board imaging may allow reductions of margins down to 5mm or less[193, 211, 212]. Greatly reducing treatment times with VMAT and flattening filter free modes may also reduce the probability of intrafraction motion[210]. For those without access to new technologies, alternative methods to reduce margins could be investigated.

Our data has demonstrated intrafraction motion of greater than 5mm in only 4.7% of fractions[164], so identifying fractions with reduced motion is one possibility. Adaptive radiotherapy offers methods to reduce PTV margins when conditions are appropriate. Previous studies have outlined offline[166-168], hybrid[170, 171] and online protocols[172-175, 213] for adaptive prostate radiotherapy. None of these have predicted daily prostate motion based on cone-beam CT (CBCT) rectal presentation.

This study investigated the relationship between rectal diameter on pre-treatment CBCT as a predictor of small intrafraction prostate motion, which could be used in an adaptive image-guided radiotherapy (IGRT) protocol. We also investigated other predictors of prostate motion such as the presence of bowel gas within treatment fields or superior to the treated volume at CBCT. We assessed the image quality of CBCT and its impact on the adaptive method.

7.2 Methods

7.2.1 Dataset selection

This study used retrospective datasets from 55 consecutive patients treated at the Townsville Cancer Centre between July 2011 to August 2012 with daily CBCT imaging prior to treatment and megavoltage electronic portal images (EPI) acquired during treatment delivery, which allowed analysis of intrafraction prostate motion. We received ethics approval from the Townsville Hospital and Health Service Human Research Ethics Committee and the Peter MacCallum Cancer Centre Ethics Committee. Eligible patients were 50 years of age or older, who received prostate 3D conformal radiotherapy (3DCRT) to a dose of 74-78 Gy in 37-39 fractions. All had biopsy proven prostate adenocarcinoma TNM stages T1-T3b, three prostate gold seed fiducial marker (FM) implants and were ECOG performance status 0-2. All patients were treated supine on Elekta XVI linacs (Elekta, Stockholm, Sweden), with CIVCO kneefix and feetfix (CIVCO Medical Solutions, Coralville, USA) indexed to the treatment couch.

7.2.2 **CBCT assessment**

All CBCTs were assessed by one observer (RO). Planning CTs were performed with 2mm slices and CBCTs were reconstructed with 2mm slices. CBCT data were fused with the planning data on FOCAL v4.62 (Elekta, Stockholm, Sweden) at a corrected position for the FMs. Each CBCT rectum was contoured on the planning CT for the length of the rectum planning contour. Maximum rectal diameter (MRD) was measured according to methods outlined previously (Oates et al., 2015). Presence of rectal gas within the treatment fields and superior to the treated volume were contoured, the number of bubbles and volumes were recorded. We considered there to be no gas for volumes less than $1cm^3$.

7.2.3 **Image quality**

To assess the usability of CBCT images, image quality was subjectively graded by one observer (RO) as Optimal, Adequate or Inadequate. Scans were considered Optimal if there was minimal artefact and structures were easily identifiable, Adequate if there was mild-moderate artefact and structures were sufficiently identifiable to achieve study aims, and Inadequate when severe artefact precluded rapid structure identification.

7.2.4 **Motion assessment**

Each fraction consisted of five treatment fields – left, left anterior-oblique, anterior, right anterior-oblique and right. EPIs were recorded at six time points during left and right field delivery and three time points during the shorter duration anterior field. Pre-treatment daily matches were performed by a variety of clinical radiation therapists. All 2D image matches were performed by one investigator (AB). Images from each field provided 2D displacements relative to the pre-treatment CBCT FM alignment in two directions: Lateral fields provided AP and SI displacements while the anterior field provided SI and LR displacements. We combined the prostate displacements measured

in various directions and at various time points during a treatment fraction into a single overall measure of prostate displacement per fraction.

To do this, we denoted the measured prostate displacement at a given time point t (within a given fraction and patient) in the AP, SI and LR directions as $d_{\mathrm{AP},t}$, $d_{\mathrm{SI},t}$ and $d_{\mathrm{LR},t}$ respectively. For each time point we then calculated the 2D prostate displacement d_t by adding the two available one-dimensional displacements in quadrature as follows.

For the left and right fields: $d_t = \sqrt{d_{\mathrm{AP},t}^2 + d_{\mathrm{SI},t}^2}$

For the anterior field: $d_t = \sqrt{d_{\mathrm{LR},t}^2 + d_{\mathrm{SI},t}^2}$

We calculated the mean d_t over the available time points for each field, and took the largest of the three resulting means as the maximum projection-detectable prostate displacement for the given fraction.

7.2.5 Normal tissue complication probability (NTCP) assessment

Each patient had a standard plan created on Eclipse 13.5 (Varian, Palo Alto, USA) using a standard margin of 10 mm PTV margin in all directions, except 6 mm posteriorly around the prostate only. An adaptive plan was created with a uniform 6 mm PTV margin around the prostate only. OAR contouring and planning objectives have been outlined previously[214]. For the standard plans, rectum dose volume histogram (DVH) data from each treatment fraction was exported in 0.1 cc bins and an average rectal DVH used for NTCP calculation. For the adaptive margin assessment, rectal DVH data were exported and an average adaptive rectal DVH was generated using the proportion of adaptive and standard fractions from the patient's treatment course, if an adaptive method had been used. The Lyman-Kutcher-Burman model was used to assess the rectum risk of Grade ≥2

toxicity with model parameters n=0.09, m=0.13 and TD50=76.9 per QUANTEC recommendations (Michalski et al., 2010). We also calculated the mean DVH V50, V60 and V70 dose delivered to the rectum to compare the scenario for if a conventional plan or an adaptive plan were delivered.

Bladder NTCP assessment only used planning bladder volumes for calculation as the CBCT scan length regularly did not include the whole bladder. NTCP was calculated for standard and adaptive plans as described above. The Lyman-Kutcher-Burman model was used to assess the bladder risk of Grade ≥1 toxicity within two years with model parameters n=0.00995, m=0.022 and TD50=77.6[215].

7.2.6 Fraction duration assessment

The CBCT acquisition and reconstruction time was manually timed using a stopwatch by one observer (AB) over three fractions in a total of 10 consecutive patients. Timing began at CBCT commencement and stopped at the RT accepting the reconstruction for viewing. The remaining fraction duration, including image matching was taken from time stamps recorded in MOSAIQ (Elekta, Stockholm, Sweden) for all patients.

7.2.7 Statistical methods

Descriptive statistics were used to summarise patient and treatment characteristics. A linear regression model was created using MRD for any fraction as a predictor of log prostate displacement. Log prostate displacement was used instead of raw prostate displacement as it yielded superior goodness of fit. Predicted log prostate displacements were then back transformed to provide predicted raw prostate displacements. We defined a critical threshold for maximum projection-detectable prostate displacement within our adaptive PTV margin, below which we considered adaptive RT to be beneficial. The regression model was then used to predict the maximum allowable MRD such that the probability of prostate displacement being below this critical threshold was over 90%. Each maximum rectal diameter and prostate displacement was considered

independent of all others – i.e. no patient effect, which would observe trends within patients, was allowed for.

The effect of gas was evaluated by considering the following three gas related parameters for inclusion in the linear regression model.

- the number of gas bubbles
- the total volume of the gas bubbles
- presence of gas superior to the contoured rectum

The effect of change in MRD from the planning MRD was evaluated in the linear regression model.

Descriptive statistics were used to report the median reduction in NTCP. Frequency analysis was carried out for image quality scores. Statistics were performed using R software v2.15.1 (www.r-project.org/).

7.3 Results

7.3.1 Data exceptions

Of 55 patients included in this study, 45 received 39 treatment fractions, five received 38, and the remaining five received 37 fractions. Four patients had a misplaced FM (i.e. placed outside the prostate capsule) which appeared to affect the intrafraction motion assessment and were excluded in a per-protocol analysis. In these datasets, we compared intermarker distances on the planning scan to locations on the treatment scans by measuring the centroid of each FM. These four datasets showed high intermarker displacements from their planned locations as the misplaced FM moved independently of the prostate. The ranges of motion of the misplaced FM compared to other FMs were 8 mm, 6.3 mm, 10 mm and 5 mm.

7.3.2 CBCT assessment

Of 2130 treatment fractions, 2125 CBCTs were available for assessment. Three scans failed to capture and two scans were only partially captured. The median MRD was 3.3 cm (range 2.2 to 6.6 cm) for both the intention to treat (ITT) and per-protocol analysis (Figure 7-1 & Figure 7-2).

7.3.3 Image quality assessment

No CBCTs were deemed to be of optimal quality. Adequate images were obtained in 1844 (86.8%) fractions, while 281 (13.2%) fractions had inadequate images due to severe artefact.

7.3.4 Motion assessment

The average number of fractions per patient available for motion analysis was 37.5 once missing data due to EPI failure were accounted for, with a total of 2061 patient fractions. For per-protocol analysis, the mean number of fractions per patient was 37.5, but with 1910 patient fractions.

The direction of per-protocol maximum displacement can be found in Table 7-1. For per-protocol analysis, of the 231 displacements greater than 5 mm, the left, anterior and right beams had 73 (31.6%), 12 (5.2%) and 146 (63.2%) respectively. Of the 174 displacements greater than 5.5 mm, the left, anterior and right beams had 57 (32.8%), 3 (1.7%) and 114 (65.5%) respectively. These data suggest that the maximum displacement most commonly occurred during the last beam. The direction of maximum displacement greater than 5 mm and 5.5 mm can be found in Table 7-2. These data indicate that the SI plane followed by the AP plane are the most common over the thresholds, however the AP plane motion is not recorded during all beams.

Table 7-1. Direction of maximum projection-detectable prostate intrafraction displacement direction for 1910 fractions from 51 prostate radiotherapy patients.

Maximum 2D Displacement Direction	Count (n)	Maximum Planar Displacement	Count (n)
AS	147	A	76
		S	71
AI	763	A	350
		I	413
PS	268	P	123
		S	145
PI	281	P	92
		I	189
LS	19	L	17
		S	2
LI	259	L	74
		I	185
RS	19	R	14
		S	5
RI	154	R	33
		I	121

Note: AS = anterior-superior, AI = anterior-inferior, PS = posterior-superior, PI = posterior-inferior, LS = left-superior, LI = left-inferior, RS = right-superior and RI = right-inferior. A = anterior, P = posterior, S = superior, I = inferior, L = left and R = right.

Table 7-2. The direction of maximum projection-detectable intrafraction displacement of the prostate greater than 5 mm and 5.5 mm for 1910 fractions.

Displacements > 5mm		Displacements > 5.5mm	
Direction	**n (%)**	**Direction**	**n (%)**
Anterior	37 (16)	Anterior	27 (16)
Posterior	40 (17)	Posterior	38 (22)
Superior	63 (27)	Superior	48 (28)
Inferior	86 (37)	Inferior	60 (34)
Left	3 (1)	Left	0 (0)
Right	2 (1)	Right	1 (1)
Total	231 (100)	**Total**	174 (100)

Note: Percentages do not sum to 100 due to rounding.

Histograms of MRD and prostate displacement, as well as the scatterplot of MRD against prostate displacement are shown in Figure 7-1 (ITT analysis) and Figure 7-2 (per-protocol analysis). Figure 7-2 demonstrates that a MRD of 3 cm gives 90% confidence of prostate displacement of approximately ≤5 mm, and a MRD of 3.5 cm allows 90% confidence of approximately ≤5.5 mm prostate displacement.

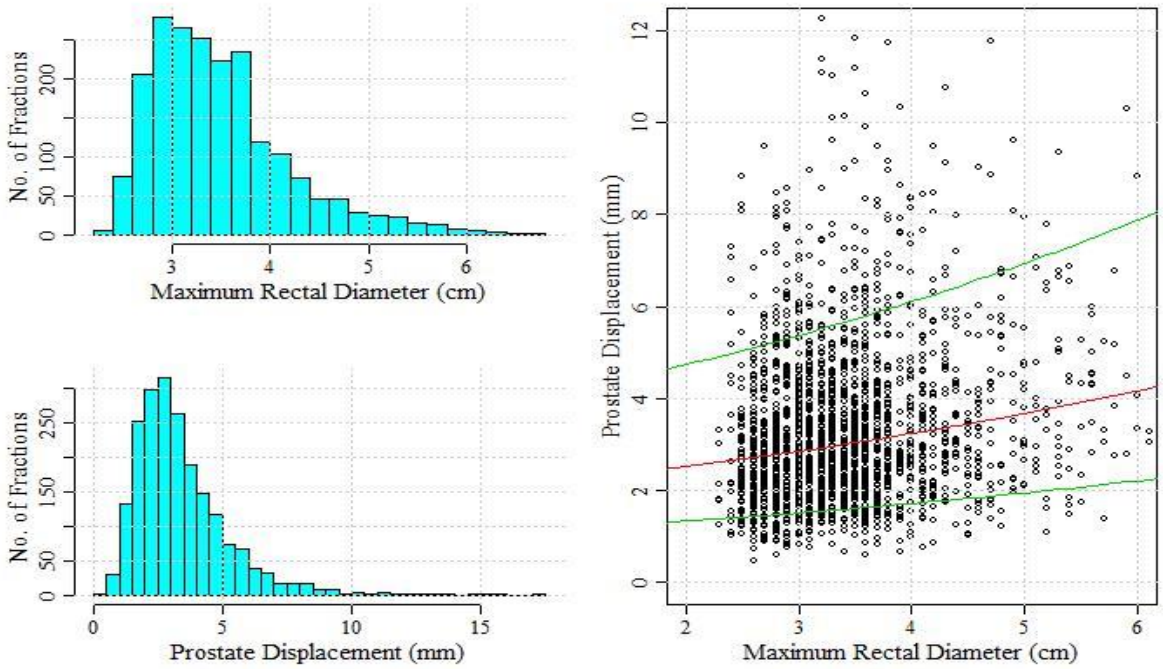

Figure 7-1. Histograms and scatterplot of maximum rectal diameter and maximum projection-detectable prostate displacement for ITT analysis. The scatterplot is overlaid with the linear regression line of best fit, and lines representing the boundaries of the 80% confidence interval. The upper boundary of the 80% confidence interval (upper green line) thus represents the 90th percentile of prostate displacement for a given MRD.

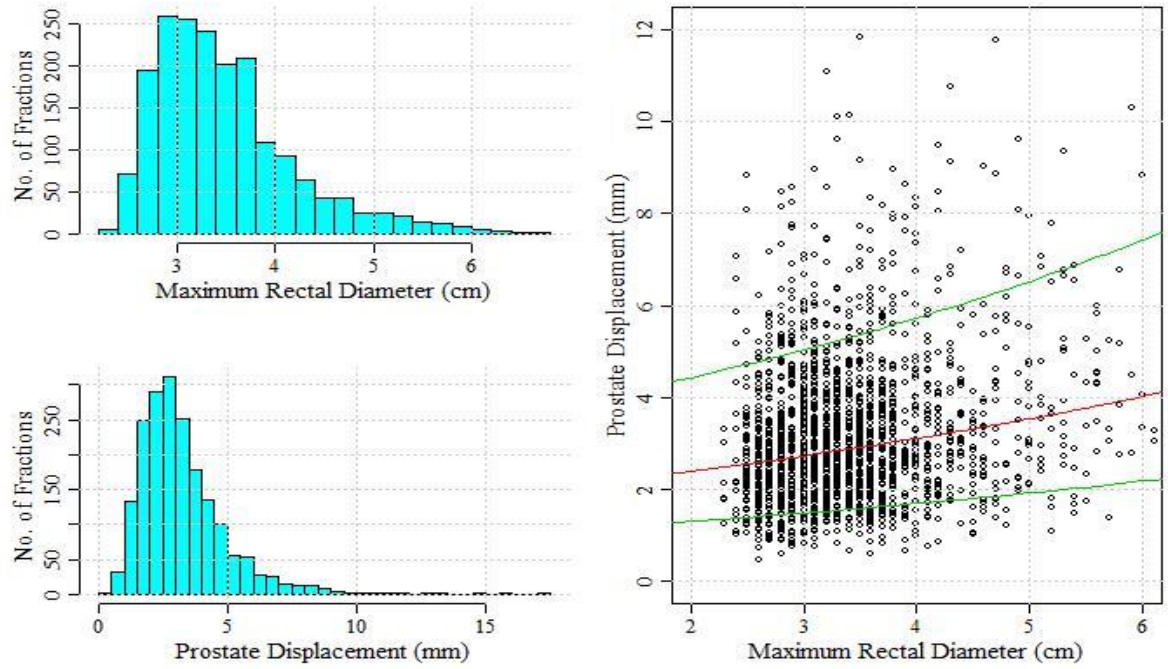

Figure 7-2. Histograms and scatterplot of maximum rectal diameter and maximum projection-detectable prostate displacement for per-protocol analysis. The scatterplot is overlaid with the linear regression line of best fit, and lines representing the boundaries of the 80% confidence interval. The upper boundary of the 80% confidence interval (upper green line) thus represents the 90th percentile of prostate displacement for a given MRD.

When modeling the relationship between MRD and prostate displacement, the inclusion of gas related parameters (the volume of gas, or the number of gas bubbles present in the contoured rectum, and gas bubbles superior to the contoured rectum) as confounders in the per-protocol regression model added no significant precision (p=0.14 for number of gas bubbles).

The median (range) MRD at planning was 3.3 cm (2.5 - 4.7 cm), with 40 patients having a MRD of 3 cm or above and 13 patients having a MRD of 3.5cm or above. The change in planning MRD and treatment MRD had a very weak relationship with prostate displacement (see Figure 7-3).

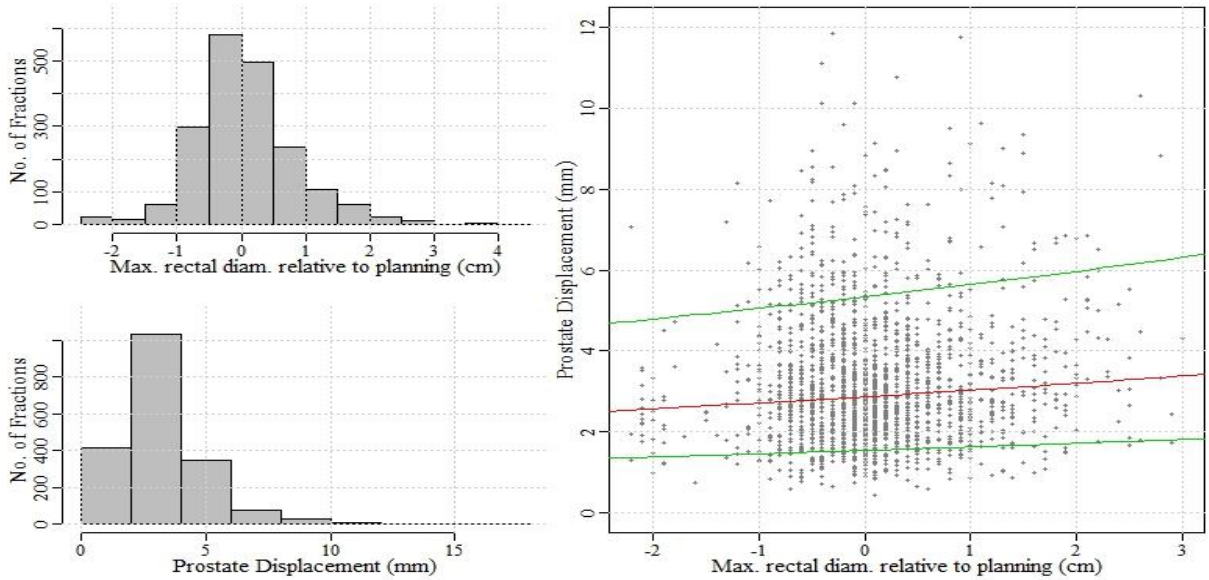

Figure 7-3. Scatterplot of the change in maximum rectal diameter from planning to treatment vs prostate displacement for per-protocol analysis. The scatterplot is overlaid with the linear regression line of best fit, and lines representing the boundaries of the 80% confidence interval. The upper boundary of the 80% confidence interval (upper green line) thus represents the 90th percentile of prostate displacement for a given MRD.

7.3.5 **NTCP assessment**

To assess possible toxicity benefit associated with using an adaptive plan (with a smaller, 6mm isotropic PTV expansion), NTCP was calculated for the standard plan and compared with the NTCP for hypothetical treatments where the adaptive plan would be delivered if the MRD was ≤3 cm and ≤3.5 cm, corresponding to probable displacements of ≤5 mm and ≤5.5 mm respectively. NTCP assessment was performed with ITT.

If an adaptive margin was applied when the MRD was ≤3 cm, the median decrease in rectum NTCP was 0.5% (95% CI 0.2-0.7%), from 9.5% for standard plans to 9% for adaptive plans. For bladder, the median decrease was 1.3% (95% CI 0.9-1.7%), from 6.6% for standard plans to 5.3% for adaptive plans. If the standard plan was delivered the rectum V50, V60 and V70 were 32.1%, 27.0% and 19.4% respectively, these dropped to 31.0%, 26.0% and 18.5% respectively if the adaptive plan was

delivered. The median (range) number of fractions where an adaptive margin was applied was 11 (range, 0-34) in a 37-39 fraction course. In this scenario, 45 patients would have the adaptive plan delivered for at least one fraction and 32 patients would have ≥10 adaptive fractions.

If a 3.5 cm MRD threshold were to be used, the reduction in NTCP was greater because the adaptive plan could be used more frequently; the median (range) number of fractions where an adaptive margin could be applied was 26 (range, 3-37) in a 37-39 fraction course. The median decrease in rectum NTCP was 1.1% (95% CI 0.8-1.2%), from 9.5% for standard plans to 8.4% for adaptive plans. For bladder the median NTCP decrease was 2.6% (95% CI 1.9-3.4%), from 6.6% for standard plans to 4% for adaptive plans. If the standard plan was delivered the rectum V50, V60 and V70 were 32.1%, 27.0% and 19.4% respectively, these dropped to 30.1%, 25.1% and 17.7% respectively if the adaptive plan was delivered. In this scenario, all patients would have the adaptive plan delivered for at least one fraction and 50 patients would have ≥10 adaptive fractions.

7.3.6 **Fraction duration assessment**

The CBCT acquisition took a median of 1 min 25 s (range: 1 min 22 s to 1 min 32 s). The median treatment duration was 3 min 53 s (range 2 min 53 s to 8 min 08 s). Overall, the median time from commencement of pre-treatment imaging to completion of 3DCRT was 5 min 18 s.

7.4 Discussion

This study used MRD and intrafraction prostate displacement data from 1910 treatment fractions (per-protocol analysis) to demonstrate a potential adaptive-predictive IGRT technique for prostate radiotherapy based upon pre-treatment CBCT MRD. MRD appears to be a fast, assessable and reliable metric for predicting a high probability of minimal intrafraction prostate displacement. Combining this with selective use of an adaptive plan with smaller PTV expansion allows for small reductions in rectum NTCP and substantial reductions for bladder NTCP.

Previous studies have outlined offline, hybrid and online protocols for adaptive prostate radiotherapy. Most experience with these protocols lies with the offline methods[166-168]. Typically these methods involve acquiring a series of repeat CTs or CBCTs to create an adaptive plan based on the organ positions within these datasets, which is then used for remaining treatment fractions. These methods have been demonstrated to reduce biochemical failure[169]. The hybrid methods involve a combination of offline adaptive re-planning with a grouping according to subpopulations of small, medium or large prostate motion, or offline re-planning with online image guidance[170, 171]. No previously identified adaptive methods have taken advantage of the possibility of predicting prostate intrafraction motion based on the appearance of the rectum, which could be implemented from the first fraction. This immediate accessibility would be advantageous, particularly considering the trend towards hypofractionation as a treatment approach[209].

Online methods involve aperture modification for 3DCRT, segment modification for IMRT, or online inverse planning[172-176]. The online methods described allow for dosimetry modification based on prostate deformations and rotations at the time of pre-treatment imaging. These methods do not alter the treatment margin on a fraction-to-fraction basis, using a standard PTV margin to account for intrafraction motion. Another online method uses MLC tracking software during VMAT delivery to account for prostate motion recorded by Calypso, but does not use image-guidance to assess organ deformation[213]. These methods are extremely promising for future prostate radiotherapy but are not currently commercially available, they are likely to be costly and/or require costly add-ons such as Calypso. Our method uses existing technologies which are widely available.

Per-protocol analysis was performed as four patients were noted to have poor FM placement, where these patients frequently showed relatively large intrafraction motion despite having small MRDs. 'Best fit' CBCT FM match for these four patients would yield inconsistent alignments amongst many

observers. CBCT matching tools can only view each FM individually in multiple planes, or multiple FMs can be viewed in individual planes. If FMs deviate from their expected position, this can make a 'best fit' match difficult to achieve due to the inability to visualise each FM relative to the others and to their planned location. This uncertainty in initial matching could account for apparent large intrafraction shifts on the planar matching. We recommend that good FM placement be a requirement before applying this adaptive method in a clinical pilot study.

Another patient appeared to have large intrafraction motion despite mostly having small MRDs. This patient had excellent FM placement, but his prostate was rotated substantially for nearly all fractions relative to the planning scan, making CBCT FM match difficult and highlighting the challenge of CBCT matching. His true intrafraction prostate displacement may be smaller than we recorded. Ideally, for CBCT FM matching in a 3D space, tools need to be developed which allow multiplanar viewing of each FM; or need to occur in a 3D reconstruction using automatic FM segmentation and planning FM contours.

Originally, we intended to use the adaptive plan for fractions where the MRD was low enough to allow 90% confidence for prostate displacement of ≤4 mm, as per our previous study[214]. Figure 7-2, however, demonstrates that this never occurs. Our previous study approximated mean prostate displacement, whereas the current study calculated maximum projection-detectable prostate displacement. Calypso studies are the current gold standard for monitoring intrafraction prostate motion and have indicated mean displacements of <2.5 mm for 95% of fractions with intrafraction repositioning[213] and displacements of >3 mm and >5 mm of approximately 14% and 3% of the fraction time respectively[163]. Our maximum projection-detectable displacement appears high compared to mean displacement Calypso data, but demonstrates more closely the worst case scenario. It was therefore reasonable to relax the prostate displacement constraints for our adaptive method to 5 mm and 5.5 mm instead. It is possible that we observed greater intrafraction

displacements due to the use of different imaging methods for prostate localisation pre-treatment and during treatment. Many observers matching the pre-treatment CBCTs and 2mm slice thickness may have contributed to the mismatch[216]. We recommend repeating this study using pre-treatment CBCT and Calypso data or a similar method to determine prostate displacement with greater fidelity and to reconstruct the dose delivered to the target. We also recognise that seminal vesicle displacement will be greater[135] and require a separate study to determine appropriate adaptive margins.

We found that image quality would make rapid assessment difficult in approximately 13% of fractions. The rectum was identified through laborious contouring which assisted rectum measurement (with some margin of error). However, most poor image quality CBCTs were due to large pockets of moving gas or faeces, in which case standard margins would be applied. Our CBCT protocol utilised a half-rotation for efficiency, while allowing adequate definition of FMs for matching. In an adaptive setting, full-rotation scans may allow for clearer rectum definition. In the per-protocol analysis we did not find any significant relationship in the regression model with gas in the rectum or gas superior to the contoured rectum, which was surprising. Potentially, most events where large bubbles of gas were in the rectum and/or gas was superior to the contoured rectum were also represented by above-threshold MRD.

Our planning study purposefully used 3DCRT instead of IMRT to provide more consistency between plans, eliminating potential impacts of optimiser settings. IMRT or volumetric modulated arc therapy (VMAT) are likely to provide even more promising results for reducing NTCP in the adaptive setting compared to 3DCRT, where dose and hotspots could be pushed off OARs.

While limited NTCP data is available for the bladder, values derived by Cheung et al, most closely represent toxicities observed in our clinic[215]. With IMRT and VMAT, rectal toxicities are becoming

less burdensome and urinary toxicity is increasingly becoming the major patient concern[57, 98]. Unfortunately, due to CBCT scan length, bladder NTCP from all fractions was not feasible in this study. Also, with our rectum DVH averaging, the rectum NTCP calculation is a conservative estimate of dose received to parts of the rectum. Deformable registration would be required to precisely assess these doses.

Due to the relationship between margin generation and prostate shape[214] not all patients derive benefit for rectum toxicity with an adaptive margin. If minimal rectum and bladder sparing was achieved with an adaptive plan, we could exclude those patients from the adaptive method to avoid daily CBCT dose. Patients with thickened rectal walls are a confounding factor, comprising many data points in the bottom right of the scatterplots in Figure 7-1 and 7-2. Rectal wall thickness assessment with MRI and individualised MRD thresholds could be determined with further research. Other fractions which do not fit the model occur during the presence of faeces and/or gas in the rectum, causing a large MRD, but no corresponding prostate motion. We would recommend against margin reduction at those fractions due to the risk of prostate deformation[144, 194]. To allow patients to present with an empty rectum more often, the authors would recommend further development of diet interventions in adequately powered trials[195, 217]. We would recommend obtaining the adaptive MRD at planning CT and good bladder baseline[218] to closely represent the adaptive treatment scenario, which should minimise prostate rotation and deformation effects. Further studies will also be required to quantify the ability and reliability of radiation therapists measuring the MRD on CBCT.

7.5 Conclusions

Our study has demonstrated a potential method for adaptive-predictive prostate IGRT, predicting small prostate intrafraction motion by measuring MRD on pre-treatment CBCT. Further research is required to demonstrate the precise relationship between MRD and prostate motion for safe clinical implementation and to explore individualised approaches such as individualised MRDs. This method utilises existing technologies and, with further understanding of the dosimetric impacts of the method, it may be advantageous in the hypofractionation setting.

Chapter 8 Discussion

Modern EBRT with image guidance and intensity-modulated beams offers excellent treatment outcomes, but there is potential for further improvement. Improving prostate EBRT is critical for patients who have good prospects of long-term survival. In the absence of clear evidence of one treatment approach over another, EBRT is an appropriate treatment option to offer adequately informed prostate cancer patients of any risk group, but particularly for intermediate- to high-risk patients. The large number of patients diagnosed with prostate cancer each year, and those surviving prostate cancer, highlights the need to continually improve treatment methods for this disease. For prostate EBRT, the reduction of PTV margins is one way to improve treatment outcomes for these patients.

The toxicity of prostate EBRT treatment not only determines how high the treatment dose can be delivered, but also the patient's quality of life during treatment and after treatment completion. So while the reported rates of toxicities are quite low[58, 98, 115, 123, 124], for patients who do experience toxicity there can be an enduring impact on their quality of life. A large proportion of patients will experience some form of GI and/or GU toxicity during treatment, and then late toxicities will peak between 1-3 years after treatment[219, 220]. It has been reported that for patients who experience late Grade ≥2 GI and GU toxicities, the median time from onset to final resolution of the toxicity is 3.4 and 3.0 years, respectively[219]. Therefore, further reducing the number and severity of toxicities of prostate EBRT treatment will be of benefit to a substantial number of patients who will be treated in future. The reduction of PTV margins will improve the therapeutic ratio, potentially allowing for lower rates of treatment toxicity and/or dose escalation. This in turn should offer improved quality of life and treatment survival outcomes.

This thesis is concerned with potential methods to safely reduce PTV margins in prostate radiotherapy. It presents two methods of margin reduction as well as an assessment of the effectiveness of current margins and how we can look to individualise our EBRT treatment approaches. There is a logical progression to the development of both methods and how the chapters contribute to a sound basis for conducting further research in this area. The diet intervention and adaptive methods proposed in this thesis are connected by the theory that both methods would be synergistic in their implementation. This discussion will first detail the changing landscape of prostate radiotherapy. Then, each chapter will be discussed in turn, relating how the information from this thesis relates to the diverse approaches currently available for prostate radiotherapy.

8.1 Prostate EBRT, many approaches for one disease

Since commencing this thesis, there has been increasing diversity in the approaches to prostate radiotherapy and less consensus around the best way to deliver treatment. Many of these changes have been driven by new technologies or the development of new devices. Because these approaches are so new, many are yet to demonstrate effectiveness in terms of improvements in disease control or quality of life. The key changes have been developments in the way treatments are fractionated, intrafraction monitoring of the prostate and devices to reduce rectal dose. The latter two of these are directly linked to the objective of the thesis, in that they aim to reduce OAR toxicity and potentially allow dose escalation.

8.1.1 Hypofractionated prostate EBRT

The alpha/beta ratio for prostate cancer is believed to be low, much lower than the surrounding critical organs at risk. This indicates a therapeutic advantage if larger fractions are used. The actual alpha/beta ratio is unknown, but most published data indicate it is below 2 Gy[209, 221]. The alpha/beta ratio for surrounding late responding tissues, for example the rectum, is believed to be 4-

6Gy[209]. This has formed the basis for many investigations into hypofractionated EBRT for prostate cancer, where a lower total dose is delivered in fewer fractions. There are two approaches to hypofractionation, moderate hypofractionation aims to deliver doses of 2.5-3.4Gy per fraction, while extreme hypofractionation delivers doses of 6-8Gy per fraction. The latter is commonly known as stereotactic ablative radiotherapy (SABR) or stereotactic body radiotherapy.

8.1.1.1 Moderate hypofractionation

Moderate hypofractionation represents a small change in practice from standard fractionation. Many early studies of moderate hypofractionation schedules have produced promising results[209]. The studies which compared iso-effective doses to modern dose-escalated schedules have produced the best outcomes and formed the basis for larger studies. Moderate hypofractionation has now been tested in four large phase III randomised studies which have all been reported recently[222-225].

The largest of those was the CHHiP study, a three-way non-inferiority randomised trial of 3216 patients[222]. Patients were randomised equally to a standard dose of 74Gy in 37 fractions, a hypofractionated dose of 60Gy in 20 fractions or a second hypofractionated dose of 57Gy in 19 fractions[222]. The CHHiP study included patients from low-, intermediate- and high-risk categories, with patients having intermediate- and high-risk disease eligible to receive ADT. The reported 5-year biochemical or clinical failure-free rates were 88.3% (95% CI 86.0–90.2) in the 74Gy group, 90.6% (88.5–92.3) in the 60Gy group, and 85.9% (83.4–88.0) in the 57Gy group. The 60Gy group was demonstrated to be non-inferior to the 74Gy group, HR 0.84 (90% CI 0.68–1.03), p=0.0018. The 57Gy group did not, however, demonstrate non-inferiority to the 74Gy group, HR 1.20 (90% CI 0.99–1.46) p=0.48, because the 90% CI exceeded the 1.208 threshold of the study design. In terms of toxicity, the acute GI toxicity was significantly higher in the hypofractionation arms, where RTOG grade ≥2 GI toxicity was 38% in both hypofractionated arms, and 25% in the 74Gy arm, p<0.0001. Acute GU toxicity was not significantly different between the arms, with RTOG grade ≥2 GU toxicity

being 46% in the 74Gy group, 49% in the 60Gy group and 46% in the 57Gy group. Late toxicities were not significantly different between the groups. The estimated 5 year cumulative incidence of RTOG grade ≥2 GI toxicity was 13.7% for the 74Gy group, 11.9% for the 60Gy group and 11.3% for the 57Gy group. RTOG Grade 2 or worse estimated cumulative incidence of bladder toxicity at 5 years were 9.1% for the 74Gy group, 11.7% for the 60Gy group, and 6.6% for the 57Gy group. The reported Grade 3 toxicities were very low in all groups. Therefore, the CHHiP study provides a sound basis for hypofractionation. However, longer follow up is required to determine if late toxicities follow the trend of conventional fractionation in the coming years.

The PROFIT study was another non-inferiority trial that compared a standard dose of 78Gy in 39 fractions to a hypofractionated dose of 60Gy in 20 fractions in 1206 intermediate-risk patients[223]. Non-inferiority was again demonstrated, where the 5 year biochemical-clinical failure event rate was 21% in both groups (HR 0.96, 90% CI: 0.80-1.15)[223]. The biochemical-clinical failure rate was higher in this study than in the CHHiP trial, however, this is perceived to be due to the lack of ADT in the PROFIT cohorts[221]. Acute gastrointestinal and genitourinary toxicity were similar between the two arms[223]. However, unlike the CHHiP study, late gastrointestinal toxicity significantly favoured the 60Gy arm. Potentially the lower rate of late toxicity for hypofractionation in the PROFIT study is due to the mandated use of IGRT and prevalence of IMRT, whereas the CHHiP study did not mandate either technology[222]. The PROFIT study reported late Grade ≥2 GI toxicity as 14% in the 78Gy arm compared to 9% in the 60Gy arm, p=0.006[221]. This study supports the findings of the CHHiP study that 60Gy in 20 fractions is non-inferior, with similar toxicity.

The RTOG 0415 trial was a non-inferiority study of 1092 low-risk prostate cancer patients comparing schedules of 73.8Gy in 41 fractions and 70Gy in 28 fractions[224]. Non-inferiority was demonstrated through the cumulative incidence of biochemical recurrence at 5 years and the estimated disease free survival at 5 years. The incidence of biochemical recurrence was 8.1% in the conventionally

fractionated group, compared with 6.3% in the hypofractionated group (hazard ratio 0.77). The estimated 5 year disease-free survival was 85.3% for conventional fractionation and 86.3% for hypofractionation (hazard ratio 0.85). Acute gastrointestinal and genitourinary toxicities were similar between the study arms. Late grade ≥2 gastrointestinal toxicities were higher in the hypofractionated arm at 22.4%, when compared to the conventional fractionation at 14.0%. Late grade ≥2 genitourinary adverse events were also higher in the hypofractionated arm, 29.7% versus 22.8% in the conventional fractionation. The authors of this study concluded that hypofractionation was non-inferior to conventional fractionation, but with greater risk of toxicity.

Lastly, the HYPRO trial was the only randomised study to investigate if a hypofractionated schedule was superior to conventional fractionation, but with equivalent side-effects[225]. The study aimed to detect a 10% improvement in 5 year relapse free survival with hypofractionation. The study assigned 804 patients with intermediate-risk and high-risk prostate cancer to receive either 78Gy in 39 daily fractions or 64Gy in 19 fractions at three fractions per week[225]. ADT was allowed in the study and similar rates of ADT use were reported between the two arms[226]. The incidence of 5 year biochemical/clinical failure-free survival was 81% in the hypofractionation arm and 77% in the conventional fractionation arm (hazard ratio 0.86; p=0.36)[225]. Acute GI toxicity was significantly higher in the hypofractionation arm with cumulative Grade ≥2 toxicity of 42%, compared with 31.2% in the conventional fractionated arm, p=0.0015[226]. Acute Grade ≥2 GU toxicity was similar with a cumulative incidence of 57.8% in the conventional fractionation arm and 60.5% in the hypofractionation arm, p=0.43[226]. By three months after radiotherapy there had been a rapid decrease in acute toxicities, both arms had grade ≥2 GI toxicity rates of 13% and grade ≥2 GU toxicity was 22% in the conventional fractionation arm, compared with 23% in the hypofractionation arm. The cumulative incidence of grade ≥2 GU toxicity at 3 years was 39% in the conventional fractionation group and 41.3% in the hypofractionation group[227]. While grade ≥2 GI toxicity cumulative incidence at 3 years was 17.7% in conventional fractionation and 21.9% in the

hypofractionation group. Overall, superiority of the hypofractionation arm in terms of biochemical control could not be demonstrated, and non-inferiority could not be confirmed for either acute or late toxicity in this study[227]. The outcomes of this study were, broadly, in line with the findings of the other studies.

These studies have demonstrated that high quality hypofractionated radiation therapy is safe and can reduce the number of treatment fractions patients need to attend. It has been suggested, with good reason, that hypofractionation delivered to 60Gy in 20 fractions should become the new standard of care[221]. The main advantages of moderate hypofractionation are the reduced number of treatment fractions and the small change in treatment approach to conventional treatment schedules. The disadvantages are few. There is a potential small increase in acute GI toxicity, and the late sequelae will be better understood with longer follow up. Hypofractionated schedules will become increasingly popular in the near future as doctors begin to prescribe these schedules and patients become more aware of the option of shorter duration treatment. Governments, healthcare insurers and providers are also likely to prefer these treatment schedules as they free up resources and cost less due to fewer fractions being required. The methods of margin reduction described in this thesis would both be suitable for moderate hypofractionation and have the potential to further improve toxicity when higher doses per fraction are used.

8.1.1.2 Extreme hypofractionation

An incremental advantage in biochemical control and side effects profile is expected from SABR treatments[209]. Many early phase studies into prostate SABR have been conducted with doses ranging from 32Gy in 4 fractions to 50Gy in 5 fractions[228]. The most common schedules are 35-36.25Gy in five fractions, and while most studies have used Cyberknife for treatment delivery, EBRT has also been safely implemented[209, 228]. Prostate SABR has also been implemented as two 10Gy EBRT boosts, analogous to HDR brachytherapy boosts[213]. The results from these early studies have

been promising. Studies reporting five year biochemical progression-free survival have indicated rates of 95-98%, 84-90.7% and 74.1-81% in low-, intermediate- and high-risk patients respectively. The toxicity results are also promising. The incidence of reported acute Grade 2 GI toxicity was 0–27%, with no Grade 3 or above toxicities reported[228]. The reported acute Grade 2 GU toxicity rates were 5–42% and only five of 921 patients in those early studies experienced Grade 3 acute GI toxicity[228]. Late grade 2 GI toxicities have been reported in 0–11% of patients and five of 1100 patients suffered GI toxicity of grade 3 or more[228]. Late grade 2 GU toxicities ranged from 0% to 29%. There were 14 of 1100 patients experience Grade 3 GU toxicity and no late Grade 4 GU toxicities have been indicated from these early studies[228]. Overall, the data from these studies indicate that the toxicity profile is acceptable for SABR, with good treatment outcomes in terms of biochemical control.

In terms of treatment planning and delivery, the jump to SABR from conventional fractionation is a big leap, particularly due to the small margins required for SABR and the sharp dose fall-off at the edge of the target volume. Typical CTV-PTV margins for prostate SABR are 3-5mm, but some studies have gone as low as 0-2mm[228]. The risk of geographical miss in SABR is high, where missing part of the tumour for one fraction could have a detrimental effect on tumour control. This requires a good departmental understanding of the impact of target delineation error, prostate deformation and rotation, and methods to account for intrafraction motion of the prostate. There also needs to be a good understanding of OAR motion and deformation, as movement of OARs into the high dose region could lead to debilitating side effects. These factors play a large role in the accurate treatment of prostate cancer regardless of fractionation, but are critically important for SABR. Every effort is required to ensure the prostate remains stable during SABR fractions. Therefore, the diet intervention described in this thesis may prove to be useful in reducing the risk of prostate motion due to rectal changes, particularly moving gas, during a treatment fraction.

At this stage prostate SABR is very much an experimental technique and should only be conducted as part of a research program. There are two large randomised trials that will give a greater understanding of the effectiveness and safety of prostate SABR in the future. They will also provide an evidence-based guideline for the safe implementation of prostate SABR to departments. The Swedish HYPO-RT-PC trial (ISRCTN45905321) will recruit 1200 men, comparing 43.7Gy in seven fractions over 15–19 days with 78Gy in 39 daily fractions. The PACE trial (ISRCTN17627211) is planning to recruit 1716 patients and compares 36.25Gy in five fractions over 1–2 weeks with 78Gy in 39 daily fractions. A second comparator is the SABR schedule with laparoscopic prostatectomy. In addition, the SPARK trial (NCT02397317) is running in Australia which is testing safe implementation of the PACE trial fractionation, but using kilovoltage intrafraction monitoring (KIM) which will be described below. The outcomes of these studies are eagerly awaited to provide sound evidence for prostate SABR.

8.1.2 Methods to monitor intrafraction motion of the prostate

With modern, pre-treatment IGRT, interfraction prostate motion is a smaller source of error in prostate EBRT than it was in the past. The prostate is, however, prone to random movement during treatment delivery, which is now a substantial cause of concern in setting margins. Great efforts are being made to monitor the location of the prostate to account for these random errors. Methods to monitor prostate location during treatment include using basic fiducial markers, complex fiducial markers, ultrasound and MRI linear accelerators.

8.1.2.1 Basic fiducial markers

The simplest method to monitor the location of the prostate during a treatment fraction is to image the location of implanted fiducial markers, typically used for pre-treatment image guidance, throughout the treatment fraction. Fiducial markers are commonly gold markers or coils that are implanted into the prostate via needles under ultrasound guidance. The fiducials can be imaged in the treatment beam or using portal images in between treatment beams. Using the treatment

beams is advantageous in that there is no extra dose delivered to the patient[229]. There are several disadvantages of using treatment beams. One key disadvantage with modern treatments using IMRT and VMAT is that the fiducials will often be occluded by the MLC leaves, offering less reliable information about prostate location[229]. Another issue is that when taken at the cardinal gantry angles the images only offer information about prostate displacement in two planes. On the other hand, when imaging at other angles, there will be displacement that potentially combines anterior-posterior and left-right components, the quantity of each is unknown in planar imaging. This problem can be solved by taking an orthogonal image with a kV imaging system. However, additional imaging dose is delivered when using KV images, and the MV dose scattered to kV imaging panels can cause degradation of that system over time. Additionally, these systems are typically only available in an experimental environment at this stage.

More elegant systems have been devised that use the fiducial markers to monitor the motion of the prostate during treatment. The most advanced of these is the KIM system developed in Australia[212]. This system uses the kV imaging system on a Varian linear accelerator to capture 2D images of the fiducials during short arcs (for example between treatment beams or during VMAT delivery). The fiducial markers are segmented and then 3D locations of the fiducials are determined using a maximum likelihood estimation of a 3D probability function. The accuracy of the system is 0.46mm[212] and it can assess rotation in all three planes[199]. The ability to locate the prostate in this system comes at a cost of imaging dose to the patient. A similar system uses the MV beam on a Varian linear accelerator during VMAT delivery to monitor the location of fiducials and estimate their 3D location using a Bayesian approach[229]. The use of the treatment beam does not add dose to the patient, but the fiducials are often partially or fully occluded by the MLC leaves. This system has only been used to monitor the prostate location in a retrospective setting[229].

Another system developed in our department uses the 2D kV projections acquired during CBCT to give information about prostate motion during CBCT capture[198]. This system can use images from both the Varian and Elekta linear accelerators. The advantages to this approach are that no additional dose is delivered to the patient, and, along with prostate motion information, a volumetric image gives information about deformation of the prostate and OARs. The disadvantage is that only motion information is available at the start of the treatment fraction. These systems are all in development, with the KIM system demonstrating clinical application in an experimental setting, while the others only have used retrospective analysis. The great advantage of these systems is that they use existing, widely available technologies incorporated into standard linear accelerators and should be limited in additional costs. A recent survey of Australian IGRT technologies has indicated that at least 97% of Australian linear accelerators have some form of kV or MV EPI or CBCT imaging capabilities[230].

There are also systems available that use imaging components independent of those on the linear accelerator. Within the treatment room, two kV x-ray imaging sources are mounted in the floor or ceiling at orthogonal angles to each other and pass through the treatment isocentre. Corresponding detectors are positioned at opposing locations to the sources. When planar image pairs are taken, the fiducial marker locations can be reconstructed in 3D. These systems can be used to fluoroscopically monitor the fiducial locations or with snapshots throughout the treatment fraction[231, 232]. They can also provide 3D target locations when non-coplanar treatment beams are used. They have demonstrated the ability to make translational corrections of the prostate to the treatment isocentre within a treatment fraction, which has allowed reductions in PTV margins[231, 232]. These systems are also crucial for robotic linear accelerators delivering hypofractionated prostate radiotherapy, which can have treatment sessions as long as 50-70 minutes[233]. Unfortunately, the systems are expensive and require modification of existing treatment bunkers to install. This has been a limitation to their uptake at treatment centres. A recent survey suggests the

current use of these systems in Australia is unknown, due to the modality being combined with infrared imaging technologies in a recent survey[230]. When combined with infrared monitoring the proportion of centres using these systems in Australia was 17%[230]. However, infrared and other external monitoring systems are of limited use in prostate cancer due to the prostate moving independently to external markers, so they will not be discussed in this thesis.

8.1.2.2 Advanced fiducial markers

More complex and expensive fiducial marker systems are available in the form of electromagnetic transponder fiducials or radioactive fiducials. The Calypso system is one of the most widely used, where beacon transponders are implanted into the prostate, allowing three-dimensional tracking of the transponders at a frequency of 10 Hz and an accuracy 0.54mm[234]. The transponder locations are detected by an electromagnetic array which is positioned above the patient, allowing pre-treatment alignment and intrafraction tracking. The system can provide rotation information of the transponders around all three planes. Calypso has been implemented with great effect, allowing accurate monitoring of the prostate without any radiation dose to the patient. The ability to correct the target position has allowed PTV margins to be reduced[163, 165, 193]. There are several disadvantages to this system. The system cannot be used for tracking in patients with a large anterior-posterior separation due to physical constraints between the machine head and the electromagnetic array[165]. The fiducials are larger than regular fiducial markers and require a larger gauge needle for insertion, which may cause more complications compared to conventional fiducials[235]. Finally, the system and the fiducial markers are very expensive and are not covered by Medicare, therefore providing additional costs to treating centres and patients. Despite the advantages and desirability of the system, the cost is likely to contribute to the low reported uptake of the Calypso system in Australia, which is only 6% of linear accelerators[230].

Two wired electromagnetic transponder systems have been reported, the RayPilot and the RADPOS systems. Both have the ability to be implanted into the prostate, but for both systems a wire leads from the implant to the external surface of the patient. The wire allows the internal antenna (the implant) to be connected to a control computer which controls the signal output. The location of the implant is detected by a receiving plate in the Raypilot system[236]. In the RADPOS system the implant location is detected by a pulsed 3D magnetic field[237]. These systems are both designed to have dosimetry capabilities as well as localisation capabilities. The RayPilot system is commercially available and can provide intrafraction motion tracking with an accuracy of 0.8mm[236]. The RADPOS system has shown an accuracy of 0.7mm[237]. The Raypilot system can give rotation information around the LR planes and AP planes, therefore, providing less information about prostate rotation than the Calypso system[238]. A key advantage of these systems will be the addition of dosimetry to treatment monitoring. Another advantage is that the implants will be removed after treatment completion, however, this may potentially lead to further complications. Some patients may not be amenable to the implant having a wire which protrudes beyond the skin, the acceptability of these implants has not been reported. Cost will be another factor in the implementation of these systems. No Australian centers have reported using Raypilot.

A key disadvantage with the electromagnetic tracking systems is that they are susceptible to electromagnetic interference, which can be from the linear accelerator or other devices in a treatment room. Another disadvantage of the Calypso, Raypilot and RADPOS systems is that they are not compatible with MRI due to the transponders creating large image artifacts[239]. Outlining the target and OAR volumes with MRI is increasingly considered an important part of the treatment planning process, so this factor could prevent the introduction of these systems at some departments. Ultimately, these systems are likely to remain niche technologies in Australia until further data is available to demonstrate they improve treatment outcomes enough to warrant the cost of implementation.

An alternative fiducial has been developed using a different approach to the electromagnetic systems. The Navotek system was developed to eliminate some of the issues associated with electromagnetic transponders, being MRI incompatible, the size of the transponders and the impacts of electromagnetic interference on those systems[239]. The fiducials also distort CT and CBCT images less than gold fiducial markers[240]. The Navotek system uses small implanted radioactive fiducials (approximately 100 mCi of Iridium 192, half-life of 74 days) and a collimator- mounted sensor system that rotate to align with the plane of the source. Multiple sensors in different planes allow the source to be localised in three-dimensions with an accuracy of 0.86mm[239]. A key disadvantage for the Navotek system is that it cannot be used for real-time tracking with 10MV or greater beams[239]. The neutron flux created by high-energy photon beams activates isotopes in surrounding environment which emit gamma photons that interfere with the detection of the fiducials[239]. If 15MV or greater beams are used for treatment, the gamma emission can continue for up to ten seconds, which severely limits the utility of the system for intrafraction monitoring. The system has FDA approval, however, there are few published articles on the implementation of the system and no reported installations in Australia. The system will likely be expensive and there are concerns about the radioactive fiducials[241].

8.1.2.3 Ultrasound

Using ultrasound for intrafraction prostate monitoring is a relatively recent development. The challenge for intrafraction monitoring with ultrasound has been to keep the US probe in place during the treatment fraction. Two approaches have been developed, one using a transabdominal probe position and the other using a transperineal position. The transrectal approach has also been considered for its improved image quality, but the risk of prostate deformation, proximity of the probe to the prostate and patient acceptability with multiple fractions have been deciding factors against its use[242]. The other disadvantage with a transrectal approach is that the rectal ultrasound

probe may bring the rectum closer to the prostate, therefore reducing the tissue sparing ability, as seen in brachytherapy studies[243].

The transabdominal positioning of the ultrasound probe has been achieved using a human-safe robotic manipulator[244, 245]. This device can be controlled from outside the treatment room to maintain the pitch and pressure of the probe to deliver good quality images throughout the treatment fraction[244]. The system has been demonstrated to detect prostate displacements before they exceeded 2.3, 2.5, and 2.8 mm in the AP, SI, and LR directions respectively. Rotation of the prostate was detected before exceeding 4.7 degrees[245]. The transabdominal approach has several disadvantages. The setup requires 25cm of clearance between the patient's anterior surface and the linear accelerator gantry head to allow for probe positioning and gantry rotation[244]. This will limit the utility in patients with large AP separations. Currently the system has only been deployed with a 2D imaging probe, which is smaller than a 3D probe, however, the authors suggest a 3D probe will be intended for future implementations[244]. The treatment beam arrangement must avoid passing through the US probe, which limits the range of beam angles available to achieve the best treatment plan, however, suitable plans can be developed[244]. For VMAT deliveries, part of the arc would need to be blocked to avoid the probe head[246]. Ideally the probe pressure should be maintained at a constant between planning and treatment to avoid any potential organ deformation or displacement[245]. Studies that have simulated free-hand transabdominal ultrasound measurements and varied probe pressure have found that displacements of greater than 2mm occurred in 16%[247] and 84%[248] of measurements respectively, which would be of clinical significance if margins were reduced.

Transperineal positioning of the US probe is the approach taken by the Clarity system, which is commercially available and in use within Australia. One key advantage of this position is that the path between the perineum and prostate is short, therefore, potentially offering improved image

quality[242]. The Clarity system uses a 2D probe in a motorised housing that performs a sweep of the prostate. For intrafraction monitoring it performs a 45 degree sweep in 2.5 seconds, which gives an image resolution of 0.35mm. Therefore, the intrafraction monitoring will not detect large, transient displacements of the prostate, but more stable displacements. Clarity can detect translations and rotations of the prostate, but deformations are not calculated by the system[242]. The accuracy of the system is within 1mm 95% of the time in phantom studies and has reported good agreement in clinical application[242]. The effect of probe pressure on prostate location has indicated that for every 1mm of superior shift of the probe, the prostate moves 0.42mm in the same direction[249]. Additionally, there was a 0.08mm drift in the superior direction per minute of treatment[249]. Therefore, ensuring equal probe pressure at planning CT and during treatment is important for the reproduction of organ positions. A great advantage of the transperineal approach is that the probe is not directly in the beam path and therefore the full range of beam angles are available for treatment planning. The cost of implementing the system is a disadvantage, as well as potential impacts on the treatment workflow, with longer treatment fractions required for probe positioning. To date the uptake of ultrasound guidance in Australia is limited, with 6% of linear accelerators having the capability[230] and potentially not all of those systems would be capable of intrafraction monitoring.

8.1.2.4 MRI linear accelerators

MRI linear accelerators are another technology that may be promising for intrafraction monitoring of prostate position. The advantage of MRI is that it offers superior soft tissue contrast, so can allow visualisation of prostate location, rotation and deformation as well as rectal and bladder changes. MRI may even be able to provide functional information relevant to extreme hypofractionation, such as oxygenation of tumour volumes[250]. The key disadvantages for implementation will be the expense of the machines and bunkers.

The only commercial system available is the ViewRay MRIdian system which uses a 0.35T MRI and a 3 headed cobalt 60 system instead of a conventional linear accelerator[251]. The ViewRay system has been clinical at the Washington University School of Medicine, USA since 2014[251]. The Elekta MRI linac consortium use a modified 1.5T Achieva Philips MRI and an Elekta 6 MV accelerator in a ring in the midtransversal plane around the MRI[252]. The Cross Cancer Institute in Alberta, Canada have developed a phase II design combining a 0.6T MR and 6MV linear accelerator[253]. The Australian MRI-Linac project uses a 1T open-bore MRI and 6MV linear accelerator and will compare inline and perpendicular beam orientations[254]. Varian and Princess Margaret Hospital collaboration in Canada are developing a MR unit which is separate to the linear accelerator[255]. Intrafraction guidance will not be possible with this system, but pre-treatment imaging will be performed on MRI and then the patient will rotate to the linear accelerator[255].

There are many challenges involved in making the MRI linear accelerators safe to implement clinically. One of the biggest challenges is due to the interaction of the scattered electrons and the Lorentz force of the magnetic field. This causes an electron return effect at air-tissue interfaces, therefore increasing the surface dosimetry at the interface[252]. There are also issues with the effect of the magnetic field on ionization chambers, which are used for reference dosimetry[252]. The magnetic field inhomogeneities, patient-specific magnetic susceptibility artifacts and chemical shift distortions must also be quantified[253]. At this stage MRI linear accelerators are a technology for the future of prostate radiotherapy and have little impact on current treatment practices.

Overall, the intrafraction monitoring methods will become far more common as they will be increasingly integrated into newer equipment. At this stage the uptake in Australia is relatively low, yet more than half of departments are looking to expand their in-room imaging technologies[230]. The availability of intrafraction monitoring methods will be useful for future diet intervention or

adaptive margin studies to develop a greater understanding of intrafraction motion of the prostate and address some of the gaps in the present research.

8.1.3 Rectal separation methods

Due to the proximity of the rectum to the prostate and the sensitivity of the rectum to radiation dose, devices have been developed with the aim of separating the rectum from the prostate. The earliest of these developments was the endorectal balloon, but the newer devices of rectal spacers and rectal retractors have more recently been introduced. Each work in a different way, all with the aim of sparing dose to the rectum, and therefore, aiming to reduce the toxicity to this organ.

8.1.3.1 Endorectal balloons

Endorectal balloons are a device with a balloon located near the end of a flexible tube and, when inserted into the rectum, can be inflated with either air or water to a consistent, pre-planned volume. The primary role of endorectal balloons in prostate radiotherapy has been to immobilise the prostate by giving a consistent rectal filling that pushes the prostate against the pubic bone[256]. Traditionally, the rectal sparing properties were seen as secondary to immobilisation[256]. The inflated balloon separates the posterior rectal wall away from the treated volume, decreasing the dose to part of the rectum[256]. This has led to an overall reduction in rectal toxicity when prostate 3DCRT is delivered to a dose of 63-67.5Gy[256]. When the endorectal balloon is filled with air, it potentially can have a tissue sparing effect on the anterior wall of the rectum. However, endoscopic investigations have found telangiectases are more focussed on the anterior rectal wall when balloons are used[257]. The reactions seen on the anterior rectal wall are not surprising given that it is pushed closer to the prostate, so will be pushed into the high-dose region[238, 241]. On the other hand, if anterior rectal wall dose-sparing is achieved, there is also concern regarding dose to the posterior prostate volume, which is frequently the site of prostate tumours. Phantom studies have shown with a 15MV IMRT plan, the dose reduction on the rectal wall surface is 15%, 8% at 1 mm and 5% at 2 mm[258]. This could reduce the dose to posterior prostatic disease or extraprostatic disease.

Another point of concern is that when seminal vesicles are included in the target volume, the rectal sparing properties of the balloon are lost[256, 259].

The ability of endorectal balloons to reduce intrafraction motion of the prostate may make them a useful device for PTV margin reduction. A significant reduction in intrafraction motion of the prostate with an endorectal balloon has been demonstrated by a group of investigators[260]. The study treated 15 patients to 80Gy in 40 fractions with an endorectal balloon and 15 patients to the same dose without a balloon. In that study prostate displacements greater than 3mm were reduced from 18.1% of treatment time without an endorectal balloon, to 7% with a balloon[260]. However, a previous study by the same institution showed 17 patients without an endorectal balloon had displacements >3mm for 13.6% of treatment time[163]. Large variations in intrafraction displacements are seen amongst patients, therefore the small sample size of these studies make the results less reliable. The immobilising effect of the endorectal balloon has been supported by another study[261]. Although, that study also found that the presence of faeces and/or gas in the rectum increases the risk of intrafraction motion of the prostate greater than 3mm[261].

While the ability of endorectal balloons to reduce prostate intrafraction motion is promising for reducing PTV margins, they have been found to deform the target volume with changes in rectal filling[256, 262, 263] and positioning errors[263]. Therefore, the positioning of the balloon and the deformation effect on the prostate still require verification, most likely with volumetric imaging[263]. The deformation and rotation of the prostate may limit the overall reduction of PTV margins achievable by endorectal balloons.

Endorectal balloons are generally well tolerated by patients[262]. Only 2.4-4% of patients will not be able to tolerate daily insertion of the balloon and will cease its use during treatment[262]. Around 21% of patients will experience pain or signs of blood with the use of a balloon[262]. Pre-existing ano-

rectal disease, such as haemorrhoids, may preclude the use of an endorectal balloon or require additional care in their application[262]. In Australia, the use of endorectal balloons has been limited and has primarily been studied in the post-prostatectomy setting[264]. The trend towards hypofractionation may increase the use of endorectal balloons, as patients are more likely to tolerate them for fewer fractions. However, the ability to overcome the error introduced by endorectal balloons in hypofractionation requires further research.

8.1.3.2 Rectal Spacers

Rectal spacers are a relatively new development in prostate radiotherapy, where a material is inserted between the Denonvilliers' fascia and the anterior rectal wall. Spacer materials used in prostate radiotherapy include polyethylene-glycol (PEG) hydrogels, collagen, hyaluronic acid (HA), blood and biodegradable balloons[241]. The spacers are inserted under transrectal ultrasound guidance with the use of a transperineal needle or, in the case of the balloons, a small perineal incision[265]. The insertion procedures and spacers are usually well tolerated with few reports of complications[265]. The spacers are designed to be stable for the duration of radiotherapy and then will degrade in the body after 3-12 months[241]. The hydrogel spacers are the most commonly reported in use and are commercially available[241].

The use of spacers has been shown to be effective in increasing the separation of the anterior rectal wall and the posterior prostate[241, 265]. The hydrogel spacers have been shown to create a perirectal space of 7-15 mm[265]. The HA spacers have demonstrated separations of 9.8-20 mm[265]. Collagen spacers have demonstrated to create a perirectal space of 8-19 mm[265]. While blood spacers have demonstrated a mean separation of 3.9 mm[241]. The balloon spacers have reported a large range of separations, with 2.2 mm being the lowest and 24.7 mm being the greatest[241, 265].

Hydrogel perirectal spacers have been the subject of a randomised trial of 222 patients, with a randomisation of two spacer patients to one control patient[266]. The study patients were blinded to their randomisation and all were treated with 79.2 Gy in 44 fractions with image-guided IMRT with 5-10 mm PTV margins. In that trial 148 patients received a spacer, where the mean (SD) perirectal distance was 1.6 (±2.2) mm, 12.6 (±3.9) mm, and 9.0 (±5.9) mm at baseline, post-spacer application, and at 3 months (±1 week), respectively. The success rate of spacer insertion was 98.7%. While significant reductions in dose received by the rectum in the spacer groups were demonstrated, there was no significant difference in acute GI or GU toxicity. There was no significant difference in late GU toxicity, but significantly higher late GI toxicity was seen in the no spacer group. The difference was small, however, with the spacer group reporting 2% grade 1 GI toxicity (three events) and no Grade ≥2 toxicity. While the no spacer group had 5.6% grade 1 GI toxicity (four events) and 1.4% Grade ≥2 toxicity (the only Grade ≥2 was one grade 3 proctitis event). There was no significant difference in patient reported GU and GI quality of life, but more patients with no spacer reported a decline in their GI quality of life. The study is limited by short follow up (15 months), and clearly demonstrated low GI toxicity with or without the rectal spacer. The investigators also highlighted the risk of treating patients with extracapsular extension, where potentially the extracapsular disease would be pushed further from the prostate[266].

The effect of hydrogel spacers on interfraction[267] and intrafraction motion[268] of the prostate has been studied. The interfraction motion of the prostate was found to be similar, although there was a slight increase in AP displacement >5mm in the hydrogel spacer group, 27% compared with 10% in the no spacer group[267]. While the mean (±SD) intrafraction displacement of the prostate with the hydrogel spacer was significantly higher than with no spacer, 1.5 (±0.8 mm) and 1.1 (±0.9 mm) respectively ($p < 0.05$) [268]. However, these values were within the margin of error for measuring prostate location with Calypso[268]. Substantial displacements are also more frequent, but not significantly so, where the mean (±SD) >3 mm displacement over the total treatment time for

patients with and without hydrogel were 7.7% (±1.1%) and 4.5% (±0.9%) respectively ($p>0.05$) [268]. There has not been an assessment of inter- or intrafraction prostate rotation and deformation with the hydrogel spacer to date, although some results hint toward greater interfractional prostate rotation with the spacer[267]. There is conflicting information about the stability of the hydrogel spacer volume over treatment, with an increase in volume during treatment observed by one group[267] and a reduction being observed by another at three months after insertion[266]. The three month window is important, as that is around the time required from implantation of fiducials and the spacer, until the end of a conventionally fractionated treatment course. Two weeks is often allowed after the implantation of fiducial markers before the planning CT scan. Another two weeks may be the time required for treatment planning and QA, while fractionated treatment may last around 8 weeks.

The use of rectal spacers will not be applicable in all patients. Spacers are not suitable for all patients, specifically those with inflammatory bowel disease, chronic prostatitis and perianal disease who may be at high risk of adhesions in the perirectal space[241]. Not all patients will have successful spacer insertion. The study of Mariados et al, only had 1.3% failure of spacer insertion[266], while in another study of hydrogel spacers, the insertion failed in 9% of participants[241]. The use of balloons spacers also failed in 10% of patients in a different study[241]. The rectal separation achieved by the spacer may not always achieve the desired dosimetric outcomes, as seen in some studies[269]. Another reason spacers may not be used in some patients is due to cost, where some patients in Australia will not be able to afford the spacer. Currently, Medicare covers the cost of the implantation procedure, but not the cost of the product itself, which may leave the patient thousands of dollars out of pocket. Although, some patients will be members of private health insurance funds who include hydrogel spacers in their coverage. Therefore, while the use of spacers is promising, alternative methods to spare dose to OARs need investigation.

A key concern with the use of spacers is that the rectal sparing achieved may lead to clinicians using existing large margins or increase margins if uncertainties, such as prostate deformation or motion, are deemed to increase with the use of spacers. Reduced margins are preferable to reduce the dose to bladder and other organs. It has been suggested that the dose to the bladder is clinically insignificant as the prostatic urethra may be the cause of GU toxicity, evidenced by post-prostatectomy studies[125, 241]. However, doses for intact prostate radiotherapy are greater than for post-prostatectomy, which usually receive doses of 64-70Gy[270]. Yet, despite the higher doses received during intact prostate EBRT, the GU toxicities are equivalent or only marginally higher, which leads us to question the notion that prostatic urethra is the main source of toxicity. Without convincing evidence for the source of GU toxicities, it is prudent to limit the dose to the bladder trigone and wall, which is aided by the reduction of PTV margins.

8.1.3.3 Rectal retractors

Rectal retractors are a device which are inserted into the rectum and then used to push the rectum posterior in the patient. The rectal retractors are made up of a cylindrical rod, 20mm in diameter and 110mm in length, which is secured to a baseplate on an indexing system. The retractor is inserted into the rectum with the patient in the supine position and then connected to the indexing system. The rectum is then mechanically retracted towards the treatment couch to a position which is tolerable by the patient[238, 271]. The index position is recorded so that the same retraction can be performed at each treatment fraction.

The evidence of success of rectal retractors in reducing dose to the rectum and immobilising the prostate is mixed. In one planning study of ten patients, the rectal retractor demonstrated significant reductions in dose received by the rectum at the higher dose levels when compared to no retractor[271]. Because the rectal volume was increased by the retractor, the volume of rectum receiving lower doses actually increased[271]. Another ten patient study found no significant

difference in dose to the PTV, CTV, bladder or rectum, with our without the retractor[272]. In terms of intrafraction prostate displacement, Nicolae et al, found that all patients had less than 3 mm prostate displacement when measured between pre- and post-treatment CBCT[272]. Their study only investigated translations of the prostate and not deformations or rotations. A study which monitored prostate location using electromagnetic fiducials in 22 patients was able to determine the effect of rectal retractors in an intrapatient setting[238]. In that study rectal retractors were found to increase prostate motion, where displacements greater than 3 mm within a 6 minute interval were 9.7% of the time and within a 10 minute interval were 15.3% of the time[238]. In contrast, when the same patients did not have a rectal retractor used, the displacements greater than 3 mm within a 6 minute interval were 3.5% of the time and within a 10 minute interval were 6.4% of the time[238]. The greatest displacement of the prostate with a rectal retractor was in the posterior direction[238], which has implications for the posterior PTV margin applied. Ultimately, due to the limited, conflicting studies on the use of rectal retractors, further research is required to determine if they have a role in prostate EBRT and what margins would be required for their use.

Overall, the evidence for rectal separation methods has not yet demonstrated a clear advantage of one method. The most promising are the hydrogel rectal spacers and with further research they may demonstrate an advantage over no spacer. They may particularly be beneficial in the setting of hypofractionation, when the dose to the rectum may risk severe toxicities. However, the reduction of treatment margins should still be pursued, as this will be beneficial for other organs at risk. Diet intervention and adaptive margins provide two potential ways to reduce the PTV margin, our investigations into these approaches will be discussed below.

8.2 Recording a patient diet during radiotherapy.

Compliance with study procedures is an important aspect of assessing the rigour of research conduct and results. While diet intervention studies for prostate radiotherapy had been conducted before

our investigations, those studies had not assessed compliance with the diet intervention[146, 148]. The conflicting results of those similar interventions and the lack of compliance measures made it difficult to attribute how much of the study outcomes were due to the intervention, or due to a potential lack of patient compliance with the intervention, or other factors.

At the time of our investigation, a review of the literature indicated there was no information available for recording a patient diet during prostate radiotherapy. The study in **chapter 3** demonstrated that a diet diary which allowed for open ended recording and estimates of food quantity could be suitably used to record a patient diet for a duration of eight weeks[190].

The overall outcome for the study in **chapter 3** is that it identified a useful tool for assessing compliance and enabling data recording for our subsequent diet intervention study presented in **chapter 4**[195]. In **chapter 4**, the diet diary was successfully used to demonstrate compliance, where 57.2% (range 20.2-76.2%) of the meals consumed by patients in the standard therapy arm contained excluded foods compared to 9.9% (range 2-23.2%) in the diet intervention arm (unpublished data). The energy intake between the two arms was very similar (standard therapy average dietary intake was 8743 kJ and for diet intervention was 8669 kJ, mean difference 74kJ [95% CI: -1528 – 1676 kJ, p = 0.925]) and the fibre intake was higher in the intervention arm (unpublished data). This gave us a good understanding of how compliant the participants were with the intervention and identified that most diet intervention patients only required 15 g of psyllium daily. We were also able to identify weaknesses in the diet diary review process and improve on them in the subsequent study. By querying the patient at weekly review if any information appeared to be missing and scoring 'nil' to indicate if a bowel motion had not occurred, we were able to improve the quality of the data captured.

The importance of having methods to assess compliance for diet interventions was recognised by McNair and colleagues[273] in response to our publication. Their findings agreed with ours that

patients were diligent in following diet interventions and were compliant in recording their dietary intake. This information provides useful reference for the future conduct of diet intervention studies and assessment of compliance in clinical practice.

8.3 Diet Intervention for prostate radiotherapy.

Diet interventions are an appealing approach to reducing PTV margins during prostate radiotherapy. They potentially represent a low-cost intervention and allow the patients to be more active in improving their treatment outcomes. Empowering patients to be more engaged in their health care may improve their quality of life during treatment and their experience of treatment[274]. A successful diet intervention would allow patients to present to treatment more frequently with an empty rectum and with reduced bowel gas. Care needs to be taken when implementing the intervention to avoid placing the patient under stress if they cannot achieve compliance or the desired outcomes in terms of bladder filling and bowel emptiness. This may have resource implications to provide education and support on a case-by-case basis. However, having the ability to adapt the treatment margin as described in **chapter 7** may provide comfort to the patient that the treatment can be delivered safely with varied states of rectal filling.

To date there is limited evidence to support the implementation of diet interventions for prostate radiotherapy, primarily due to a range of small studies reporting on a broad range of interventions. A recent review of diet interventions and other rectal preparations for prostate cancer radiotherapy found that there is still not conclusive evidence available in the literature to support one method over another[217]. Diet interventions are the most commonly reported studies, with five studies using a combination of laxatives and antiflatulent diets[146, 148, 149, 152, 195] and one study using a high-fibre prescription[150]. Four used magnesium-based laxatives and antiflatulent diets with contradictory results as outlined in the introduction[129, 131, 132, 135], while the study presented in **chapter 4** was the only one to use a psyllium laxative[195]. The high-fibre diet by McNair and

colleagues was outlined in the introduction and did not produce consistent rectal filling[150]. Another two small studies have suggested macrogol laxatives may be effective in reducing rectal variability[275] or Kampo formulas (Japanese herbal medicines) may be effective in reducing rectal gas[276], but both of those studies produced low quality evidence.

Physical rectal evacuation techniques were another method outlined by three studies in the McNair review[217]. Two of those studies required invasive approaches daily before treatment, but were reportedly well tolerated and demonstrated reduced prostate motion. The last study was vague on how the rectal emptying was achieved and was only enforced at study-specific CT scans[217]. The use of enemas was reported in five studies with promising results for reduction in prostate motion, however, the reviewers suggested randomised data is needed to support the evidence and guidelines on timing and method of administration need to be incorporated in to such a study[217]. A further small, retrospective study has suggested that enemas do reduce intrafraction prostate motion by removing faeces and gas[277]. However, intrafraction motion was only measured mid-fraction[277], whereas the risk of motion increases with greater time on the treatment couch[144, 164]. Additionally, the use of enemas also usually requires the resources of suitably trained staff for their application[217, 277].

Another method of interest is the use of probiotics to reduce gas accumulation in the gut. In one randomised study participants were assigned to either take a probiotic capsule containing 1.0×10^8 colony-forming units of *Lactobacillus acidophilus* or a placebo capsule twice daily[278]. Megavoltage CT was acquired daily to measure rectal volume and compare percentage rectal volume change (PVC_R) from planning. They found the intervention arm had a significantly smaller median (range) rectum volume 27.9 cm^3 (15.6 -78.6 cm^3) than the placebo arm 28.5 cm^3 (15.4 -101.1 cm^3), p=0.018. The same was found for PVC_R, the intervention arm had a median PVC_R of 8% (-33.9-147.5 %), compared to 18.5% (-29.2-264.5 %) for the placebo group, p<0.001. The study protocol required the

use of an enema to empty the rectum if pre-treatment MVCT found a dilated rectum, which was required a mean of 2.1 times in the intervention group versus 2.8 times in the placebo group, p=0.054. Their study also required that patients empty their rectum immediately before treatment, which may indicate that patients receiving the probiotic may empty their rectum more effectively. They noted that some patients in the probiotic group also showed unexpected excessive rectal distention[278]. The McNair review was concerned that the optimal dose, probiotic strains used and effects on gut microbiota have not been established[217].

Another concern from the study by Ki et al[278] is that they did not consider the patient effect, where the rectal volume of every fraction from every patient was treated as independent of all others. Our study in **chapter 4** considered the patient effect in the analysis. If, however, the diet intervention study presented in **chapter 4** were analysed without assessing the patient effect we would also obtain significant results. Our median (range) rectal volume for the diet intervention arm was 49.2 cm^3 (19.5-107.6 cm^3) compared to 55.7 cm^3 (24.2-168 cm^3), p=0.045. The median (range) PVC_R for the intervention arm was 22.5% (-46.6-194.3 %) compared to 27.4% (-35.6-314.2 %), p=0.007. We consider interventions are likely to have varied effects from patient to patient, so the patient effect should be accounted for and potentially may confound the results reported by Ki et al[278].

The literature on probiotic preparations for prostate radiotherapy has also not provided consistent results. A small study by Hamilton et al[279] trialled one capsule of 1.25×10^{10} units of Lactobacillus acidophilus NCFM and Bifidobacterium lactis Bi-07 a day in five patients compared with 3.5g of psyllium husk per day in five patients. They found that the probiotic group had a significant mean increase in difference from planning rectal volume, rectal CSA and relative CSA (p = 0·001, 0·008 and 0·007, respectively) [279]. Again they did not consider the patient effect, but their study suggested that the probiotic group had a worse outcome from the intervention. They suggested that the dose of Lactobacillus acidophilus in their study, being 10 times higher than in the study by Ki et al, may be

excessive and lead to gas production in the gut[279]. This supports the concerns of McNair and colleagues who identified the ideal dose needs to be determined[217], but also raises the question of the need for individualised dosing as Ki et al noticed excessive rectal distension in some patients[278]. Further research in this area is required to determine the effectiveness of probiotic interventions. Additionally, the use of probiotics with other diet interventions could be investigated for effectiveness/superiority and may provide another fruitful avenue of research.

Overall, because of a lack of clear results favouring one method, or strong evidence of efficacy over no bowel preparation, many authors have recognised that further study is warranted. The importance of undertaking adequately powered randomised trials has been highlighted by several authors[146, 217, 280]. Interestingly, the use of enemas, diet interventions with antiflatulent diets and laxatives appear to be widespread in the literature despite the lack of evidence of efficacy, with many departments in the Asia-Pacific region implementing these regimens[58, 280-286]. For the purpose of prostate SABR treatment, diet interventions, laxatives and enemas are commonly recommended[228]. While the evidence for these interventions is limited, moderate hypofractionation and SABR provide an opportunity for research in this area. Because the duration of these treatment schedules is shorter, there is a greater likelihood that compliance can be monitored accurately and achieved by the patients. If demonstrated to be successful, diet interventions may also be applicable to proton therapy and HDR brachytherapy.

Confusingly, a recent review paper has recommended the use of enemas at CT and developing diet interventions for use in departments, despite the same article also highlighting a limitation of having no strong evidence that the interventions reduce bowel gas[287]. We believe further investigation in this area should be undertaken to provide an appropriate level of evidence to support the use of interventions. The study presented **in chapter 4** has been the only study identified to propose a sample size for an adequately powered randomised trial based on early phase study data[195]. The

study was also able to demonstrate patient compliance with the intervention through the use of a diet diary. This information provides a sound basis for the conduct of a larger diet intervention study.

8.4 Assessment of treatment margins

Reducing PTV margins when patients present with an empty rectum, but keeping a larger margin for safety when prostate motion is likely, is an appealing approach to adapting treatment when the conditions are preferable. Before embarking on studies into adaptive methods, we first wanted to understand how our current margins were working based on new data available from our diet intervention study, as presented in **chapter 5**[288]. The study found that events of intrafraction motion beyond the PTV as recorded at the end of treatment occurred in about 9% of treatment fractions and were more likely in some patients, particularly those with larger prostates[288]. In **chapter 5** we chose not to define the volume of a large prostate as we recommend conducting a larger study to confirm our observations. Approximately 50 cc may be a suitable threshold, which is commensurate with many brachytherapy guidelines. The exact size could depend on the way the volume is measured and needs to be determined in future studies.

The study in **chapter 5** included data from both arms of the diet intervention study and extreme events of prostate motion were observed in both arms. It should be expected to observe large intrafraction motion in the diet intervention arm, despite undertaking the intervention. There are other reasons for intrafraction prostate motion such as gross movements of the patient, muscle clenching and bladder filling[217]. Cine-MRI data from our institution has demonstrated that some patients will display motion of bony anatomy which indicates gross changes in patient position[289]. This is in agreement with earlier data[140]. Due to the imaging methods used for the study in **chapter 5**, we could not assess changes in bony anatomy location, patient contour or muscle clenching to make an assessment of these. This is a potential weakness of the study and some of the

intrafraction changes in prostate position which we suggested were due to rectum changes may have actually been due to other factors. Overall, the diet intervention should reduce the frequency of large prostate motions due to rectal filling changes, but also should allow patients to present with an empty rectum more frequently. More detailed imaging such as pre- and post-treatment CBCT or Cine-MRI would be required to make such assessments and quantify the causes of motion in a future diet intervention study.

Due to the difficulty in identifying the borders of the prostate on CBCT, it is reasonable to consider that the effect of contouring error using CBCT data would over-estimate the PTV margin required to cover prostate intrafraction motion. We would not suggest expanding PTV margins as it may lead to worse outcomes in terms of toxicity without sound evidence to support it. The evidence from Calypso studies and Engels et al[202], suggests that the current margins are adequate, however, further studies should help to clarify the effects of prostate translations, rotations and deformations over the course of a treatment. We recommended further study be performed with better imaging modalities. The imaging should also take into account the trends in prostate motion, where the prostate will dwell in the high dose region for most of the treatment fraction over the course of treatment. Cine-MRI is currently the best method to achieve this.

MRI studies so far have looked at large number of patients (55 and 42) with single Cine-MRI to assess prostate and rectal movement[140, 142]. Other studies have used repeated Cine-MRI in a small number of patients (10 and six) to assess prostate and rectal deformation[143], and the relationship between rectal filling and prostate displacement[144]. Another study has used a single Cine-MRI in 11 patients to assess prostate motion in relation to seminal vesicle motion[136]. Axial MRI scans at planning and repeated during treatment in 25 patients have been used to assess deformation of the prostate relative to fiducial markers[138]. There still remains an opportunity to capture a greater number of repeated scans in a large patient group to gather a greater understanding of how all of

these factors combine. This would give a clearer picture of prostate intrafraction motion and how much of the motion is specific to subgroups of patients, i.e. patients with large prostates or at high risk of motion[288]. An ideal imaging protocol would capture a volumetric image, a series of cine-loop slices in the transverse and sagittal planes and then another volumetric image, the duration of which could simulate the length of a treatment fraction. We would also recommend taking into account seminal vesicle motion which we have not considered in our studies, but is an important part of setting margins, particularly for intermediate- and high-risk patients. Such an imaging study would be an ideal sub-study in larger randomised diet intervention study and would allow assessment of the impact of diet intervention on reproducing the planned rectum and the effect on prostate rotation, deformation and seminal vesicle location.

8.5 Modeling adaptive radiotherapy

Adaptive approaches to prostate radiotherapy are popular in concept, but few have been implemented clinically. The challenge of adaptive prostate radiotherapy is to account for the substantial changes in volume of the bladder and rectum surrounding the prostate, and the changes in the target positions. The work required to achieve adaptive prostate EBRT has typically been intensive, either in modification of treatment plans based on repeated volumetric imaging, or development of elaborate systems that can account for these changes. An enormous amount of work has been described for methods which are yet to be implemented clinically. Of the methods that have been implemented, there have been offline approaches that deliver a modified plan after collecting data on changes in structure positions, and online methods that change the treatment delivery based on the location of the target during a treatment fraction.

The offline methods have had the longest history of implementation, with the first method using repeated CT scans being demonstrated in 2001[167]. A similar approach, but using treatment CBCT scans was demonstrated in 2008[166]. Broadly, these approaches collect data on the target and OAR

positions on repeated imaging, and then deliver an adapted plan with a reduced margin which aims to account for the potential organ positions for the remainder of the treatment course. At the William Beaumont Hospital they have demonstrated their offline adaptive method improves rectal toxicity and biochemical control when compared to other published series[169, 290]. The main disadvantage with offline methods is that they require intensive use of resources. The approaches use re-scanning with planning CTs or importation of treatment CBCTs into planning systems. The scans require re-contouring, a new plan is then generated and QA is then required for the adapted plan to be delivered. All of this needs to be done in a short time-frame as the patient is continually treated with a large PTV margin until the adapted plan is ready for delivery. Additionally, the offline method using repeated planning CTs add radiation dose, whereas CBCT has a function of treatment verification. Offline methods that only use early treatment scans do not account for changes that can occur over a treatment course, e.g. patients may develop constipation during the treatment course. So, while this approach has been demonstrated to be effective, it is intensive and may not be reflective of the day-to-day patient presentation.

Deutschmann et al, have implemented an online adaptive method which corrects for inter- and intrafractional rotations and translations of the prostate and proximal seminal vesicles[291]. Their department had delivered this method to more than 39 patients at the time of publication. The method works by aligning to the fiducial markers on orthogonal kV images using autosegmentation and then transforming the contours of the target and organ at risk structures with six degrees of freedom to the fiducial marker locations. This then allows the system to adapt the MLC segments developed for a forward-planned IMRT delivery without any adjustment of the monitor units. Intrafraction displacement of the prostate is monitored during the treatment beams and movement of 3mm triggers repeated orthogonal kV imaging and adaptation of the MLC segments. The method assumes prostate and seminal vesicles move as solid structures and that the deformation of the rectum can be ignored. The method did not account for deformation, but relied on a diet

intervention to keep organs in the same shape. The upper limit for implementing the adaptation was maximum translations of 2 cm and prostate rotation of <30 degrees. No volumetric imaging was used in this approach to confirm the dose delivery. The study reported 82% of treatment fractions showing marker migration of <2 mm. This may mean there was deformation of the prostate for remaining 18% of fractions. The authors discuss narrowing of the intermarker distances due to reduction in prostate size, but failed to discuss if this factor was involved where changes greater than 2mm. Our own investigation into intermarker displacement for the publication in **chapter 7** identified that patients with good marker placement had intermarker distance changes that appeared to correlate with maximum rectum diameter. There is the potential that some changes in the intermarker distance were due to substantial prostate deformation. Overall, this system is appealing in that it uses commercially available equipment and is open-source, so it is available to interested researchers. Volumetric imaging with CBCT could help determine if the principle of solid organ transformation is upheld when the structures are contoured on treatment images. Dose deformation may also determine if the dose is delivered appropriately.

Adaptive prostate radiotherapy with Calypso and MLC tracking has demonstrated feasibility in an Australian study of 15 patients[213]. The MLCs were able to adjust to the real-time position of the prostate as registered by the Calypso beacon locations to a threshold of 8mm prostate displacement. If greater than 2.5 mm displacements of the prostate were detected before each treatment arc, a couch shift was applied during treatment to correct this. If the prostate was detected at greater than 8mm from the corrected position, a beam hold was triggered until the prostate returned to within 8mm, or a persistent excursion would be corrected with the couch. The difference from planned in dose delivered to the following structures with MLC tracking versus non tracking respectively were, PTV D99% -0.8% ± 1.1% versus -2.1% ± 2.7%; CTV D99% -0.6% ± 0.8% versus -0.6% ± 1.1%; rectum V65% 1.6% ± 7.9% versus -1.2% ± 18%; and bladder V65% 0.5% ± 4.4% versus -0.0% ± 9.2% (P<.001 for all dose-volume results). At present their method does not account

for rotations of the prostate except for an assessment of prostate coverage by the PTV at the commencement of the treatment fraction if the prostate rotation is greater than 10 degrees. They plan to include prostate rotations into the tracking system in the future. This method is a promising approach to adaptive and has the potential to reduce margins when rotations are included in the tracking program. However, the lack of anatomical information when using the Calypso system only for localisation means that potential deformations of the target volume cannot be assessed at the time of treatment.

These methods which have been clinically implemented represent great advances in prostate EBRT, but, as outlined, they are not without flaws. In most cases they have allowed for a modest reduction in the PTV margin. In the case of the William Beaumont experience, the individualised PTV margin was reduced in most patients to around 7.5 mm, but the PTV margin was increased in a few patients[167]. In the offline method described by Nijkamp et al, the margin was reduced to 7 mm[166]. The online method described by Deutschmann et al, achieved a margin reduction to 5 mm for most patients[291], however, up to 7 mm was required for 8 patients. While Colvill et al used a 7 mm margin with 5 mm posterior for standard fractions and a far more radical 5 mm margin with 3 mm posterior for SABR boost fractions[213]. Each of the methods described accounted for specific parts of the error associated in prostate radiotherapy. The offline methods primarily targeted interfraction errors, although the method by Nijkamp et al, also aimed to reduce intrafraction error with a diet intervention[166]. The method by Deutschmann et al[291], accounted for inter- and intrafraction translations and rotations, but did not account for deformations of the prostate or surrounding structures. While the method described by Colvill et al[213], accounted for inter- and intrafraction translations of the prostate, but not rotations and deformations of the prostate and surrounding organs.

The proposed methods of adaptive radiotherapy have investigated offline replanning with online image-guidance, which will account more completely for interfractional variation, but not intrafraction error[170, 171]. The various methods of online replanning or reoptimisation are also targeted toward correcting interfractional translations, rotations and deformations[172-174, 176]. These methods still require margins large enough to account for intrafraction motion and deformation, contouring uncertainty and accuracy in treatment delivery. The greatest concern is intrafraction motion and deformation. The online adaptation methods usually require contouring of the target and OAR structures, correction of the treatment targets to the isocentre, replanning/reoptimisation, QA of the new treatment plan and then sending the new treatment plan to the record and verify system. These processes take 5-10 minutes, with generation of new contours usually taking around 3 minutes[173]. During that time there may be substantial intrafraction displacement and deformation of the prostate[144]. Using one of the intrafraction monitoring methods described previously, the intrafraction translations of the prostate could be corrected in the online approach, however, the advantage of correcting interfraction deformations and rotations with reoptimising may be lost.

The generation of new contours is the longest of the processes involved in online adaptive methods and it is also time-consuming in the offline methods. Autocontouring via deformable image registration is an attractive way to automate and speed up this process. Deformable image registration methods are improving but still need review by a radiation oncologist and usually require corrections[292, 293]. The image quality produced by CBCT should theoretically lower the performance of deformable registration, however, it has been noted to produce similar results to CT[294]. The pelvis is also a difficult region for deformable registration, where the most challenging organs are the bladder and rectum. These structures are impacted by large changes in volume and variable filling of gas/faeces, which can make it difficult for the programs to define the organ boundaries[293-295]. A method that combines previous day contours with the planning contours to

create a patient atlas is promising for accurate pelvic autocontouring[292]. However, it requires several days of verified and corrected contours to reach a clinically suitable level of accuracy and processing of the atlases to generate contours will take one-to-two minutes per fraction[292, 296]. The atlases produced 87% of contours which were clinically acceptable in that small study, with bladder and prostate overlap being the greatest concern[292]. Curiously, those authors have not mentioned bowel gas interference or image artefact in their study[292]. Our studies have shown that around 13%[297] of images will be poor quality, whereas in the study by Godley et al[292], it must be assumed that the image quality of the selected 9 CBCTs per patient were of adequate quality. A larger sample of scans is required to demonstrate suitability of this autocontouring method for adaptive radiotherapy.

Ultimately, the online methods proposed will be time constrained, which creates an environment of increased risk. QA processes have been developed to account for some of those risks[298]. These methods can check for the quality of treatment plan in terms of correct plan parameters used, fractionation and scheduling, beam models used and DVH characteristics[298]. They can also perform a monitor unit calculation check and the correct transfer to the record and verify system[298]. The QA of the plan delivery is needed to be performed in an offline setting, however, depending on the re-optimisation method, pre-clinical testing can determine if this is likely to produce acceptable plans[175]. There are steps that still require human inspection, such as checking the accuracy of contouring and the quality of the dosimetry[298]. DVH parameters may not necessarily represent a good plan and without accurate contouring the DVH could be misleading. Performing these tasks under time pressures could lead to human error, but on the other hand, slowing down the process introduces the risk of random intrafraction motion errors.

Our proposed adaptive method in **chapter 6** goes some way in reducing part of these errors. The interfraction translations of the prostate are largely eliminated with pre-treatment image guidance.

The interfraction rotation and deformation of the prostate should be reduced if the rectal volume from planning is approximately reproduced. Volumetric imaging at the start of the treatment fraction can be used to confirm that the rotation and deformation of the prostate and seminal vesicles are within an acceptable range. The time between imaging and the start of treatment delivery is limited, as there are few assessments and decisions to be made, therefore reducing the risk of intrafraction displacement. The risk of prostate intrafraction motion is taken into account as the rectal filling may be used as a predictor of motion. Finally, there is reduced risk when treatment plans are pre-prepared. Adequate time is available to ensure that contouring is accurate and can use multi-modality imaging. Treatment plan optimisation can be exhaustive, to ensure the best treatment plan has been achieved based on the information available. All QA procedures can be performed safely with adequate time available. This is not to say that the method does not have shortcomings in terms of daily accuracy of dose delivery to the target and OAR structures. However, the simplicity of the approach is an appealing way to reduce margins.

8.6 Adaptive radiotherapy retrospective study

8.6.1 Effect of intrafraction motion on margin used

The study presented in **chapter 7** used pre-treatment CBCT to identify a MRD threshold that would predict reduced prostate displacement and allow for a reduced PTV margin[297]. From that study, we consider the MRD of 3.5 mm, which will predict with 90% confidence a maximum 2D displacement of 5.5 mm or less, would be the most beneficial to investigate further. Due to the fact that our data was not a mean 3D displacement, nor a mean translational displacement, the magnitude of the displacement within a treatment fraction sounds high. As the largest mean of the 2D displacements determined by the plane of imaging, it likely represents something closer to the largest substantial excursion of the prostate than a mean measured over the full fraction. Seventy-seven percent of the maximum displacements were captured in the lateral beams, giving 2D displacements in the AP and SI planes, which are known to be the major components of prostate motion.

We chose to discuss our displacement data in contrast with Calypso displacement data, as it is arguably the gold standard in measuring prostate intrafraction displacement. Overall, the Calypso data has indicated small mean displacements. In an eight minute tracking session for 11 patients, the mean (±SD) of the maximum differences were 0.91 (±0.35) mm, 3.61 (±3.13) mm, and 3.92 (±4.32) mm in the LR, SI, and AP directions respectively[299]. When continuous monitoring was used in a full course of treatment for 35 patients, displacements >3 and >5 mm for cumulative durations of at least 30 s were observed during 41% and 15% of sessions[165]. Some of these larger displacements are likely to have been detected in our maximum 2D displacement. Using Calypso data from 1157 fractions in 35 patients, the PTV margin to achieve 95% target dose coverage in 90% of patients was calculated for a situation when the target volume is aligned once prior to treatment[200]. This simulated the correction strategy used for gold marker implants, where the images are taken and time is allowed to match to fiducials and correct the patient to the isocentre. The resulting PTV margins from this scenario were 1.9, 4.1 and 3.9 mm in the LR, SI and AP directions respectively[200]. This further supports our assumption that a 6 mm margin would be adequate when reduced prostate displacement is predicted.

In our study we suspected that there may have been some intermodality discrepancy when CBCT imaging was used for pre-treatment alignment and MV imaging was used to monitor intrafraction motion. Our data indicated that the mean minimum displacement on the first set of intrafraction images (left lateral) were 1.6 mm in the AP direction and 1.6 mm in the SI, so an approximate minimum 2D displacement of 2mm on average. We considered this is higher than expected so early in the treatment fraction. Our experience with tracking prostate motion in the SI direction during CBCT using the method outlined in Gehrke et al[198], is that over one minute the mean SI displacement is 0.2 mm and the available AP data gave a mean displacement of 0.2 mm in the AP plane (unpublished data). It is also higher than expected with our institution's experience with intrafraction displacement[164]. A potential reason for this may be due to CBCT matching to fiducials

leading to greater error than with kV imaging[216]. In **chapter 7** we had many observers matching to CBCT[297], which would lead to more variability than in **chapter 6** where we had one observer performing the CBCT matches[214]. There may have also been a mismatch between the CBCT and MV imaging systems, and only one investigator performed the MV matches. We, therefore, consider that the study should ideally be repeated with Calypso data to confirm the true prostate displacement and to give a better understanding of the margin required.

8.6.2 CBCT pre-treatment imaging

The use of CBCT as an imaging modality may introduce uncertainty into our adaptive method, as well as increasing the treatment fraction duration. The image quality of CBCT offers poorer soft tissue contrast than in other imaging methods. This is known to make the identification of prostate borders difficult. When contouring the prostate on CBCT the average standard deviation for centre of mass displacements based on interobserver contouring were 0.7, 1.8 and 2.8 mm in the LR, AP and SI directions, respectively in one study[204] and 0.4, 1.1 and 1.7 mm, respectively, in another[300]. This is similar to the reported interobserver alignment from pre-treatment CBCT when performed by radiation oncologists, experienced RTs and junior RTs. The mean (±SD) of the differences between observers for CBCT registration translations along the LR, AP and SI direction were 1.9 (±2.7) mm, −0.7 (±3.6) mm and 0.9 (±3.6) mm respectively, and rotation around the AP axis was −1.8 (±5.0) degrees[301]. Another study found the Bland-Altman 95% level of agreement for soft tissue matching with CBCT amongst observers was ±3 mm[302]. The interobserver agreement of pre-treatment alignment can be improved by matching to implanted fiducial markers. The Bland-Altman 95% level of agreement for fiducial marker matching with CBCT amongst observers was ±2 mm[302].

The interobserver variation in identifying the surrounding OARs on CBCT is also a challenge. The bladder and rectum both exhibit greater interobserver variation when contouring on CBCT than on planning CT. The mean interobserver conformity index for the contouring the bladder was 0.79 for planning CT, and 0.75 for CBCT[303]. For the rectum, the mean interobserver conformity index for

using CT was 0.80 and for CBCT was 0.74[303]. Similar results were reported by other authors for rectum and bladder on CBCT compared to CT and MRI[300]. The interobserver conformity index reported in the latter study for CBCT bladder was 0.82 and for rectum was 0.70[300].

The time that is taken to perform online corrections and make plan selection decisions can have a substantial impact on the accuracy for prostate radiotherapy. There is little data available for treatment decision time for prostate radiotherapy with pre-treatment CBCT imaging. Information can be gleaned from other pelvic imaging techniques, where for bladder plan selection the mean time taken was 130 seconds[304]. A comprehensive review of CBCT treatment decision making times has been recently published, where 117,301 volumetric registrations from 4592 patients were analysed[305]. The study found that CBCT image assessment takes 79 seconds on average when all tumours sites are included except for SABR techniques[305]. When GU specific tumours were considered, the mean decision time was approximately 90 seconds, which was likely due to the greater corrections required for these tumour sites and the additional OAR considerations such as bladder and rectal filling[305].

The time required for treatment decision making and the accuracy of soft tissue assessments can be improved with training programs. Training programs are considered an essential part of introducing volumetric image-guidance techniques, particularly with soft tissue assessment[304, 306-308]. It has been demonstrated that training programs can improve RTs ability to identify the soft tissue borders of the bladder[306] and to select the correct plan of the day in adaptive rectal cancer radiotherapy[309]. In the setting of post-prostatectomy radiotherapy, it has been demonstrated that there is a small discrepancy between RTs and radiation oncologists when placing the treatment isocentre and selecting a plan of the day based on soft tissue assessment[310]. The ability of RTs to correctly identify pelvic structures has been shown to improve with training programs[311]. The training programs may help improve the accuracy of isocentre placement and plan of the day selection in

post-prostatectomy setting, but similar programs should be delivered to RTs in the intact prostate setting to improve soft tissue identification[312].

Training programs would help RTs quickly and accurately preform MRD measurements in the adaptive method we have outlined in **chapter 6**. The decision making process for the method we have described is simplified by only needing to select between a standard and adaptive margin plan. This may reduce the time required for volumetric image assessment over other plan of the day adaptive methods described which have multiple plan choices[309, 310, 313]. The identification of a MRD threshold measurement also helps to remove some of the ambiguity in plan selection. However, the advantage of pre-treatment CBCT is the ability to assess the target and OAR deformations at the start of treatment. Tolerances for prostate and seminal vesicle rotation and deformation could be determined so that they receive adequate dose when treated with the reduced PTV margin. These tolerances, that are yet to be defined, will require further research and additional RT training.

8.6.3 Adaptive prostate radiotherapy with hypofractionation

As outlined previously, several of the adaptive methods described by other authors require information from early fractions to adequately adapt the treatment. Offline methods require interfraction information to develop new target and OAR structures, while some online methods may require several fractions of corrected contouring before autocontouring can be reliably used for reoptimisation/replanning. The adaptive method we outlined is advantageous in that it can be implemented from the first fraction, and therefore is better suited to hypofractionation. If combined with a successful diet intervention, the margin could be adapted more frequently, therefore improving the therapeutic ratio. An opportunity may also exist to investigate dose-adaptive therapy, where the dose is escalated during fractions when a reduced margin can be applied and a more conventional dose is used for fractions that require a large margin.

For prostate SABR, intrafraction monitoring is required to ensure that the target structures stay within the small PTV margins required. Only adaptive radiotherapy in the form of target tracking such as the method outlined by Colvill et al[213], plays a role in prostate SABR at this stage. The ability to predict prostate displacement by measuring the MRD may play a role in prostate SABR, particularly for studies like the SPARK trial.

8.6.4 Adaptive radiotherapy and rectal separation

The method outlined in **chapter 6** and **7** could benefit from the inclusion of hydrogel spacers. The impact of margin reduction on reducing GU toxicities would be retained, while further reducing to dose to the rectum may also prove beneficial for reducing GI toxicities. The endorectal balloons and rectal retractors, on the other hand, would be contraindicated in this method as introducing a foreign body into the rectum would make the measurement of MRD redundant. Quantification of the effects of hydrogel spacers on the rotation and deformation of the prostate is required to understand how margin reduction would be impacted by these factors.

8.7 Limitations and recommendations for future studies

Our studies have reported potential improvements to treatment outcomes based on surrogate measures such as rectal volume variation and DVH metrics. The clinical outcomes of the approaches studied are yet to be determined with further research. Future studies should collect clinical toxicity data to determine if the theoretical benefits are delivered by the interventions. The impact of CBCT image quality has been highlighted throughout this thesis and may limit the reliability of our results. The frequency of imaging to determine intrafraction effects is also a limitation of our work. As outlined in the discussion, we believe Cine-MRI and Calypso data would be ideal for future diet intervention and adaptive studies which predict reduced prostate motion. The use of these imaging methods in larger studies will provide a greater understanding of prostate target motion and deformation over the course of treatment and reliably measure the impact of the interventions. A key limitation of our work is that newer intrafraction monitoring methods may largely solve the

problem of intrafraction prostate motion and rotation. However, at this stage the uptake of these newer technologies is limited and may remain limited if healthcare budgets remain constrained.

We mostly restricted our measurements and contouring to one observer to improve the reliability of our results. The lack of interobserver variation may limit the generalisability of our studies, however, it is expected that the conclusions drawn would remain the same with other observers. Future studies are required to quantify the interobserver reliability of measuring MRD and how training programs can reduce interobserver variation. There is also the opportunity with pre-treatment CBCT to perform soft tissue assessments of rotation and deformation. This requires RT training and assessment in further studies.

Our studies were tailored to deliver population-based margin changes. There is the potential to investigate personalised treatment approaches, with margins developed to capture the heterogeneity observed within the prostate cancer population. One of the main limitations of the studies is that they have primarily used small sample sizes which limit the generalisability of the results. Adequately powered studies are required to demonstrate efficacy of the interventions. Due to the resources required to conduct large studies, there is the potential for diet intervention and adaptive margins studies to be conducted as sub-studies of larger trials. Potentially large hypofractionation trials would be the best fit.

Chapter 9 Conclusion and future directions

In the near future, a large number of Australian men will be diagnosed with prostate cancer and will require treatment for their disease. The main modes of treatment for these patients will continue to be surgery or radiotherapy in the form of brachytherapy and/or EBRT. It is foreseeable that all of the modalities of treatment will continue to improve in the coming years as new equipment and research is incorporated into routine practice. EBRT will need to continue to improve in parallel. This thesis has focussed on improving treatment outcomes for EBRT by reducing treatment margins, primarily in the setting of conventional fractionation or moderate hypofractionation.

As outlined throughout this thesis, it has been reported in institutional series and in large multi-centre randomised trials that the toxicity of modern prostate EBRT is low, however, there is still room to improve. In addition to reducing treatment toxicity, survival outcomes may be improved by escalating doses, particularly in intermediate- and high-risk patients. Reducing the PTV margin which allows for treatment error and therefore, the healthy tissue within the irradiated target volume will allow for treatment toxicity to be reduced and potentially dose escalation.

The diet intervention in **chapter 4** and the adaptive margins method in **chapter 6** and **7** offer two approaches to reduce the PTV margin required for prostate radiotherapy. Potentially individualised margins could be beneficial to patients with different sized prostates as outlined in **chapter 5**. Although, at this stage further research is required to demonstrate safety and efficacy of these approaches. If demonstrated to be effective, it would be beneficial to implement the two methods together to provide a more frequent PTV margin reduction for these patients. With further research, the diet intervention and a similar approach to adaptive margins based on rectal diameter may be useful for other pelvis EBRT treatments, such as post-prostatectomy, endometrial and rectal cancer patients.

The timeframe for further research and implementation of a diet intervention and adaptive margins may be limited in the context of the newer EBRT treatment approaches being available, such as Calypso, KIM, SABR treatment and MRI linear accelerators. However, it is important to consider the cost factor involved in establishing these newer approaches. Calypso has been available commercially for many years now, but the uptake in Australia has been limited by cost. KIM is an attractive option, but will potentially be some years away as a commercial product and is likely to add cost to install. MRI linear accelerators are currently a technology for the future in the Australian setting. The methods proposed in this thesis would not require any new equipment. The main costs to departments would be resources for training RT staff in CBCT soft tissue anatomy and technique implementation. We therefore feel that it is worthwhile investigating these approaches as methods to reduce the PTV margin, based on the currently available resources in Australia and, in the broad context, internationally.

9.1 Future directions

Future directions for our research include:

A study demonstrating interobserver agreement for RTs when measuring MRD, potentially before and after a training program. Training RTs to assess prostate and seminal vesicle rotation and deformation could also be part of this study.

The adaptive study should ideally be repeated with a dataset which includes Calypso intrafraction prostate motion data and pre-treatment CBCT. We are aware of one such dataset and will endeavour to collaborate with that team. Subsequent to that, we could demonstrate safe implementation of the adaptive method with a pilot study using Calypso to verify that the prostate remains within the reduced PTV margin during adaptive fractions.

An ideal scenario beyond that would be a concurrent study of diet intervention and adaptive margin to demonstrate efficacy of both methods. This study would need to collect toxicity data to provide a comparison to standard treatment. Potentially this could be conducted as a sub-study to a larger hypofractionation trial. Longer term, dose escalation and individualised margins could be pursued.

The use of knowledge-based planning and autocontouring tools could be assessed in the implementation of adaptive margins for prostate radiotherapy. Knowledge-based planning has the potential to provide the most optimised results for planning the adaptive margin plans by utilising knowledge of the expected optimum dosimetric outcomes. Knowledge-based planning, therefore, could be assessed to determine if it can further improve dosimetric outcomes for adaptive fractions. Autocontouring and atlas-based contouring could be assessed to determine if it can be utilised in reducing contouring workload in the initial planning phase, or used to generate contours on CBCT for assessing the performance of the adaptive margin.

The implementation of hydrogel spacers needs further assessment for sound clinical implementation. Determining methods that improve the consistency of hydrogel insertion to provide reliable dosimetric results could be an avenue of research. The use of hydrogel in conjunction with adaptive margins, vessel-sparing and bladder-sparing may be another avenue of research. If the rectum can be reliably separated from the posterior prostate, the plan optimisation can focus on reducing doses to other critical structures such as the erectile vascular elements, external sphincter and bladder trigone.

The practical implementation of intrafraction motion management will be an increasingly important development in prostate radiotherapy in future. Ensuring safe implementation and assessment of the required departmental PTV margins with intrafraction motion management will be a necessary part of this process. Further information surrounding the effects of prostate rotations and

deformations on required margins will assist in setting PTV margins and training RTs in safe application of these technologies. The development of guidance statements will be important for disseminating this knowledge.

In the distant future, as MRI linacs become available for clinical implementation in Australia, the experience and recommendations from the prostate soft tissue training study for RTs could be used as a guide to developing programs in MRI soft tissue assessment. This would provide a valuable opportunity to continue study in this area of RT education and role expansion. Also, as with other intrafraction monitoring techniques, PTV margins and action thresholds for prostate rotations and deformations will need to be determined in the setting of an MRI linac.

Finally, in the event of a proton EBRT facility being available for prostate radiotherapy in Australia, the developments that have been driven toward photon EBRT will need to be assessed for suitability in the proton setting. The image guidance equipment available with the facility will determine what PTV margin reduction approaches are best suited to achieving better outcomes for proton EBRT patients.

Chapter 10 References

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Chapter 11 Appendices

11.1 Diet Diary Tool

INTRODUCTION

Thank you for taking part in this study.
You have been given this book to measure and record everything you eat and drink for the course of your treatment. The information from the diary will be used by the study coordinators to estimate your fibre and fluid intake. If you don't usually prepare your meals, ask the person who does to read this and help to record your food and drink.

HOW TO USE THE DIARY

1. **It is important that you do not change your eating and drinking habits during the time you are recording your intake unless advised by your dietitian or doctor**

2. Start a new page each day. Use as many pages as you need each day.

3. Write down **everything** you eat or drink during the recording period. It may help to keep the diary with you when you go out.

4. Record your bowel motions (passing faeces) by recording the time(s) of day you pass a motion.

HOW TO MEASURE YOUR FOOD & DRINK

* Overall estimate the amount of food you are eating & fluid you are drinking.

* To measure food and drink you can use items such as a measuring jug, cup,
glass, tablespoon and teaspoon e.g. yoghurt, soup, sugar, rice, coffee, juice.

* If you have household measuring scales you can also use these, if easier.

* It would be useful if you could measure the amount of fluid or food your regular dishes or drinks are. For example you could measure the amount of fluid your teacup holds and how much cereal your bowl holds.

* Estimate the size of your fruit or vegetable intake by using small, medium or large (or you could weigh them).

* If you are eating out, try to estimate the amount and record the ingredients as closely as possible.

HOW TO FILL IN YOUR FOOD DIARY

Please fill in all five columns

Columns 1 and 2. Time and Place
* Each time you eat or drink something, write down the time and place.

Column 3. Food or Drink Item
* Use a new line for each food or drink item
* You can use more than one line to describe one food eg. a sandwich.
* For sandwiches and rolls list each ingredient and the number of sandwiches or rolls eaten.
* If a dish is made up of a mixture of foods, name the dish eg. Lasagne and list each of its separate ingredients if known.
* Record foods added to others such as milk and sugar in coffee, margarine on bread and gravy to meat.
* Include all drinks including alcohol

Column 4. Cooking method / preparation/brand
* If a food is cooked, write down how it was cooked eg. boiled
* If food is coated write down how it is coated eg. crumbed.
* Write down if you remove the skin from fruit and vegetables.
* Write down the brand name of the food or product eg. Kraft or the name of the place of purchase eg. Bakery.

Column 5. Amount
* Estimate the amount of food or fluid you eat and drink and write it down

PLEASE REFER TO THE EXAMPLE ON THE FOLLOWING PAGE

Pt:01 Date: 27/10 Day: Monday

Bowel motions (times): 8am & 5pm

RT Initials: RWO

Time	Place	Food or Drink Item	Cooking Method/Brand	Amount (estimated) gram/ml/cm/cup/tsp/tbsp/slice/etc
7.00 am	Home	Cornflakes	Kellogs	35 grams
		Milk	Reduced fat - Rev	250 ml
		Orange Juice	100% - Berries	200 ml
		Asprin		
10.30 am	At Work	Sweet biscuit	Monte Carlo - Arnott's	2
		Apple Juice	100% - Prima tetra pack	1 tetra pack (125ml)
12.30 pm	At Work	Sandwich		
		Brown bread	Tip Top high fibre	2 slices
		Margarine	Golden Canola	1 teaspoon
		Ham	Don's small goods	1 slice
		Tomato		2 slices - 4cm diameter
		Lettuce		1 leaf
3.30 pm	At Work	Yoghurt - Fruit	Yoplait - lowfat	1 tub (250 gm)
		Apple		1 large
6.00 pm	Home	Chicken fillet	Grilled	150 grams
		Pumpkin	Roasted with water	3 tablespoons
		Potato	Roasted	1 medium
		Tea	Lipton	200 ml
		Milk	Low Fat - Rev	20 ml
		White Sugar	CSR	2 teaspoons
		Chocolate Ice Cream	Pauls	2 scoops
8.30 pm	Home	Crackers	Arnott's	2
		Cheese	Devondale Light	1 slice

Pt: Date: Day:

Bowel motions (times):

RT Initials:

Time	Place	Food or Drink Item	Cooking Method/Brand	Amount (estimated) gram/ml/cm/cup/tsp/tbsp/slice/etc

11.2 Conference/Seminar Presentations

Oates R, Lim Joon M, Schneider M, Kron T. *Margin Reduction for Prostate Radiotherapy*. Peter Mac Radiation Nursing Module 2, Melbourne, November 2015. (Invited Presentation)

Oates R, Brown A, Tan A, Gill S, Foroudi F, LimJoon M, Kron T, Herschtal A, Bressel M, Schneider M. Real time image-guided adaptive prostate radiotherapy using rectal diameter as a surrogate of motion. 2014 Combined Scientific Meeting, Melbourne, September 2014. (Oral Presentation)

Oates R, Jones D, Gill S, Ramachandran P, Foroudi F, Schneider M, Lim-Joon M & Kron T. Geographical miss of the prostate during image-guided radiotherapy with a 6mm posterior PTV expansion margin. ASMMIRT, Hobart, March 2013. (Oral Presentation)

Oates R, Lim Joon M, Schneider M, Kron T. *Margin Reduction for Prostate Radiotherapy*. Peter Mac Radiation Nursing Module 2, Melbourne, October 2012. (Invited Presentation)

Oates R, Ramachandran P, Kron T, Cramb J, Gill S, Foroudi F. *Assessment of intrafraction prostate motion using fiducial markers and projections from Cone Beam CT (CBCT).* The Royal Australian and New Zealand College of Radiologists 2011 Annual Scientific Meeting (RANZCR Melbourne 2011), Melbourne, October 6 – 9, 2011. (Oral Presentation)

Oates R, Lim Joon M, Schneider M, Kron T. *Margin Reduction for Prostate Radiotherapy*. Peter Mac Radiation Nursing Module 2, Melbourne, October 2011. (Invited Presentation)

Oates R, McPhee N, Lim Joon M, Schneider M, Kron T. *Diet modification for radical prostate radiotherapy*. Peter Mac Nutrition Oncology Day 'Talking about the 'C' word', Melbourne, September 23, 2011 (Invited Presentation)

Oates R. *Prostate Cancer Radiotherapy, History, Treatment and Research* – Monash Student Tutorial Day, Bendigo, September 2010. (Invited Presentation)

Oates R, McPhee N, Lim Joon M, Schneider M, Kron T. *Do Patients Comply with a Diet Diary during Prostate Radiotherapy and Can Radiation Therapists Aid Compliance?* 16th ISRRT World Congress, Gold Coast, September, 2010. (Oral Presentation)