Motion monitoring during prostate radiation therapy treatment: clinical considerations, and patient preferences and perspectives

Thesis submitted by

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Bachelor of Medical Sciences (Radiation Therapy);

Masters by Research

for the degree of Doctor of Philosophy

in the College of Public Health, Medical and Veterinary Sciences

James Cook University

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Acknowledgements

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To all of the participants who have so generously contributed to the various studies in this thesis.

This thesis is dedicated to you.

Statement of the Contribution of Others

Contribution	Name and Affiliation
Intellectual	
Advisor - Primary	A/Prof Tilley Pain, Townsville Hospital and Health Service & James Cook University
Advisors – Secondary	A/Prof Alex Tan, Townsville Hospital and Health Service (*Until Sept 2021*) and James Cook University (*Current*) A/Prof Emily Callander, Monash University & James Cook University Prof Kerrianne Watt, James Cook University & Queensland Ambulance A/Prof Richard De Abreu Lourenco, University of Technology Sydney
Research Proposals & Protocols	Advisory team as above
Data Analysis & Statistical Advice	Advisory team as above; with Dr Robyn Preston for qualitative analysis
DCE design & analysis advice	Prof Deborah Street, University of Technology Sydney
DCE Consumer Investigator	Mr Lux Anable
Scoping Review – Screening and Data Extraction	Dr Jackie Yim , University of Technology Sydney Dr Scott Jones, Radiation Oncology Princess Alexandra Hospital Raymond Terrace
Professional development, mentoring and peer support	Advisory team as above JCU Doctoral Cohort Program
Other Assistance	
Data entry & Transcribing	Ms Ashley Shackleford
Editorial	Katharine J. Fowler *Editorial intervention was restricted to Standards D and E of the Australian Standards for Editing Practice.*
Financial Support	
	Townsville Hospital and Health Service research grants CPHMVS College HDR support grant

Research Impact Arising from Thesis

1) Disinvestment in fiducial markers at Townsville Cancer Centre
2) Adoption of reduced margins with transperineal ultrasound motion monitoring for intact prostate cancer treatment at Townsville Cancer Centre

Note: Further detail regarding translation and impact is discussed in Chapter 7

Publications Arising from Thesis

Brown A, Pain T, Preston R. Patient perceptions and preferences about prostate fiducial markers and ultrasound motion monitoring procedures in radiation therapy treatment. J Med Radiat Sci 2021;68:37–43. https://doi.org/10.1002/jmrs.438.

Brown A, Pain T, Tan A, Anable L, Callander E, Watt K, et al. Men's preferences for image-guidance in prostate radiation therapy: A discrete choice experiment. Radiotherapy and Oncology 2022;167:49–56. https://doi.org/10.1016/j.radonc.2021.11.032.

Brown A, Tan A, Anable L, Callander E, de Abreu Lourenco R, Pain T. Perceptions and recall of treatment for prostate cancer: A survey of two populations. Tech Innov Patient Support Radiat Oncol 2022;24:78–85. https://doi.org/10.1016/j.tipsro.2022.10.001.

Brown A, Yim J, Jones S, Tan A, Callander E, Watt K, et al. Men's perceptions and preferences regarding prostate cancer radiation therapy: A systematic scoping review. Clin Transl Radiat Oncol *in press* https://doi.org/10.1016/j.ctro.2022.10.007.

Contributions of Others to Publications

Chapter	Publication	Authors
2	**Brown A,** Pain T, Callander E, Watt K, Tan A. Reducing margins in prostate cancer image-guided radiation therapy: a pilot randomised controlled trial *Currently Under Review with Journal of Medical Radiation Sciences*	AB designed the study with the assistance of TP, AT, EC and KW. AB recruited, organised and collected questionnaire data. Data input was partly outsourced through a research grant, and the rest completed by AB. AB led analysis, with interpretation input from all authors. AB wrote the manuscript. All authors provided critical revision, editing and approved the final manuscript.
3	**Brown A,** Pain T, Preston R. Patient perceptions and preferences about prostate fiducial markers and ultrasound motion monitoring procedures in radiation therapy treatment. J Med Radiat Sci 2021;68:37–43.	AB designed the study with the assistance of TP and RP. AT, EC and KW provided comments on the study protocol. AB recruited, collected questionnaire data and undertook all interviews. Transcription was outsourced through a research grant. Thematic analysis was led by AB, with input from TP and RP. AB wrote the manuscript. All authors provided critical revision, editing and approved the final manuscript.
4	**Brown A,** Pain T, Tan A, Anable L, Callander E, Watt K, et al. Men's preferences for image-guidance in prostate radiation therapy: A discrete choice experiment. Radiotherapy and Oncology 2022;167:49–56.	AB designed the study with the assistance of TP, AT, LA, EC, KW, DS and RDAL. DS completed the DCE design, with AB constructing the rest of the survey with input of all authors. AB and TP managed participant queries. Analysis was led by AB with the mentorship of RDAL. All authors contributed to data interpretation. AB wrote the manuscript. All authors provided critical revision, editing and approved the final manuscript.
5	**Brown A,** Tan A, Anable L, Callander E, de Abreu Lourenco R, Pain T. Perceptions and recall of treatment for prostate cancer: A survey of two populations. Tech Innov Patient Support Radiat Oncol 2022;24:78–85.	AB designed the study with the assistance of TP, AT, LA, EC, KW and RDAL. AB and TP managed participant queries. Analysis was led by AB, with interpretation input from all authors. KW provided statistical advice. AB wrote the manuscript. All authors provided critical revision, editing and approved the final manuscript.
6	**Brown A,** Yim J, Jones S, Tan A, Callander E, Watt K, et al. Men's perceptions and preferences regarding prostate cancer radiation therapy: A systematic scoping review. Clin Transl Radiat Oncol 2023;38:28–42.	AB designed the study with the assistance of TP, AT, EC, KW, RDAL, JY and SJ. Manuscript screening was undertaken by AB, with JY and SJ. Data extraction and analysis was led by AB with JY and SJ. AB wrote the manuscript. All authors provided critical revision, editing and approved the final manuscript.

Author initials: AB – Amy Brown; TP – Tilley Pain; AT – Alex Tan; EC – Emily Callander; KW – Kerrianne Watt; RDAL – Richard De Abreu Lourenco; RP – Robyn Preston; DS – Deborah Street; LA – Lux Anable; JY – Jackie Yim; SJ – Scott Jones

Additional Publications During Candidature Demonstrating Research Capacity

de Silva K, **Brown A,** Edwards C. Impact of transperineal ultrasound on perineal skin dose in prostate radiation therapy. Tech Innov Patient Support Radiat Oncol 2022;23:27–32. https://doi.org/10.1016/j.tipsro.2022.08.003.

Brown A, Edelman A, Pain T, Larkins S, Harvey G. "We're Not Providing the Best Care If We Are Not on the Cutting Edge of Research": A Research Impact Evaluation at a Regional Australian Hospital and Health Service. Int J Health Policy Manag 2022:1–12. https://doi.org/10.34172/ijhpm.2022.6529.

Brown A, Jones S, Yim J. Health preference research: An overview for medical radiation sciences. J Med Radiat Sci 2022;69:394–402. https://doi.org/10.1002/jmrs.580.

Vaitiekunas L, Coomer K, Turner C, **Brown A,** Sabesan S. Medical Oncology Care Plan: a tool for improving the provision of clinical information to patients. Intern Med J 2021;51:1332–5. https://doi.org/10.1111/imj.15449.

Joshi A, Larkins S, Evans R, Moodley N, **Brown A,** Sabesan S. Use and impact of breast cancer survivorship care plans: a systematic review. Breast Cancer 2021;28:1292–317. https://doi.org/10.1007/s12282-021-01267-4.

Smith J, Woolley T, **Brown A,** Vangaveti V, Chilkuri M. Smoking cessation in head and neck cancer patients: Factors influencing successes and failures. J Med Imaging Radiat Oncol 2021;65:233–41. https://doi.org/10.1111/1754-9485.13158.

Otty Z, **Brown A,** Sabesan S, Evans R, Larkins S. Optimal Care Pathways for People with Lung Cancer-a Scoping Review of the Literature. Int J Integr Care 2020;20:14. https://doi.org/10.5334/ijic.5438.

Shanker MD, Kim ANH, **Brown A,** Tan AHM. Anatomical and dosimetric assessment of the prostate apex: A pilot comparison of image‐guided transperineal ultrasound to conventional computed tomography simulation. J Med Imaging Radiat Oncol 2020;64:839‐44. https://doi.org/10.1111/1754-9485.13045.

Edelman A, **Brown A,** Pain T, Larkins S, Harvey G. Evaluating research investment and impact at a regional Australian Hospital and Health Service: a programme theory and conceptual framework. Health Res Policy Syst 2020;18:30. https://doi.org/10.1186/s12961-020-0542-y.

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Sabesan S, **Brown A,** Poxton M, et al. Implementation of a Teletrial model in the Northern Cluster (North Queensland, Australia): A Case Study. Asia Pac J Clin Oncol 2019;15(S8):3–14. https://doi.org/10.1111/ajco.13249

Sabesan S, Senko C, Schmidt A, Joshi A, Pandey R, Ryan CA, Lyle M, Rainey N, Varma S, Otty Z, Ansari Z, Vaughan K, Vangaveti V, Black J, **Brown A** Enhancing chemotherapy capabilities in rural hospitals: Implementation of a telechemotherapy model (QReCS) in North Queensland, Australia. J Oncol Pract 2018;14. https://doi.org/10.1200/JOP.18.00110.

Brown A, Tan A, Cooper S, Fielding A. Obesity does not influence prostate intrafractional motion. J Med Radiat Sci 2018;65:31–8. https://doi.org/10.1002/jmrs.255.

Awards, Presentations and Supervision During Candidature

Grants & Funding

Project Title	Amount	Date	Funding Body	Status
Specific to PhD				
Patient preferences and perspectives, and clinical considerations in motion monitoring during prostate radiation therapy treatment *(Principal Investigator – PhD Scholarship)*	$30,500	June 2021	Townsville Hospital and Health Service SERTA	Completed
Patient preferences for image guidance procedures during radiation therapy for prostate cancer: a discrete choice experiment *(Principal Investigator)*	$22,000	June 2019		Completed
Health Technology Assessment of The Clarity Autoscan System *(Principal Investigator)*	$11,290	June 2017		Completed
Related to PhD				
Clarity Autoscan Implementation & Evaluation *(Principal Investigator)*	$319,000	Sept 2017	QH New Technology Funding and Evaluation Program	Completed
Other – demonstrating capacity as researcher				
Analysis of seminal vesicle motion in patients treated on the MR-linear accelerator *(Co-investigator)*	$48,600	Aug 2022	Townsville Hospital and Health Service SERTA	In Progress
Evaluation of the impact of a radiation therapist-led model of care for Magnetic Resonance Linac adaptive cancer treatments *(Co-investigator)*	$41,379	Aug 2022		In Progress
Waiting time is marking time: Using a discrete choice experiment to explore patient preferences for choice of health professional and length of wait time when referred to public hospital outpatient clinics *(Co-investigator)*	$49,900	Aug 2022		In Development

Project Title	Amount	Date	Funding Body	Status
Evaluation of the impact of a radiation therapist-led model of care for Magnetic Resonance Linac adaptive cancer treatments *(Co-investigator)*	$28,730	Dec 2021	Health Practitioner Research Scheme	In Progress
Implementing a survivorship care plan for women with early breast cancer and evaluating its impact on value-based patient-centred outcomes *(Co-investigator)*	$43,070	Dec 2021	Tropical Australian Academic Health Centre Seed Funding	In Progress
Implementing a survivorship care plan for women with early breast cancer *(Co-investigator)*	$14,550	June 2021	Townsville Hospital and Health Service SERTA	In Progress
Building research leaders in allied health *(Co-investigator)*	$125,992	June 2021		In Progress
Patient experiences and perceptions of the new MR-Linac treatment machine in radiation oncology *(Co-investigator)*	$48,217	June 2020		In Progress
An economic evaluation of the costs and consequences of a clinical practice change in radiation oncology *(Co-investigator)*	$23,510	June 2020		In Progress
Implementation and evaluation of referral pathway for people with lung cancer in Townsville Hospital and health Service (*Co-investigator)*	$33,650	June 2020		In Progress
Analysis of the impact of radiologist training on accuracy of pelvic contouring *(Co-investigator)*	$49,910	June 2019		In Progress
Linking Research Engagement with Health System Performance: An Evaluation of Research Investment at THHS *(Principal Investigator)*	$49,238	July 2018		Completed

Awards

2021	Townsville Health Research Showcase – Best Presentation
	Rick Speare Award for Outstanding Oral Presentation (James Cook University)
	My Research Rules (James Cook University) – Runner Up, Late PhD Candidate
2020	My Research Rules (James Cook University) – Runner Up, Late PhD Candidate
2019	Health Services Research Association of ANZ 11th Conference 3MT winner
2018	Runner up - Rick Speare Award for Outstanding Oral Presentation (James Cook University)
2017	Townsville Hospital and Health Service Excellence in Clinical Research Allied Health - 2017

Conference Presentations

***Denotes PhD Related presentations**

Invited Keynote	"Meaningful Consumer Engagement in Health Research: A Call to Action," TropiQ Research Symposium (November 2022)
***Presentation**	ASMIRT (May 2022) **-** "Men's preferences for image-guidance in prostate radiation therapy: a discrete choice experiment"
***Presentation**	ANZUP ASM (Oct 2021) **-** "Men's preferences for image-guidance in prostate radiation therapy: a discrete choice experiment"
***Presentation**	RANZCR ASM (Oct 2021) – "Improvement in male pelvis magnetic resonance image contouring following radiologist-delivered training"
***Poster**	RANZCR ASM (Oct 2021) – "Men's preferences for image-guidance in prostate radiation therapy: a discrete choice experiment"
***Presentation**	Townsville Health Research Showcase (Oct 2021) "Men's preferences for image-guidance in prostate radiation therapy: a discrete choice experiment"
Presentation	Townsville Health Research Showcase (Oct 2020) "An evaluation of research investment and impact at a regional Australian hospital"
***Presentation**	Townsville Health Research Showcase (Oct 2020) "'You've gotta do what you've gotta do'. Prostate cancer patients' perspectives on image guidance in radiotherapy"
Presentation	11th Health Services and Policy Research Conference in Auckland (Dec 2019) – "An evaluation of research investment and impact at a regional Australian hospital"
***Presentation (3MT)**	11th Health Services and Policy Research Conference in Auckland (Dec 2019) "You've gotta do what you've gotta do'. Prostate cancer patients' perspectives on image guidance in radiotherapy."

Invited Keynote	"Real-time prostate tracking with Clarity Autoscan: Townsville Cancer Centre experiences," Elekta Australasian User's meeting (November 2017).
Presentation	ASMIRT (March 2017) - "Implementation of ultrasound-guided intrafraction monitoring and correction in prostate cancer treatments at Townsville Cancer Centre"

Supervision

Current Co-Supervisor

Honours Student (Queensland University of Technology), expected completion November 2023

Topic: Hypofractionation utilisation in radiation therapy: a regional department evaluation

Honours Student (Queensland University of Technology), expected completion November 2022

Topic: Evaluation of the utilisation of a 6 degree of freedom couch in a radiation therapy department

Previous Supervision

Honours Student (Queensland University of Technology), completed in 2021 with First Class

Topic: A comparison of intrafraction magnetic resonance image soft tissue changes in pelvis radiation therapy patients

Honours Student (Queensland University of Technology), completed in 2020 with First Class

Topic: Dosimetric Impact of the Clarity Autoscan Ultrasound Probe Pressure in Perineal Skin Dose in Prostate Cancer Patients

Abstract

Introduction

The treatment of prostate cancer (PCa) can be a complex journey for the patient, with a number of treatment options for them to consider. Radiation therapy is but one treatment option which is continually advancing in technology and treatment techniques. A critical advance over the last decade has been image-guidance radiation therapy (IGRT) whereby imaging is used either prior to treatment delivery to correct the target area positioning for radiotherapy delivery for day-to-day anatomical differences (known as interfraction motion), or intrafraction motion monitoring, to monitor and correct for any prostate motion during radiation delivery.

The requirements to perform prostate motion monitoring can result in very different experiences for the patient. Two main technologies utilised in monitoring prostate motion are: 1) fiducial markers (FM) inserted in the prostate during a once-off surgical procedure and used to track motion throughout treatment delivery, and 2) transperineal ultrasound (TPUS) used to monitor prostate motion, requiring daily placement of an external ultrasound probe against the patient's perineum during treatment.

This thesis aimed to use a patient-centred approach to improve prostate cancer radiation therapy, through evaluation of different aspects of prostate motion monitoring in radiation therapy treatment, including clinical considerations and patient perspectives.

Methods

A number of studies were conducted, using different methods to answer five research questions.

Firstly, a pilot single-blinded randomised control trial (RCT) was conducted to evaluate the clinical outcomes of reduced margins (n=26) in conjunction with TPUS monitoring, with a control arm of standard margins (n=27). Clinician-graded toxicity and patient reported outcomes during radiation therapy treatment and up to 2 years follow up were evaluated and compared.

Secondly, perspectives of the patient experiences with fiducial marker insertion and TPUS were explored through a sequential explanatory mixed methods study. A quantitative experience survey followed by qualitative interviews was conducted. The survey data were analysed using descriptive and inferential statistics, and interviews using thematic analysis.

Thirdly, a discrete choice experiment (DCE) was undertaken to elicit preferences for image-guidance in men with prostate cancer and men from the general population. The DCE was developed from the qualitative findings, a literature review and expert consensus. Analysis included multinomial logit modelling (MNL), latent class analysis (LCA), and calculation of marginal willingness to pay.

Fourthly, as part of the DCE survey, free-text comments provided by both cohorts included in the DCE were analysed using content analysis. Additional questions asked only of respondents with PCa to recall their PCa treatment/s and their responses were compared to hospital records. The patient recall and hospital records were analysed using proportion statistics and kappa coefficient.

Finally, a scoping review investigating patient' perspectives and preferences for prostate radiation therapy was undertaken to situate the above studies within the current literature.

Results

Overall, the pilot RCT found low toxicity in both control (n=27) and intervention arms (n=26). There was a statistically significant reduction in toxicity rates for gastrointestinal toxicities (flatulence (p=0.03) and bloating (p=0.03)) for acute toxicities, and proctitis for late toxicities (p=0.02) in the intervention arm of reduced margins. There was greater frequency of urinary retention in the control group (p=0.04). Quality of life (QOL) varied amongst participants, with no significant differences found between arms. The reduced margins in the intervention arm necessitated more treatment delivery pauses and corrections to ensure accuracy of delivery. One or more pauses due to prostate motion outside of margin threshold were required in 92% of patients in the intervention arm compared to 26% of patients in the standard arm.

The perceptions of patients (n=40) who experienced both TPUS and FM varied considerably as demonstrated in the mixed-methods study. 46% of the 40 respondents reported FMs more

invasive than US and 49% reported the same level of invasiveness for the two procedures. The mean scores for grading invasiveness of FM and TPUS were 3.6 and 2.1 (respectively) out of a possible 10. While mean scores were higher for FMS (pain: 3.3; physical discomfort: 3.2; psychological discomfort: 2.9) than TPUS (1.1, 1.2 and 1.7 respectively), the only significant between group difference was the pain score ($p<0.05$).

Three themes emerged from the interviews (n=22): expectations versus experience; preferences linked to priorities; and motivations. Eleven patients (50%) preferred TPUS; however, 10 (45%) could not express a preference, predominately due to indifference or a deference to trust in the health professionals.

Results from the DCE demonstrated that the most important attributes for both PCa patients (n=236) and general population (n=240) in choosing between alternative approaches to image guidance were pain, cost and accuracy ($p < 0.01$), based on relative attribute importance. PCa patients were willing to pay more to avoid the worst pain than the general population, and willing to pay more for increased accuracy. Three groups were revealed in the LCA: two were focused more on the process-related attributes of pain and cost, with Class 1 (28.9%) also considering side effects, and Class 2 (34.3%) also considering additional appointments; and Class 3 (36.8%) focused on the clinical efficacy attributes of accuracy and side effects.

Content analysis of free-text comments in the DCE survey resulted in five themes: sharing experiences of treatment; preferences insights and reflections, mindsets; survey feedback; and factors missing from the DCE attributes. Recall of treatment amongst men with PCa was good, with proportions of correct recall ranging from 97.3% to 66.8% (for receipt of prior chemotherapy and hormones, respectively). Proportions of men with PCa correctly recalling IGRT related procedures were 87.3% for TPUS and 91.4% for FMs. There was a tendency for younger men (<70 years old) to recall their hormone treatment more correctly.

The scoping review demonstrated a paucity of literature regarding patient preferences and perceptions for prostate cancer radiation therapy. Twenty-seven studies were included covering major themes of information needs, preferences and decisions, general experiences, side effects and support. There were only four preferences studies, with remaining reporting

on perceptions, which when considering the breadth of clinical and technical evidence regarding prostate cancer radiation therapy, highlights future research opportunities.

Conclusion

Reducing margins in conjunction with prostate motion monitoring during prostate cancer radiation therapy was feasible in the pilot study however further validation is recommended. From the patient perspective, TPUS is acceptable and tolerable. Men with prostate cancer and men from the general population of Australia preferred IGRT with less pain, less cost and increased accuracy, although men with prostate cancer were willing to pay more for increased accuracy and less pain. Previous treatments and image-guidance techniques were recalled by men with prostate cancer to a high level, however hormone therapy treatment recall was poorer.

This PhD fills the knowledge gap regarding the acceptability of TPUS, and the preference for IGRT by patients and also men in the community. It has led to local practice change of disinvestment in fiducial markers and adoption of reduced margins. Suggested areas of future work include further outcomes research with prostate motion monitoring and contemporaneous hypofractionated treatment schedules, further exploring poor recall of hormone therapy, and further embedding patient perceptions and preferences in prostate radiation therapy treatment.

Table of Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Term
ABS	Australian Bureau of Statistics
ADT	Androgen deprivation therapy
CBCT	Cone Beam computed tomography
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCE	Discrete choice experiment
EBRT	External beam radiation therapy
ED	Erectile dysfunction
EORTC	European Organization for Research and Treatment of Cancer
FM	Fiducial markers
GenPop	General population
HTA	Health technology assessment
IGRP	Image-guidance related procedure
IGRT	Image-guided radiation therapy
IMRT	Intensity modulated radiation therapy
kV	Kilovoltage
LCA	Latent class analysis
MNL	Multinomial logit modelling
MR	Magnetic resonance
MRL	Magnetic resonance linear accelerator
PCa	Prostate cancer
PSA	Prostate-specific antigen
PTV	Planning target volume
QOL	Quality of life
RCT	Randomised controlled trial
RT	Radiation therapy *(also known as radiotherapy)*

Abbreviation	Term
SBRT	Stereotactic body radiation therapy
TCC	Townsville Cancer Centre
THHS	Townsville Hospital and Health Service
TPUS	Transperineal ultrasound
VMAT	Volumetric modulated arc therapy
WTP	Willingness to pay

Preface: A Self Reflection

The reality of research in an ever-changing clinical practice environment

Self-reflexivity

This preface outlines my self-reflexivity, positioning myself as the researcher. I am particularly grateful to the Cohort program for learnings and advice in adopting reflexivity, regardless of quantitative or qualitative methodologies. I am also guided by the work of Davis (2020).[1]

My first research project

I conducted my first research project in my backyard when I was about 9 years old. There was a garden bed full of bromeliads, the type of plant with a spikey leaf structure that collects water. That summer I realised that the garden was a mosquito breeding ground. I set about to find a solution that 1) would either kill the larvae or at least discourage the mozzies from laying in the standing water and 2) wouldn't kill the bromeliad itself. I raided the kitchen (unbeknownst to my parents) and devised an experiment. In a quarter of the plants, I put salt; in the next quarter, sugar; in the next, vinegar; and in the final, chilli powder. I used an old turkey baster to extract some of the water/mix into a clear takeaway container and counted the larvae and recorded it in a notebook and repeated this a number of times during 'the great summer experiment'. The result: bromeliads are tough, but so are larvae – there was no distinguishable difference to either plant or mosquito count. From memory, I kept this up for about a week until my attentions were drawn elsewhere – to other fun summer holiday activities like art, beach trips and backyard cricket.

It will come as no surprise to anyone who knows me, I've always been somewhat 'nerdy'. When it came to selecting subjects for my senior years of high school, I choose all three sciences (biology, chemistry and physics) but also art – I've always been drawn to creative pursuits and expressions. Little did I know or appreciate that research would allow me to stretch both scientific and creative muscles.

My clinical career

My career choice came about through research, of sorts. In my early years of high school I was already considering a health career (see above subject list!) and it was my original intent to pursue medicine. My high school offered a program that gave participants an overview of different health careers, including a hospital/facility tour. While I remained determined to study medicine, I did take note of one profession that I had never heard of: radiation therapy, the delivery of radiation to treat cancer. Radiation therapy was essentially mentioned in passing, but I remember being struck by the combination of very technical knowledge skills combined with patient care. Fast forward a few years and, after re-evaluating my options after a year of studying biomedicine, I applied for radiation therapy. Ultimately, I wanted a career where I could help people, but also be intellectually stimulated.

In beginning my clinical career, I took a position at a regional hospital, signing a contract for four years. The plan of my husband and I was to see the four years out and then consider 'moving on' to another city. However, we quickly became embedded in the city through work, other pursuits and social communities. And so, we remained. This allowed me to progress in my clinical career, with opportunities afforded to me that would not be so readily available in other departments. It also means I have only ever known the one department, and one hospital service. This can be both an advantage and disadvantage when brought to a research project, something I am mindful of. Being actively involved in various committees and groups such as the Queensland Health State-wide radiation therapy research group as well as national and international conferences and meetings, I ensure my research remains externally valid outside of our own department.

I very much enjoyed being a radiation therapist. I particularly appreciate that we get to know and build a rapport with the patients we are treating, as we see them on a daily basis for up to 8 weeks. I also like the technical challenges in planning (also known as dosimetry) – this involves working with the radiation oncologist to tailor a treatment plan individualised to the patient. I like that the field of radiation oncology is very technology-driven, and that we are always improving our treatments.

Finding research passion

My first research project in my career was somewhat of an accident. Towards the end of the first year of my clinical practice, the department director asked for volunteers to conduct a small pilot study. I put up my hand, as my contract was for another three years, and I thought it wise to get involved in the department. Until then, my only other formal research exposure was undertaking a literature review at university. Little did I know that I would find my passion for research in this small departmental study. It was nothing particularly novel, but I loved it... and better yet, we changed practice because of it (albeit several years later after toppling down a few hurdles). Over the next 10 years I developed my clinical and technical competencies and skills, and dabbled in education and management, but kept coming back to research as my passion. I came to realise that the days I was rostered to research were the days I most looked forward to going to work.

PhD Journey

When I embarked on my PhD journey, I had completed my research masters approximately five years prior, and continued to be involved in departmental research. My main research interests were in improving prostate radiation therapy through understanding prostate motion, and patient reported quality of life. My own research pursuit took a backseat as I supported my husband in completing his PhD (we decided that for the sake of stress levels, we would avoid being PhD candidates concurrently!).

An opportunity to implement a new technology serendipitously aligned with the right timing to put together my PhD proposal: transperineal ultrasound (TPUS). TPUS, also known by the vendor name “Clarity”, monitors for prostate motion during radiation therapy. The Clarity implementation aligned closely with my research interests, and I resonated with the saying attributed to Seneca: “Luck is what happens when preparation meets opportunity”. While I very much wanted a clinical outcomes focus, I also wanted to stretch myself by learning some qualitative research methods, and had a very early interest developing in health economics after a ‘crash course’ of 3 days, so I set about incorporating both of these into my PhD.

I’ll admit, I came to Clarity with a personal view/bias: would patients really allow us to apply an ultrasound probe to their perineum every day for treatment? The vendor assured me it

was well tolerated in other centres using it around the world, but having been in the room assisting fiducial insertions and witnessing the men's embarrassment during this procedure, I had my doubts. I didn't want to only go on the vendor's word.

By the time we started recruiting to my study, we had treated approximately 60 patients with Clarity and hadn't had one man refuse. As I built rapport with this initial Clarity cohort, I would chat to those first few patients we treated about their experiences, and they very kindly did pilots on my survey and one man generously did a pilot interview with me. I very quickly shook off my pre-conceived notion that the TPUS would be too embarrassing. While the "gotta do what you gotta do to treat the cancer" theme hadn't fully cemented (it did so in the first few research interviews), I realised that these men were focused on treating the cancer, and they placed their trust in us to do so. What a privilege! However, with my initial personal view in mind, the investigator-developed questionnaire and the interview questions were carefully developed and piloted to ensure there was no bias.

As often happens in research, I went into the PhD journey with what I considered to be a solid plan… only to encounter the unforeseen realities of clinical research. Clinical practice changed during my RCT recruitment: firstly, a regional cancer centre opened in the hospital catchment area, which meant fewer referrals; secondly, there was a shift in referral patterns with more patients undergoing a prostatectomy rather than primary radiation therapy; thirdly, an evidence-based change in fractionation from 39 fractions to 20 fractions was implemented at our centre. The change in fractionation, with equivalent dose delivered over a shorter amount of time, meant that there may be differences in clinical outcomes due to the fractionation (particularly side effects), and not the margin reduction being investigated. While it was considered, my advisors and I decided not to amend the protocol to incorporate different fractionations. Finally, in early 2020 (and in tandem with the fractionation changes), the COVID-19 pandemic meant that the majority of prostate cancer patient's radiation therapy courses were delayed (while remaining on hormone therapy treatment) while we waited to see how the pandemic would 'pan out' in Australia. At this point, RCT recruitment was ceased.

I was also surprised at the decline rate of those approached to consider participation in the RCT. Admittedly, up until this study I had not personally recruited to an RCT, only to observational-type studies. In previous experience recruiting and consenting patients, there

was an overwhelming sense of altruism, agreeing to participate with the understanding that the research may not personally benefit themselves but help future patients. I found that when there was a change proposed to their personal treatment there was more reticence. Interestingly enough, some men I approached wanted to be assured allocation to the experimental arm, whereas one man wanted to be assured allocation to the control arm. While I can understand the drivers for such choices, I found myself explaining that I was grateful that they were interested but could not recruit them to a particular arm, and therefore could not recruit them into the study. As a clinician and researcher, this gave me further insight into the mindsets and decision-making of our patients.

The early close of the RCT meant the original plan of conducting an economic analysis and health technology assessment (HTA) were abandoned. I have a keen interest in health economics and wanted to incorporate this within my PhD. I also recognised the opportunity for an HTA around the Clarity system – something which I believe is not robustly undertaken with many new technologies in Radiation Oncology (discussed further in Chapter 7: Discussion and Conclusion).

The patient perspective

While initially being very clinically focused, my research interests have shifted, or perhaps more correctly, expanded to understand the patient perspective. I'll confess, previously I had thought that collecting patient QOL was engagement. It certainly begins to capture the patient perspective, but there's so much we as clinicians and researchers can learn from the patient. My PhD journey was my first, but not my last, foray into qualitative and mixed-methods research. The benefit of the patient perspective in addition to the quantitative and clinical/technical data is insightful.

I was also very conscious of this potential power imbalance when developing my PhD project, particularly the qualitative component. I wanted to do the patient interviews myself for my research learning, however also realised that patients may feel uncomfortable or may not tell me their whole perceptions if I was one of their treating radiation therapists. For this reason, we built into the protocol that the fact I may be treating them would be withheld at time of consent/interview, and if I was to treat a participant, I would give them the option to retract

their interview. As it turned out, by the time recruitment commenced, I had moved into full-time research and thus only encountered this potential conflict with one patient when I was called to relieve on treatment one day. He was very firm in his decision to allow the interview data to be kept, as he would not have said anything differently if he knew I would be treating him.

As I have developed a further interest in health literacy during this PhD, I gave a lot more thought to potential power imbalances, particularly regarding knowledge and understanding. My reflection was first prompted very early on when my personal view that experiencing two types of image-guidance should be enough for the patient to elicit a preference was challenged. It was during the interviews that I more fully appreciated that different people have different information needs, with some wanting to know the bare minimum and others wanting to know every small detail. But knowing and preferring also were revealed to be very different for individuals. I now have a much greater understanding of the knowledge imbalance between myself as a clinician-researcher and the patient. I believe in general, radiation oncology clinicians instinctively, but not necessarily intentionally, tailor information delivery to patient needs.

I was also aware of my different lens during the interviews with participants. Firstly, I have no personal insights into their perspective and experience, having only experienced the IGRT procedures from the clinician perspective. Secondly, as a younger female, some participants may not have been as open during interview as they may have been with a male interviewer – this was mitigated as much as possible by giving the participant an option to have someone else present, such as a partner. In memoing after each interview, I noted how most of the men openly shared about their experiences.

As a part of this PhD, I have incorporated a consumer investigator as part of the research team for the Discrete Choice Experiment study. Previous to my personal experience, I had viewed 'consumer engagement' as a buzz word, quite frankly. This is something I'm keen to engage with more – that is, where appropriate, to include consumer investigators. "Nothing about us without us" is the apt research request of Indigenous peoples, and I think this could apply in human research more broadly. The consumer investigator we worked with, Lux, brought so

much to every team discussion. Bringing lived experience to the research team strengthens the project, particularly a project investigating patient preferences.

It was an interesting experience – made more challenging by the fact the hospital had not previously had a consumer-investigator on an investigator-led project, so many discussions were had with the ethics committee and the governance office, as well as the hospital consumer-lead to agree upon processes. Hindsight being 20/20, I would now consider having a consumer-investigator co-interview with me, as this may lead to further insights given in interviews.

Research journey & career trajectory

Fortuitously, a research fellow position within my workplace was established part-way through my PhD. I have found that many of the 'mechanisms' of research that I had learnt through my own experience have become useful in this role. As I work across the cancer centre and not just in radiation oncology, I find myself continually challenged. I look forward to continuing my passion for research. My love for research was highlighted in the beginning of 2022, where due to a local surge of the COVID-19 pandemic, all research activity was paused from January into March, and researchers re-deployed to assist with clinical demands. While it was good to 'get back onto the tools' and spend those few months treating patients in radiation therapy, I was very glad when the pause was lifted, and I could return to my research role. I consider it a privilege to be able to undertake and support research full-time, and look forward to taking what I have learnt through my PhD into my continued research career.

What has changed during this PhD? What have I learnt during this PhD?

I now have a more nuanced understanding of the complexities experienced and perceived by prostate cancer patients – not just in choosing their primary treatment, but in going through their cancer pathway, traversing the information, the experiences, and the side effects. I now understand that while I thought simply experiencing two different kinds of image-guidance should be enough for a patient to articulate their preference for one over the other, for some men this is not the case. I appreciate through this PhD, how much trust the patient puts in the clinicians/treating team – a responsibility and an honour not to be taken lightly.

I recognise the value of consumer engagement through collaboration – they can bring so much of their patient experience and expertise to a research study, working with the clinicians/researchers.

I have gained a greater appreciation for qualitative and mixed-methods methodologies, and the rich data they provide. I thoroughly enjoyed my research interview experience. I reflected on each interview both immediately afterwards, and throughout the data analysis stages, completing memos throughout the process. I also specifically choose to participate in a number of qualitative studies with research interviews throughout my candidature. The purpose of this was two-fold: to gain an understanding of what it's like to be the interviewee in this setting; and to gain insight into how other researchers approach their interviews.

Local setting reflection

A majority of the data for this thesis was collected at the Townsville Cancer Centre (TCC) Radiation Oncology department of Townsville University Hospital (TUH), in Townsville, Queensland, Australia. The TCC Radiation Oncology department is the only public radiation therapy centre in Northern Queensland. TUH serves a population of 700,000 over a geographically dispersed area.[2] Additionally, more complex patients are referred from outside of this area for comprehensive cancer care including radiation therapy and chemotherapy. It is recognised however that the data, particularly the qualitative data, may have regional biases, and there may be some differences in patients residing in more metropolitan areas.

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Chapter 1 Introduction & Background

Radiation Therapy Treatment of Prostate Cancer

Prostate cancer is one of the most common cancers impacting men, for which radiation therapy is a primary treatment option.[1,2] Prostate motion that can occur during radiation therapy delivery is a challenge for treatment, causing potential differences in planned versus delivered dose to the prostate.[3–5] Developments in image-guidance technology to address the impacts of prostate motion continue and include insertion of fiducial markers or electromagnetic beacons that can be tracked during treatment delivery, and the use of other imaging modalities such as transperineal ultrasound (TPUS) or magnetic resonance to monitor organ motion in real-time.[6–10]

Improved clinical outcomes following real-time monitoring have been documented.[11,12] However, most literature reports technical or dosimetric advantages rather than measured clinical outcomes.[4,7,13] Importantly, the way patients experience these different image-guidance methods varies greatly. The insertion of fiducials or beacons requires a once-off surgical procedure, whereas the use of TPUS requires the placement of the probe against the patient's perineum each day of treatment.[14,15]

The overarching aim of this thesis was to improve prostate cancer patient care during radiation therapy treatment. This was achieved through two focus areas:

1) The clinical outcomes of reducing treatment margins with real-time prostate motion monitoring

and

2) The patient perceptions and preferences of different image-guidance techniques and related procedures.

Image-Guidance in Prostate Radiation Therapy

The use of image-guidance in the delivery of radiation therapy (also known as image-guided radiation therapy, or IGRT) to the prostate is now standard practice in most radiation oncology centres worldwide.[16,17] IGRT is utilised in the treatment of both intact prostate or post-prostatectomy radiation therapy, however this thesis focuses on intact prostate IGRT only. The ability to correct for daily variations in prostate position, known as interfraction motion, is achieved through imaging acquired prior to daily treatment delivery. Interfraction motion is well understood and is largely influenced by factors including bladder and bowel filling and systematic errors in daily patient set-up. The two most common methods for prostate IGRT are the implantation of surrogates for prostate position such as fiducial markers which can be detected by a linear accelerator's on-board imaging capabilities, or the use of cone-beam computed tomography with a soft-tissue match performed by the treating radiation therapists.[18]

Intrafraction prostate motion is the potential movement of the prostate during daily radiation delivery. This motion is largely characterised as a slow drifting motion due to bladder and bowel filling during treatment delivery, although may be a sudden, transient motion due to other factors including patient breathing changes (including coughing or sneezing), peristalsis, or tensing and releasing of the surrounding pelvic muscles.[19] The potential impact of intrafraction motion has been extensively studied through measuring motion and/or dosimetric studies.

There are several technological advances to monitor prostate motion, including surrogate monitoring (through fiducial markers (FM), electromagnetic beacons, or electromagnetic catheter), the use of non-ionising TPUS, or with the recent implementation of magnetic resonance capable linear accelerators, monitoring through magnetic resonance (MR) cine-imaging.[6–10,19–26]

Predominately, FMs are utilised to evaluate interfraction motion, and often utilised in conjunction with CBCT to allow for surrounding soft-tissue evaluation.[23,27] Some emerging techniques utilise the existing kilovoltage hardware of most linear accelerators to enable intrafraction FM monitoring however requires additional radiation dose.[28,29] Electromagnetic

beacons are implanted in a similar procedure to FMs, do not require additional radiation but do require additional equipment.[21,30,31] There are also reported body habitus limitations with the detector plate equipment, and increased capital costs and ongoing consumable costs for the beacons when compared with FM.[6,32] CBCT evaluates interfraction motion, however advances in technology are increasing the intrafraction motion capabilities, particularly if used in conjunction with FM.[31] Again, additional radiation dose is required for CBCT, and this increases with CBCT intrafraction monitoring.[31] TPUS can be utilised for both inter- and intrafraction motion monitoring.[33] Unlike CBCT, TPUS does not give complete soft-tissue information (such as seminal vesicle and bowel position) and therefore is often utilised primarily for intrafraction motion monitoring, in conjunction with CBCT for interfraction motion monitoring.[15] This thesis focuses particularly on TPUS motion monitoring, with some comparison to FMs.

Reduced Margins

Adding margins to the treatment target in radiation therapy accounts for set-up systematic and random errors during daily treatment delivery.[34,35] In prostate radiation therapy, one of the largest random errors is prostate motion. Prostate margins have historically been up to 1 cm to account for potential prostate motion during treatment which could not be easily monitored.[36]

With the increased accuracy of delivery provided by intrafraction motion detection and correction, margins can be safely reduced around the prostate target.[17] This reduction should theoretically lead to improved patient outcomes as fewer surrounding tissues, particularly the bowel and bladder, are irradiated, with an expected reduction in side effects.[37,38]

Clinical Outcomes

Clinical outcomes in prostate radiotherapy are measured through biological outcomes (such as biochemical recurrence detected through PSA tests, and the presence of metastatic

disease), toxicity and patient-reported outcomes such as quality of life. There is a balance to cure the cancer while minimising the side effects to optimise quality of life.

Toxicity, or side effects, occur either acutely (during, and up to 1 month post, treatment) or late (months to years after treatment). Common toxicities in prostate radiation therapy are summarised in Table 1.1.

Table 1.1
Overview of common toxicities associated with prostate radiation therapy treatment[39]

	Gastrointestinal	**Genitourinary**	**Other**
Acute	Diarrhoea	Cystitis	Fatigue
	Increased bowel frequency	Dysuria	
	Rectal Urgency	Nocturia	
	Pain	Frequency	
	Bleeding	Urgency	
		Retention	
Late	Proctitis	Cystitis	Erectile dysfunction
	Bleeding	Urethral stricture	Impotence
			Femoral fracture

There are a number of accepted toxicity grading systems utilised within radiation oncology. Our centre utilises the Common Terminology Criteria for Adverse Events (CTCAE) grading system.[40] This grading system rates each of the relevant toxicities on scale of 0 to 5, with 0 being no toxicity, and 5 being the most severe, with a defined scoring matrix for each symptom.

Patient-reported quality of life (QOL) outcomes are increasingly utilised within clinical practice.[41] There are several validated QOL measures available for research and clinical use. Two of the most commonly used within prostate radiation therapy research are the validated European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 form and the Expanded Prostate Cancer Index Composite (EPIC).[42–47]

In Australia, prostate cancer radiotherapy patients are monitored for up to 5-years post treatment by their radiation oncologist at which time they are discharged from the oncology clinic to the care of their general practitioner. Monitoring of tumour control occurs predominately through biochemical measures of PSA, however imaging such as MRI may also be ordered when warranted. Monitoring also includes toxicity outcome measures, particularly late side effects (Table 1.1).[39]

Clinical Considerations with Image-Guidance

The increased precision of intrafraction motion image-guidance is demonstrated to improve clinical outcomes in two key aspects:

1) Improved tumour control through more targeted treatment delivery.[12,48,49]
2) Less unintentional dose delivered to surrounding health organs/tissues, particularly rectal or bladder, during treatment delivery. This reduces toxicity, and improves QOL.[11,50]

There are, however, additional implications for radiation oncology departments to consider, including: capital outlay costs for equipment and associated ongoing consumables; staff training and IGRT competencies (such as specific image-matching); additional time on the treatment couch per fraction (for both application of the intrafraction monitoring, and any additional time to pause and correct for motion); and quality assurance requirements.

Patient-Centred Care: Experience and Preferences

Patients' experiences and their preferences are important when balancing cure of cancer, while optimising QOL through minimisation of side effects. There has been an increasing emphasis on patient-centred care in healthcare over the last decade or so, and this is no different in cancer care and radiation oncology.[51–53] Patient-centred care recognises that the care provided is happening to the patient, keeping them at the forefront with "care that is

respectful of and responsive to individual patient preferences, needs and values, and ensuring that patient's values guide all clinical decisions".[54]

Within Australia, the key domains of patient-centred care are defined as:

- Respect for patient's preferences and values,
- Emotional support,
- Physical comfort,
- Information, communication, and education,
- Continuity and transition,
- Care coordination,
- Involvement of family/carers, and
- Access to care

which are reflected within the Australia Safety and Quality Framework for Health Care.[55] To deliver patient-centred healthcare, the preferences of patients need to be enumerated and understood. Health preferences research is increasingly being utilised to understand patient preference, informing health policy and patient-centred care in oncology and more broadly.[56,57]

Discrete Choice Experiments

Discrete choice experiments (DCE) are one of a suite of patient preference elicitation and valuation methods, increasingly used within health research. DCEs elicit preferences of the respondents through a series of hypothetical choices presented to survey respondents.[58–60] Modelling of the choices made can inform the overall preferences of the study population and identify sub-sets of the study population based on differences in the choices made.[59,61]

Gaps in Knowledge

In developing this PhD program and its studies, a number of gaps in knowledge were identified:

- There was no prospective data published on reduced margins with real-time TPUS monitoring.
- The patient experience of TPUS was not documented, and much of the literature around FMs was focused only on side effects and tolerability rather than experience.
- There was no evidence on patient preferences for prostate IGRT.

Thesis Overview

To achieve the overarching aim to use a patient-centred approach to improve prostate cancer radiation therapy, two main focus areas of clinical considerations and patient perceptions and preferences were investigated, with a number of research questions developed (Figure 1.1):

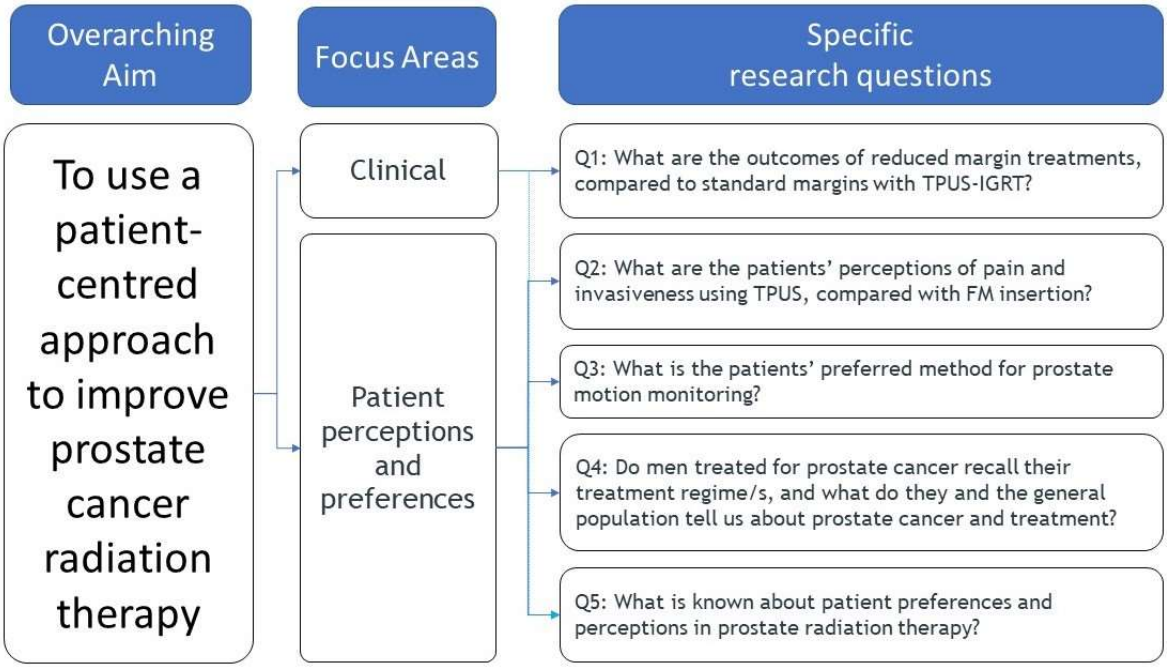


Figure 1.1 Schematic of overarching aim, focus areas & research questions of this PhD

Research Questions

1) What are the outcomes of reduced margins compared to standard margins with TPUS-IGRT?
2) What are the patients' perceptions of pain and invasiveness using TPUS, compared with gold seed insertion?
3) What are the patients' preferred method for prostate motion monitoring (if both methods are presumed to achieve the same outcome) and what factors do patients consider if choosing between different technologies and procedures?

These first 3 questions were developed as a part of my initial PhD proposal. The final two questions were developed after attempting to answer Question 3 around patient preferences. It was initially expected that because the participants within the sub-study answering Questions 2 & 3 experienced both procedures, that they would be able to articulate their preference for one or the other, however this was not the case. Thus, a discrete choice experiment was developed to more completely answer Question 3.

I also wanted to understand if previous patients who had prostate cancer could recall their treatment, as a measure of their understanding. There was little evidence in the literature of prostate cancer treatment recall, and none specifically regarding image-guidance.

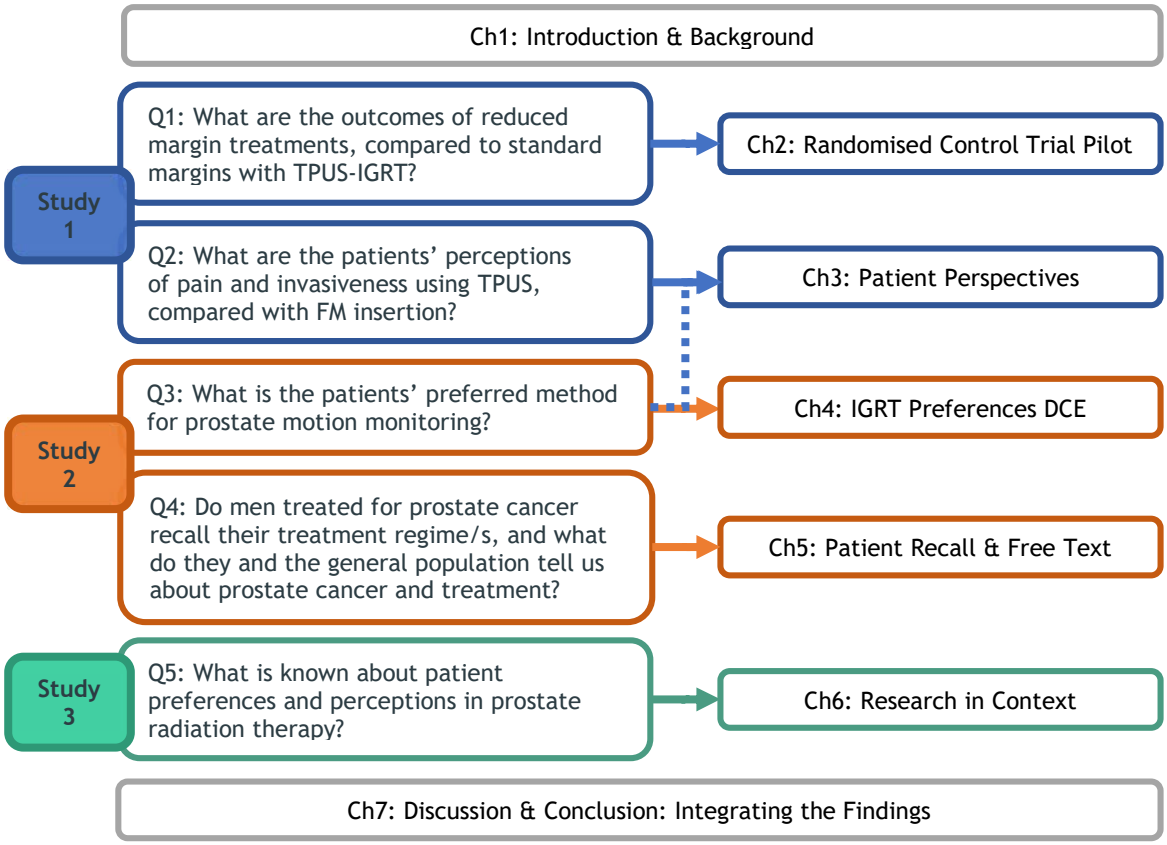
The volume of free-text comments provided in the DCE was unexpected, promoting further investigation into the importance of the comments provided. Thus, the following question was developed:

4) Do men treated for prostate cancer recall their treatment regime/s, and what do they and the general population tell us about prostate cancer and treatment?

Finally, I wanted to understand what the literature said about patients with prostate cancer and their preferences for radiation therapy, and thus a final research question was developed:

5) What is known in the literature about patients' perceptions of prostate cancer radiation therapy?

These questions were answered via three studies, presented in the chapters outlined in the schema of Figure 1.2. Chapters 2 to 6 represent a manuscript, as per Thesis by Publication guidelines. Concluding each chapter, an infographic is provided, distilling each manuscript into a translation format for the lay reader.



Note: TPUS: Transperineal Ultrasound; IGRT: Image-guided radiation therapy; FM: Fiducial Marker; DCE: Discrete Choice Experiment

Figure 1.2 Schematic overview of thesis

Chapter 2: RCT pilot study

Note: This study is currently under peer review with the Journal of Medical Radiation Sciences.

A randomised controlled trial pilot study was conducted, investigating the clinical outcomes of reducing the planning target volume (PTV) margins in prostate cancer image-guided radiation therapy. Outcomes measured include acute and late side effects and patient-reported outcome measures for up to two years post treatment completion.

Chapter 3: Patient perspectives

Note: This study was published in Journal of Medical Radiation Sciences.[62]

This study aimed to understand patients' perceptions and preferences for image-guidance. A concurrent triangulation mixed methods study was conducted, with participants completing an investigator-developed questionnaire, with a sub-sample invited to participate in a semi-structured interview. Participants were eligible if they had experienced both fiducial marker insertion and TPUS prostate monitoring.

Chapter 4: Patient preferences discrete choice experiment

Note: This study was published in Radiotherapy and Oncology.[63]

This chapter details the DCE to elicit preferences of a prostate cancer population and men in the general Australian population. Patients receiving a radiation oncology consult at Townsville Cancer Centre between 2011 and 2020 were invited to complete the DCE survey. Additionally, a general population sample were recruited through the online survey company Pureprofile, ensuring we had a representation of ages and locations throughout Australia. This allowed comparison of patient preferences with those of the general population, providing information for policymakers on what those in the wider community may prefer.

Chapter 5: Patient recall and free-text content analysis

Note: This study was published in Technical Innovations & Patient Support in Radiation Oncology.[64]

As a part of the follow up questions in the DCE survey, the prostate cancer population was asked to recall details of their prostate cancer treatment. They were given the choice to identify themselves to enable detail in their medical charts to be compared with their responses. This comparison allowed us to evaluate patient recall of treatment and image-guidance related procedures. The high level of engagement in responding to optional free-text comments allowed further analysis of preferences and perceptions regarding prostate cancer and its treatment

Chapter 6: Research in context

Note: This study was published in Clinical and Translational Radiation Oncology.[65]

A scoping review was undertaken to assess the breadth of literature regarding patient perceptions and preferences for aspects of prostate cancer radiation therapy. This was motivated by the two focus areas of the thesis, and serves to bring both clinical and patient preference focus areas together.

Chapter 7: Discussion: conclusion and future directions

This concluding chapter brings together the findings of the individual studies, and highlights the areas for future research.

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Chapter 2 Reduced Margins Pilot RCT

Article: Reducing margins in prostate cancer image-guided radiation therapy: a pilot randomised controlled trial

This manuscript is currently under peer review with the Journal of Medical Radiation Sciences.

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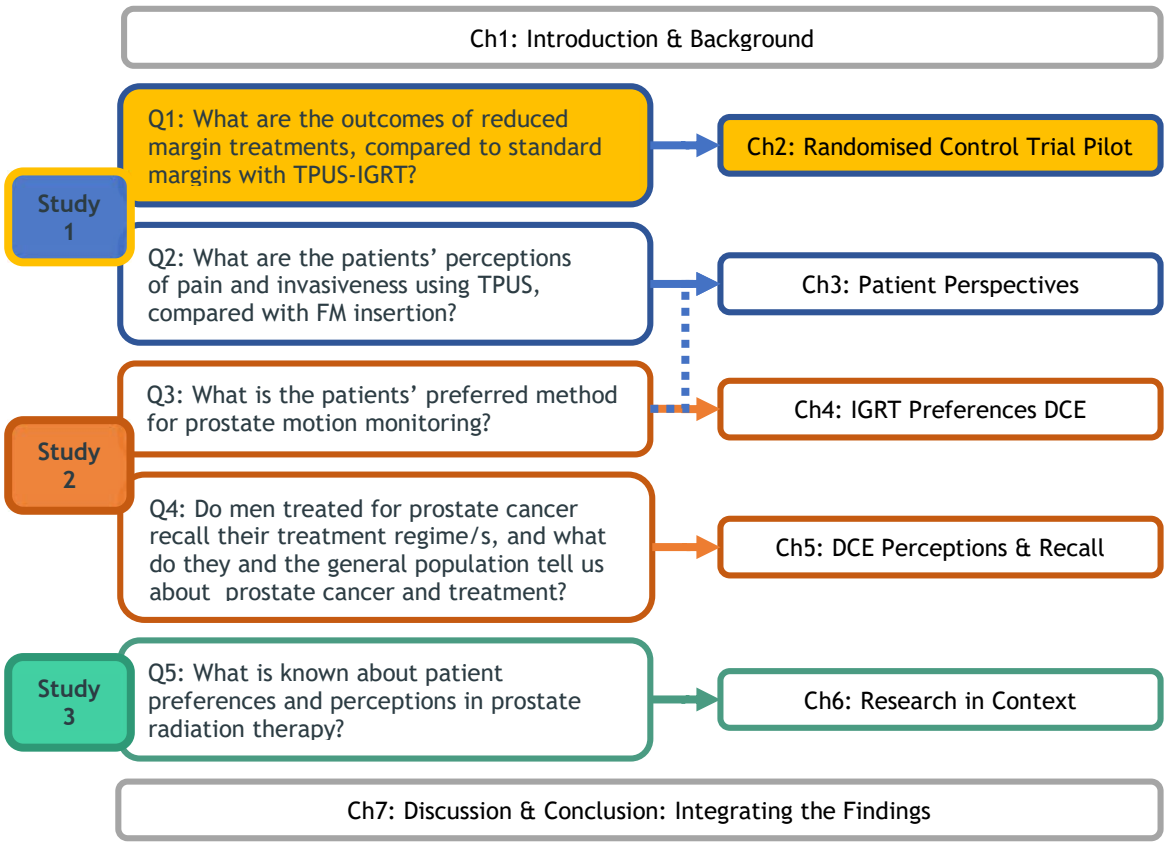
This chapter includes an exact copy of the submitted manuscript, except the formatting of section sub-headings, figure, table and reference numbers have been edited for the purpose of the thesis.



Note: TPUS: Transperineal Ultrasound; IGRT: Image-guided radiation therapy; FM: Fiducial Marker; DCE: Discrete Choice Experiment

Figure 2.1 Schematic overview of thesis: Study 1, Chapter 2

Context of study 1

This study was developed following a systematic literature review (Appendix G). The clinical motivation was to take advantage of the motion monitoring capabilities and increased accuracy of the recently installed TPUS system through reducing margins, while doing so under a controlled research study.

Abstract

Introduction

Novel motion-monitoring technology allows for more precise targeting in prostate cancer radiation therapy, potentially reducing toxicity and increasing quality of life (QOL). This study aimed to evaluate patient outcomes when treated with motion monitoring and reduced planning target volume (PTV) margins.

Methods

A pilot randomised controlled trial was conducted with 27 patients treated with standard PTV margins (control), and 26 patients with reduced PTV margins (intervention). Clinician-rated toxicity and patient-reported QOL during treatment and up to and including two years follow-up were analysed.

Results

While there were few significant differences in short-term toxicity during treatment, there was a reduction in long-term toxicity during follow-up in those treated with reduced PTV margins compared to standard PTV margins. For acute toxicity, there was a significant difference in bloating (p=0.01) and flatulence (p=0.01) with greater severity in the control group, and urinary retention with greater severity in the reduced margin group (p=0.02). In late toxicities, there was greater proctitis in the standard margin group (p=0.02). QOL varied across participants, however trended with a worsening at end of treatment and improving over time. The reduced margins in the intervention arm necessitated more treatment delivery pauses and corrections

Conclusions

This pilot study demonstrates the feasibility of reduced PTV margins with intra-fraction monitoring regarding toxicity and QOL, however further validation through larger studies is required.

Background

One of the challenges in treating prostate cancer with radiation therapy is the potential for prostate motion.[1,2] Traditionally, a "safety margin" is added to the prostate to allow for potential target motion.[3–5] The bladder and rectum, which are adjacent to the prostate, are quite sensitive to radiation and the cause for most radiation-related toxicities in prostate EBRT, with reported gastrointestinal (GI) late toxicities of 16.2% and genitourinary (GU) late toxicities of 28% in a meta-analysis of nine studies.[6] Reducing the safety margin, and consequently the volume of bladder and rectum irradiated, has the potential to reduce toxicity and increase quality of life (QOL). However, reducing the safety margin without means to correct for motion can potentially reduce efficacy of EBRT and increase toxicity.[7]

Technologies allowing real-time tracking of the prostate motion during radiation therapy delivery include the use of transperineal ultrasound (TPUS) TPUS is non-invasive, does not require additional radiation, and is well tolerated by the patient.[8] Thus, it poses no additional risk to the patient, and provides increased accuracy and certainty of radiation dose delivery to the prostate.[9] The existing evidence is mostly in phantom studies or small pilot studies and demonstrates the accuracy of the TPUS system in monitoring prostate position.[10–12]

With limited clinical data published, this study aimed to compare the outcomes of standard margins and reduced margins in TPUS-guided radiation therapy treatment of prostate cancer. The outcomes evaluated were clinician-rated toxicity and quality of life (QOL).

Methods

A single-blinded randomised controlled trial (RCT) was undertaken at a single institution. Institutional ethics approval was granted (HREC/17/QTHS/9 and H6970 – Appendix A). Participants provided written consent and were randomly allocated into a reduced margin

group (intervention) or a standard margin group (control) (Table 2.1). Randomisation occurred through block randomisation with a ratio of 1:1, with participants blinded to which group they were allocated.

Table 2.1
Planning target volume margin applied for each group

Structure	Group 1 (Intervention): Reduced margins	Group 2 (Control): Standard margins
Prostate	5mm isotropic except 3mm in the posterior direction	10mm isotropic except 7mm in the posterior direction
Seminal Vesicles (Proximal)	1cm isotropic except 7mm in the posterior direction	

Participants were eligible if they had a histologically confirmed malignant neoplasm of the prostate, were referred for radical radiation therapy and were suitable for both fiducial marker implementation and TPUS tracking capabilities. Participants were excluded if they had evidence of distant metastases, had a life expectancy of less than a year due to other illness which would prohibit follow-up, or were not capable of completing the questionnaires due to cognitive, language or literacy difficulties.

All patients, regardless of standard or reduced margin group allocation, received 78Gy in 39 fractions, utilising an Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) technique, with real time prostate motion monitoring through the Clarity Autoscan TPUS system (Elekta Ltd, Missouri, USA). The threshold to pause treatment delivery and make a correction was determined by the PTV margins, that is 5mm isotropic except 3mm in the posterior (Intervention) and 10mm isotropic except 7mm in the posterior (Control). A brief transient motion necessitated only a pause in treatment delivery only, , whereas a correction was required when a slow, drift motion occurred.[13] Prostate motion data was extracted for analysis from the TPUS system. All patients had bladder and bowel preparation prior to each treatment as per departmental protocol, consisting of an empty rectum through a stool softener and a full bladder achieved through drinking a pre-determined volume of water at a specified interval prior to treatment.

Urinary and bowel toxicity was scored by the treating radiation oncologist or radiation oncology registrar using the Common Terminology Criteria for Adverse Events (CTCAE)

gradings V4[14] and entered into the MOSAIQ oncology information management system (Elekta Ltd, Missouri, USA). Clinicians were not blinded to the arm of the participant, as they generate the margins at time of planning.

QOL was measured via self-report, specifically the validated European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, along with the prostate-specific PR25 module; [15,16] and the EuroQOL EQ-5D were used.[17]

Baseline QOL data was captured at the participant's CT simulation appointment. Toxicity and QOL data were captured every 2 weeks during treatment (defined as acute) and at follow up (3-, 6-, 12- and 24-months post treatment completion; defined as late). Questionnaires during treatment were given to the patient by treatment staff to complete and return at the next fraction. Questionnaires during follow up were posted to the patient, with a postage-paid envelope to return.

Statistical analysis

Characteristic differences between groups were analysed with fisher's exact or Mann-Whitney U tests. The QLQ-C30 and PR25 QOL scores were linearly adjusted according to the EORTC scoring manual. GI and GU toxicities were combined for further analysis. The between-group differences in toxicity and QOL using fisher's exact tests. Analyses were undertaken using R statistical software, with a p-value of <0.05 considered significant.

Results

Demographics

A total of 73 eligible patients were approached consecutively to consider the RCT from May 2017 to March 2020. Sixteen declined, with two men citing they wanted to dictate which treatment group they were assigned, 14 indicating they were not interested (10 indicating lack of interest due to the QOL questionnaire commitment), and two did not give a reason for declining. One patient approached agreed to be a part of the mixed-methods sub-study only, but not the RCT.[18]

A total of 56 patients were recruited, with 28 randomised to the reduced margin group and 28 to the standard group. Three patients were not included in analyses: one patient did not complete any QOL data (control group), one patient did not complete the course of treatment due to another urgent medical issue arising unrelated to the prostate cancer (intervention group), and another patient had a separate serious medical issue 2 weeks after completing treatment and was not suitable for long-term follow up (intervention group). Therefore, 27 patients in the control group and 26 patients in the intervention group were included in final analyses. There were no significant differences in characteristics between the groups (Table 2.2). There was a decrease in return rate of questionnaires over time (Table 2.4 (supplementary).

Motion frequency

There were a total of 22 fractions (1%) requiring a table correction during treatment delivery due to prostate motion, four in the standard group, and 18 in the reduced group (Table 2.2). Prostate motions requiring correction were predominately in the posterior and superior directions (Table 2.2).

Table 2.2
Patient characteristics

	Control: Standard (n = 27)		Intervention: Reduced (n = 26)	
	n	%	n	%
Age at consent (years)*		74.0 (SD: 7.1)		73.9 (SD: 6.2)
Stage*				
T1	3	11.1	2	8
T2	12	44.4	15	60
T3	11	40.7	8	32
T4	1	3.7	-	
Gleason*				
3+3=6	4	14.8	7	26.9
3+4=7	12	44.4	7	26.9
4+3=7	4	14.8	4	15.4
4+4=8	3	11.1	3	11.5
4+5=9	4	14.8	5	19.2
Presenting PSA*				
<10	15	55.6	16	61.5
10-19.9	8	29.6	7	26.9
>=20	4	14.8	3	11.5
ADT*				
Yes	25	92.6	21	80.8
No	2	7.4	5	19.2
Number of intrafraction pause required (per patient over entire course) †				
0	20	74.1	2	7.7
1	3	11.1	5	19.2
2	2	7.4	7	30.8
3	2	7.4	4	19.2
4	0	0.0	4	15.4
5	0	0.0	2	7.7
Number of intrafraction corrections required (per patient over entire course) †				
0	22	85.2	15	57.7
1	4	14.8	7	26.9
2	0	0.0	2	7.7
3	0	0.0	1	3.8
4	0	0.0	1	3.8
Frequency of motion requiring correction by direction‡				
Anterior	0	0.0	2	7.4
Posterior	4	100.0	13	48.1
Superior	0	0.0	7	25.9
Inferior	0	0.0	1	3.7
Left	0	0.0	1	3.7
Right	0	0.0	3	11.1

**No significant difference between standard and reduced groups p<0.05*
†Correction does not include pauses of treatment delivery for transient motion, but rather drift motion necessitating a table shift to correct for displacement.
‡Note: Motion in more than one translation (such as posterior and superior) were observed in 8 fractions
SD: Standard Deviation; ADT: Androgen Deprivation Therapy; PSA: Prostate-Specific Antigen

Toxicity outcomes

Toxicity outcomes are presented in Table 2.3 for both acute and late timeframes, with mean toxicity over time presented for GU and GI toxicity (Figure 2.2). Generally, GU and GI toxicity was low in both groups. There was a statistically significant difference in acute toxicities between the two groups for bloating and flatulence, with participants in the control group experiencing greater severity of both symptoms (bloating: ≥G1 9.2% control vs 1.0% intervention p=0.01; flatulence: ≥G1 21.3% control vs 8.7% intervention p=0.01). There was also a statistically significant difference in acute urinary retention, with greater severity in the intervention group (≥G1 0.9% control vs 7.7% intervention p=0.02). In late toxicities, there was a statistically significant difference in proctitis, with two participants in the control group scoring a CTCAE grade 2 versus no grade 2 proctitis in the intervention group (p=0.02). A time trend was prominent in both groups for urinary toxicity (including frequency, incontinence and retention), with a peak in frequency during the last half of treatment, then an improvement during follow-up (Figure 2.2). Similarly, there was a peak in diarrhea in Week 8 of treatment for both groups. There was no statistically significant difference in combined toxicities of GU and GI (Table 2.3).

QOL outcomes

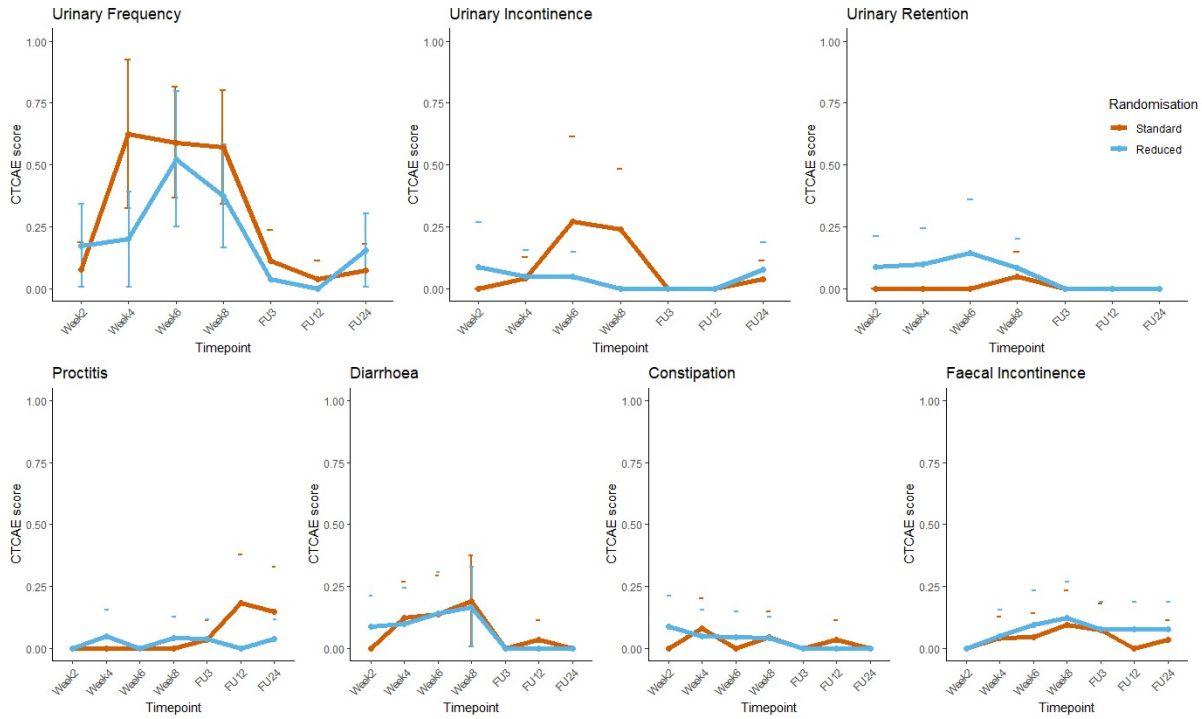
A summary of general QOL is presented in Figure 2.3 Overall, QOL was high with minimal differences between the two groups reported. Figure 2.4 presents the prostate specific QOL summary. The time trend of increasing urinary symptoms noted in both groups during radiation therapy was also reflected in urinary QOL outcomes.

Table 2.3

Frequency of toxicity scoring for gastrointestinal and genitourinary symptoms by randomised group

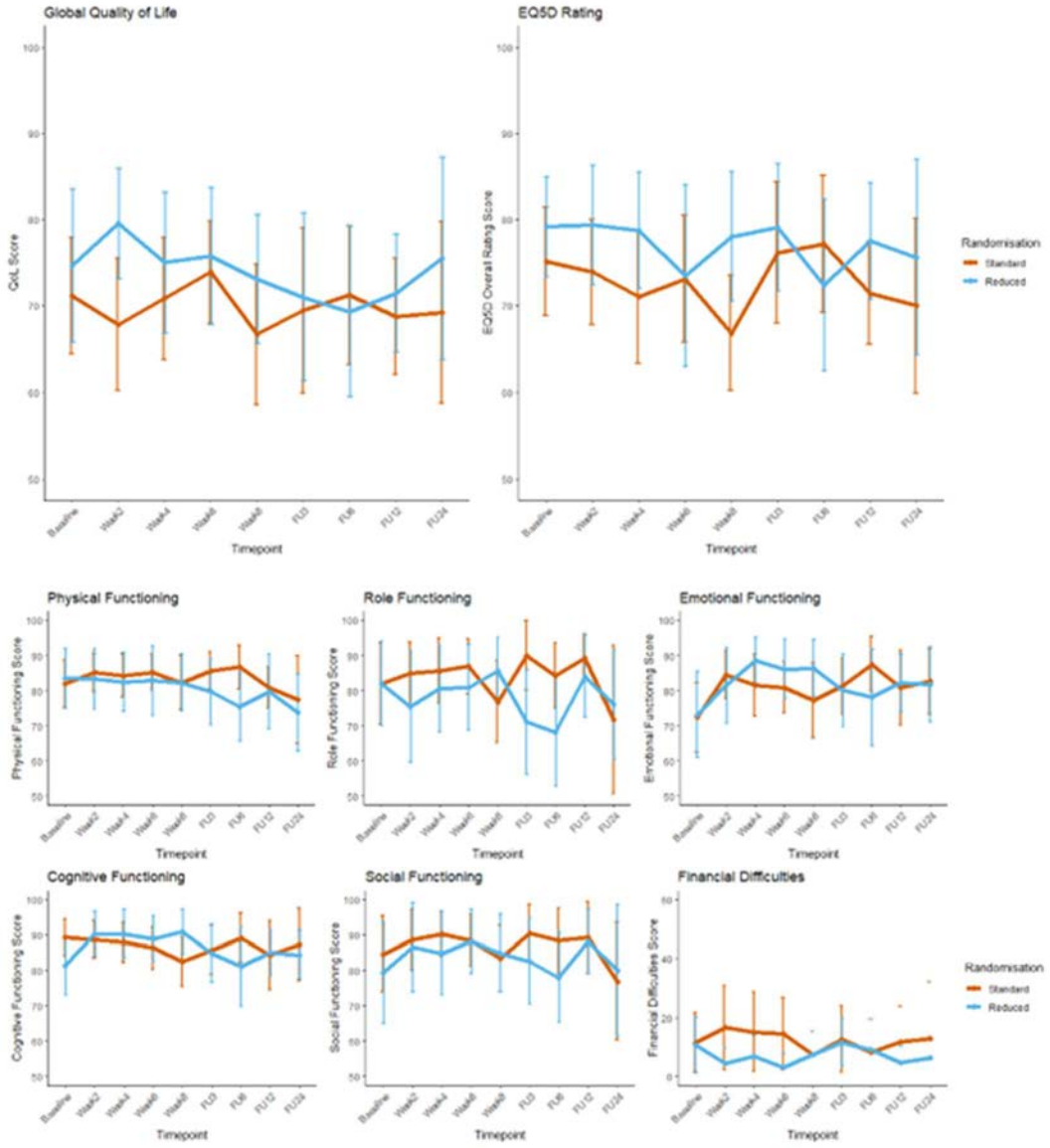
			Acute					Late				
			Control: Standard (n=27)		Intervention: Reduced (n=26)		p-value	Control: Standard (n=27)		Intervention: Reduced (n=26)		p-value
	Specific Symptom	**CTCAE Score**	**Count**	**%**	**Count**	**%**		**Count**	**%**	**Count**	**%**	
Gastrointestinal	Bloating†	0	83	76.9	87	83.7	**0.01**	81	100	78	100.0	-
		1	9	8.3	1	1.0		-	-	-	-	
		2	1	0.9	-	-		-	-	-	-	
		Missing	15	13.9	16	15.4		-	-	-	-	
	Constipation	0	90	83.3	83	79.8	0.49	80	98.8	78	100.0	0.97
		1	3	2.8	5	4.8		1	1.2	-	-	
		Missing	15	13.9				-	-	-	-	
	Diarrhoea	0	83	76.9	77	74.0	0.82	80	98.8	78	100.0	0.98
		1	10	9.3	11	10.6		1	1.2	-	-	
		Missing	15	13.9	16	15.4		-	-	-	-	
	Faecal Incontinence	0	89	82.4	82	78.8	0.22	78	96.3	72	92.3	0.32
		1	4	3.7	6	5.8		3	3.7	6	7.7	
		Missing	15	13.9	16	15.4		-	-	-	-	
	Flatulence†	0	70	64.8	79	76.0	**0.01**	81	100.0	77	98.7	0.49
		1	22	20.4	9	8.7		-	-	1	1.3	
		2	1	0.9	-	-		-	-	-	-	
		Missing	15	13.9	16	15.4		-	-	-	-	
	Proctitis‡	0	93	86.1	86	82.7	0.24	73	90.1	76	97.4	**0.02**
		1	-	-	2	1.9		6	7.4	2	2.6	
		2	-	-	-	-		2	2.5	-	-	
		Missing	15	13.9	16	15.4		-	-	-	-	
Genitourinary	Nocturia	0	7	6.5	12	11.5	0.19	-	-	-	-	-
		1-5	71	65.7	68	65.4		-	-	-	-	
		5+	13	12.0	8	7.7		-	-	-	-	
		Missing	17	15.7	16	15.4		81	100.0	78	100.0	
	Urinary Frequency	0	53	49.1	61	58.7	0.09	75	92.6	73	93.6	0.98
		1	39	36.1	26	25.0		6	7.4	5	6.4	
		2	-	-	1	1.0		-	-	-	-	
		3	1	0.9	-	-		-	-	-	-	
		Missing	15	13.9	16	15.4		-	-	-	-	
	Urinary Incontinence	0	85	78.7	85	81.7	0.58	80	98.8	76	97.4	0.62
		1	5	4.6	2	1.9		1	1.2	2	2.6	
		2	2	1.9	1	1.0		-	-	-	-	
		3	1	0.9	-	-		-	-	-	-	
		Missing	15	13.9	16	15.4		-	-	-	-	
	Urinary Retention†	0	92	85.2	80	76.9	**0.02**	81	100.0	78	100.0	-
		1	1	0.9	7	6.7		-	-	-	-	
		2	-	-	1	1.0		-	-	-	-	
		Missing	15	13.9	16	15.4		-	-	-	-	
Combined	Total *n* with maximum of <u>*any*</u> GI toxicity	*1*	19	70	15	58	0.49	9	33	7	27	0.48
		2	2	7	0	0		2	7	0	0	
	Total *n* with maximum of <u>*any*</u> GU toxicity	*1*	21	78	16	62	0.06	6	22	6	23	1.00
		2	1	4	3	12		0	0	0	0	
		3	2	7	0	0		0	0	0	0	

† p<0.05 for Acute toxicity; ‡ p<0.05 for Late toxicity; CTCAE: Common Terminology Criteria for Adverse Events. Scoring increases with toxicity severity. Missing data – where CTCAE scoring was not completed by the clinician. The count aggregates each timepoint (a total of 4 per participant for acute; and 4 per participant for late).



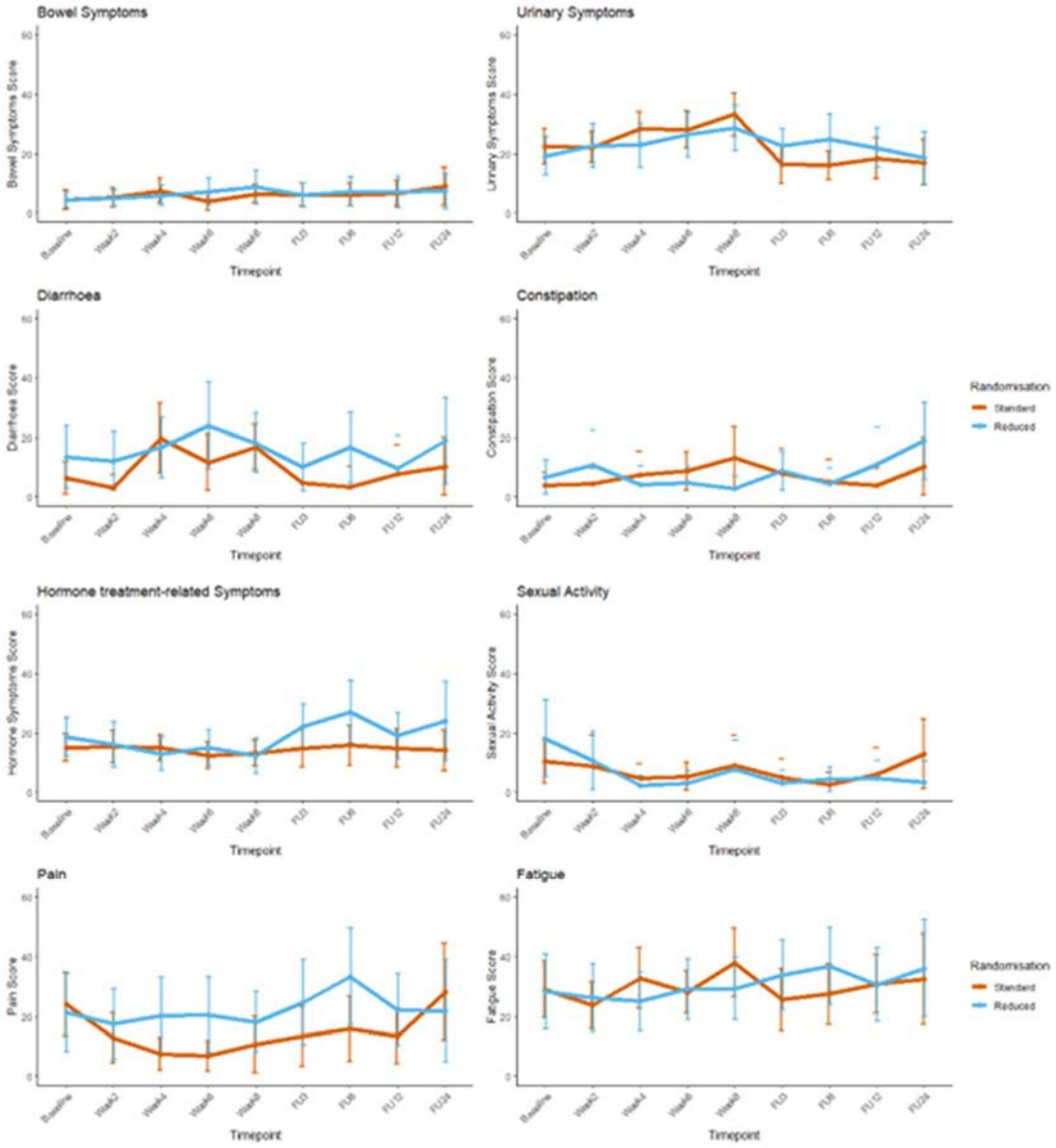
CTCAE: Common Terminology Criteria for Adverse Events. Scoring increases with toxicity severity.

Figure 2.2: Mean toxicity scoring by timepoint by randomised group



Mean ± SD presented. Scores generated from European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire; and EuroQOL EQ-5D. Scoring decreased with worsening QOL.

Figure 2.3: Mean general quality of life scores over time, by randomised group



Mean ± SD presented. Scores generated from European Organization for Research and Treatment of Cancer (EORTC) questionnaire prostate-specific PR25 module; and EuroQOL EQ-5D. Scoring increases with worsening QOL.

Figure 2.4: Mean prostate-specific quality of life scores over time, by randomised group

Discussion

This pilot study demonstrated a trend for lessened GI toxicity in the intervention group with reduced margins. Overall, QOL was high across both groups. The toxicity gradings measured in our study are in keeping with the literature,[19–22] noting the inherent difficulty in comparing different outcomes measures, including different fractionation schedules, image-guidance protocols and toxicity gradings/scales.

Our study findings demonstrate less GI and GU late toxicity compared to populations without intrafraction motion monitoring but with similar fractionation schedules. This result indicates the increased precision through motion monitoring may reduce long-term impacts of treatment.[19,20] Reported acute toxicities from populations treated using intra-fraction correction with more hypofractionated schedules (72Gy/30#, 35Gy/5# and 70Gy/30#) reported increased GI and GU Grade 1 and 2 toxicities, with an absence of grade 3 toxicities.[21,22] The global quality of life and specific prostate domains reported by our population is in keeping with studies reporting on prostate radiation therapy utilising the EORTC QOL tools, however again, there are differences in both fractionation schedules and image-guidance protocols.[23,24]

This study was originally intended to have a sample of 260 participants, sufficiently powered to detect a 20% in reduction of ≥G2 rectal toxicities, with 90% power and alpha of 0.05. However, several factors contributed to slow accrual. Firstly, we anticipated 100 eligible patients per year and thus reach the target recruitment in 3 years, however this was dramatically reduced due to changes in referral patterns, including increased prostatectomies and the opening of another regional radiation oncology centre. Secondly, 22% of potential participants declined, which was greater than our predicted 10% decline rate based on previous departmental accrual. The main reasons given for declining participation in this study (namely, inconvenience and concerns regarding randomisation) are also reported in the literature.[25,26] Finally, the emergence of the COVID-19 pandemic meant that prostate patients who could be maintained on hormone therapy had their radiation therapy treatment course delayed until the local impact of the pandemic was known, and this ultimately closed the recruitment for this study.

Clinician-scored toxicity gradings for prostate cancer are most prevalent in the clinical setting. Implementation of patient-reported outcome measures has been more sporadic within the clinic in part, due to lack of robust interpretation of their clinical importance as these QOL measures decline.[27,28] Additionally, different QOL tools have been adopted in different clinical trials and clinics. The PCa-specific EORTC QLC-PR25 utilised in this study demonstrate moderate content validity and internal consistency.[29] There is a known limitation for patient-reported proctitis measures in the EORTC forms utilised, which has since been addressed with

the development and validation of a proctitis-specific module. However, this new validation was not included in this present study as it was not available at time of study development.[30]

Limitations of this study include some potential impacts on toxicity and QOL such as co-morbidities which were not collected; the group allocation was blinded to the patient but not the clinician; missing toxicity and QOL data, and small sample size. Our study did not collect co-morbidity information, and therefore the potential impact of co-morbidities is not accounted for. A worsening of QOL has been found in PCa patients following radiation therapy when compared to a reference population, with a noted correlation with co-morbidities such as heart or lung conditions.[31] This study was single-blinded to the participant. The information regarding the randomisation was not notated in the MOSAIQ system where the clinicians document their scoring, however, clinicians may have remembered PTV margins of individuals which may have had an impact on toxicity scores. It is also recognised that missed data may therefore not have fully captured toxicity or QOL impacts.

The challenge of conducting RCTs in radiation therapy with rapid innovation and technological evolutions is recognised.[32,33] Due to slow accrual, this study was not sufficiently powered to draw conclusions on our hypothesis. However, it provides pilot data to investigate margin reduction further. Additionally, longer-term outcome data including survival is not captured, however could be revisited at 5-years post treatment.

Since the inception of this study, advances including hypofractionated schedules and daily adaptation have become increasingly adopted. With the adoption of hypofractionated schedules such as 60Gy in 20 fractions, the results presented here need to be interpreted with consideration of the difference in fractionation and associated toxicity profile. in mind. However, published results for minimal long-term toxicity and outcome differences between the longer and hypofractionated arms are encouraging.[34–36] With ultra-hypofractionated schedules, the intrafraction protocol becomes more critical in ensuring accurate dose delivery as any inaccurately delivered treatment fraction is a proportionally greater fraction of the patient's overall treatment.[37,38] The low frequency of prostate drift necessitating table corrections suggests that impact of motion monitoring on treatment time (i.e. increased time on bed) is minimal should reduced margins be adopted.

Conclusion

This pilot study found a trend for reduced toxicity in the reduced margin group, particularly for late rectal toxicities. These results demonstrate the feasibility of reduced PTV margins with intra-fraction motion monitoring. Efficacy confirmation with larger cohorts is required, particularly with contemporary hypofractionated treatment schedules.

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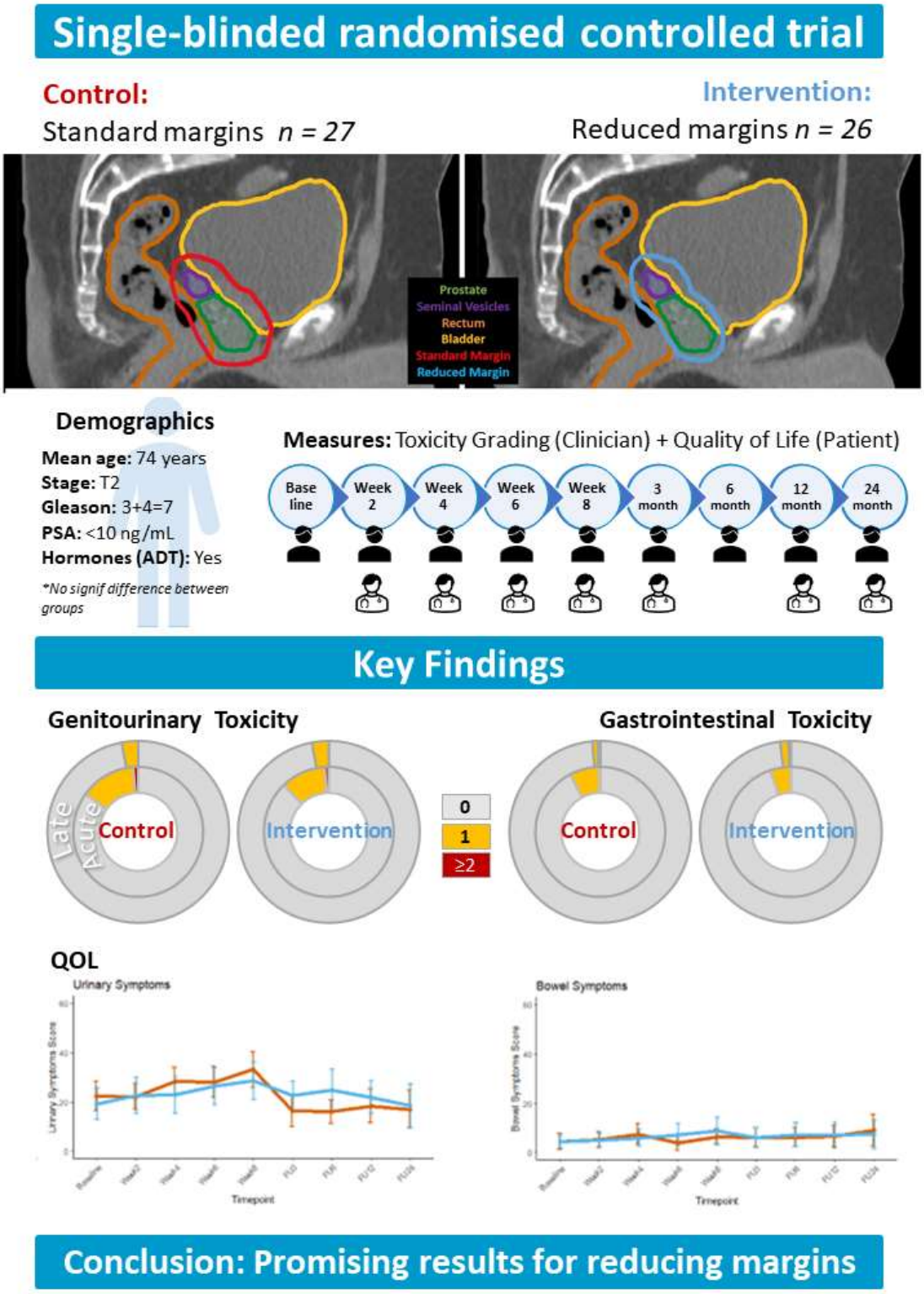
Supplementary

Table 2.4 (supplementary)
Frequency of missing data for toxicity and QOL by timepoint and group

		Control		***Intervention***	
		n	%	n	%
CTCAE	Wk2	1	3.7	3	11.5
	Wk4	3	11.1	6	23.1
	Wk6	0	-	0	-
	Wk8	5	18.5	5	19.2
	FU 3	0	-	0	-
	FU 12	0	-	0	-
	FU 24	0	-	0	-
QOL	Base	1	3.7	1	3.8
	Wk2	4	14.8	3	11.5
	Wk4	5	18.5	2	7.7
	Wk6	4	14.8	5	19.2
	Wk8	3	11.1	3	11.5
	FU 3	6	22.2	2	7.7
	FU 6	7	25.9	4	15.4
	FU 12	9	33.3	3	11.5
	FU 24	14	51.9	10	38.5


Single-blinded randomised controlled trial
Control:
Standard margins n = 27
Intervention:
Reduced margins n = 26
Prostate
Seminal Vesicles
Rectum
Bladder
Standard Margin
Reduced Margin
Demographics
Mean age: 74 years
Stage: T2
Gleason: 3+4=7
PSA: <10 ng/mL
Hormones (ADT): Yes
*No signif difference between groups
Measures: Toxicity Grading (Clinician) + Quality of Life (Patient)
Base line
Week 2
Week 4
Week 6
Week 8
3 month
6 month
12 month
24 month
Key Findings
Genitourinary Toxicity
Gastrointestinal Toxicity
Late
Acute
Control
Intervention
0
1
≥2
Control
Intervention
QOL
Urinary Symptoms
Bowel Symptoms
Conclusion: Promising results for reducing margins

Linking to Subsequent Chapter

The most significant finding of this study was a trend for reduction in gastrointestinal toxicities in the interventional reduced margins group.

This finding led to the adoption of reduced margins at Townsville Cancer Centre, with further discussion presented in Chapter 7.

This chapter addressed Research Question 1:

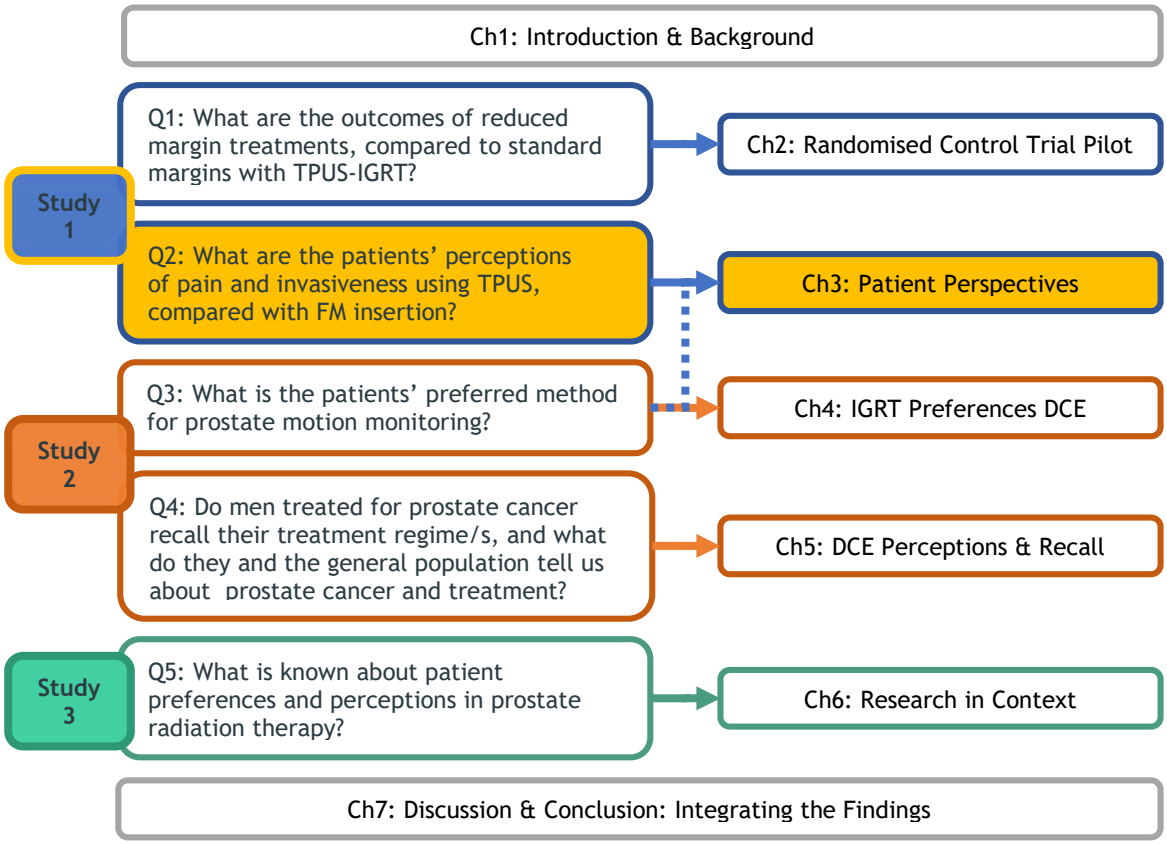
What are the outcomes of reduced margins compared to standard margins with TPUS-IGRT?

Chapter 3 Patient Perceptions and Preferences

Article: Patient perceptions and preferences about prostate fiducial markers and ultrasound motion monitoring procedures in radiation therapy treatment

Brown A, Pain T, Preston R. Patient perceptions and preferences about prostate fiducial markers and ultrasound motion monitoring procedures in radiation therapy treatment. J Med Radiat Sci 2021 68:37-43 https://doi.org/10.1002/jmrs.438

This chapter includes an exact copy of the published manuscript, except the formatting of section sub-headings, figure, table and reference numbers have been edited for the purpose of the thesis.



Note: TPUS: Transperineal Ultrasound; IGRT: Image-guided radiation therapy; FM: Fiducial Marker; DCE: Discrete Choice Experiment

Figure 3.1: Schematic overview of thesis: Study 1, Chapter 3

Context of study 1 – mixed methods sub-study

This sub-study was conceptualised prior to the installation and implementation of the Clarity TPUS system at TCC. During preparation for implementation, questions were often posed by clinical staff regarding the acceptability and tolerability of the transperineal ultrasound probe by patients. As the clinical staff of TCC had a number of years of experience with fiducial marker (FM) insertion and therefore first-hand experience of the small percentage of patients who could not tolerate the FM procedure due to factors such as pain/discomfort and embarrassment, it was a natural curiosity. There was no existing literature, so this study was developed to gain insights of the men with prostate cancer experiencing both FM and TPUS during our implementation period.

Abstract

Introduction

Patient experiences and preferences of image guidance procedures in prostate cancer radiotherapy is largely unknown. This study explored experiences and preferences of patients undergoing both fiducial marker (FM) insertion and Clarity ultrasound (US) procedures.

Methods

A sequential explanatory mixed method approach was used. A questionnaire (n=40) ranked experiences from 0 to 10 (worst) in the domains of: invasiveness; pain; physical discomfort; and psychological discomfort. Responses were analysed with descriptive and inferential statistics. Semi-structured interviews (n=22) obtained further insights into their perspectives and preferences and were thematically analysed.

Results

Perceptions of invasiveness varied with 46% reporting FMs more invasive than US and 49% the same for the two procedures. The mean score for FM was 3.6 and 2.1 for US. Mean scores for pain, physical and psychological discomfort were higher for FMs with 3.3, 3.2, 2.9 respectively and 1.1, 1.2, 1.7 respectively for US, however only pain achieved significance ($p<0.05$). Three themes emerged from the interviews: Expectations versus experience;

Preferences linked to priorities; and Motivations. Eleven patients (50%) preferred US, however 10 (45%) could not express a preference.

Conclusion

Participants found both of the FM and US image-guidance procedures tolerable and acceptable. Men's preference was elusive, suggesting a more rigorous preference methodology is required to understand preferences in this population.

Background

Gaining perspectives from patients is important in healthcare provision and research and is gaining traction in the radiation oncology setting.[1–3] Rapid technological advancements in radiation oncology present an opportunity to gain patient perspective into different techniques and technologies to complement the clinical and technical data, particularly those with equipoise. For example, options for monitoring prostate motion during external beam radiation therapy treatment delivery include gold seed fiducial markers, Calypso beacons and Clarity ultrasound. However, a paucity of literature exists regarding patient perspectives on these technologies.

Gold seed fiducial markers (FMs) are commonly utilised in prostate radiotherapy to accurately locate the prostate on daily imaging. FMs are surgically implanted using trans-rectal ultrasound guidance and patients are not routinely sedated for the insertion.[4,5] Three electromagnetic beacons are inserted into the prostate for Calypso technology using the same technique as FMs.[6]

In contrast, Clarity involves the placement of an external ultrasound probe against the patient's perineum every day for the duration of treatment delivery.[7] While non-invasive, the placement of the probe requires treating staff to ensure the patients' scrotum is out of the way and applying some pressure to gain a clear ultrasound image.[8] Thus, the procedure may be considered "personally invasive".

This study aimed to explore patient perceptions of the surgical procedure for FM insertion compared to the daily placement of the ultrasound probe using Clarity. Patients were asked

for their preference of the two procedures. Additionally, we aimed to explore the factors patients considered when choosing between different technologies and procedures.

Methods

This sequential explanatory mixed methods study was completed as a subset of a larger randomised control trial [ACTRN12617001102369]. The study was approved through Townsville Hospital and Health Service HREC (HREC/17/QTHS/9) and James Cook University HREC (H6970) (*Appendix A*) and all patients provided written informed consent. Patients were eligible if they had both FMs and Clarity ultrasound image-guidance performed during the study period.

Participants firstly completed a "Procedures Experience" questionnaire (*Appendix B*). This questionnaire was developed by the investigators and included both open and closed questions, covering physical and psychological experiences. Closed questions used a 10-point Likert-type scale to assess patient perceptions of pain and invasiveness of both the FM insertion procedure and the Clarity procedure. Participants were provided with the questionnaire on the day of FM insertion and Clarity simulation. Five patients piloted the questionnaire to assess for comprehensibility prior to data collection which were not included in final analysis.

Semi-structured interviews were also conducted, with the aim of qualitatively exploring the patient's procedural experiences and preference. Purposive sampling was used to ensure a breadth of demographics, experiences and views based on the questionnaire responses. Interviews took place between the day of insertion and the first week of treatment to limit recall bias. It was however ascertained in the interviews that the participants understood that Clarity was a daily application as part of their treatment. The interviews were conducted by one investigator (AB), with the use of an interview guide (*Appendix C*). The interviewer was a clinician, but not directly involved in the treatment of participants.

The interviews were performed in-person or by telephone (by choice of participant), recorded and transcribed verbatim. Participants could choose to have a support person present for the interview.

Data and analysis

Descriptive statistics and Fisher's exact test were used to analyse the questionnaire responses in R statistical software Version 3.6.1.[9]

The transcripts, interview recording, and researcher notes were entered into NVivo (QSR) version 12 for analysis. The first five interviews were coded independently by two investigators (AB and TP), with the code list compared and ratified. Reflexive thematic analysis was performed, with both deductive and inductive coding.[10,11] The remainder of interviews were coded by one investigator (AB). Interviews and analysis were performed concurrently to maintain focus and develop analytical depth and integration of the data. Interviews were conducted until pragmatic saturation was reached.[12] To confirm trustworthiness, the findings were discussed with and reviewed by a third team member not involved in data collection and analysis (RP).[13] Excerpts of the transcripts are provided in the following results section to exemplify the identified themes, with all identifying information removed.

Setting

This study was conducted at a regional tertiary hospital and health service in Australia. The radiation oncology department services a large geographical catchment area, and patients may travel up to 800 kilometres from rural and remote regions for radiation therapy treatment. At our centre, both male and female health professionals perform the FM insertion and the Clarity set-up.

Results

Demographics

The demographics of participants in both the questionnaire (n=40) and the interview (n=22) are summarised in Table 3.1.

Table 3.1
Demographics of participants in the questionnaire and interviews

	Questionnaire	Interview
Number of participants*	40	22
Mean Age in years (range)	73 (60 to 85)	72 (62 to 84)
Staging		
T1c	4 (10%)	2 (9.1%)
T2a	3 (7.5%)	2 (9.1%)
T2b	9 (22.5%)	7 (31.8%)
T2c	12 (30.0%)	7 (31.8%)
T3a	10 (25.0%)	4 (18.2%)
T3b	1 (2.5%)	0
T3c	1 (2.5%)	0
Androgen Deprivation Therapy		
Yes	35 (87.5%)	21 (95.5%)
No	5 (12.5%)	1 (4.5%)
Number of Biopsies		
1	32	16
2	5	5
4	1	1

**Each participant had undergone both fiducial insertion and Clarity procedures at time of questionnaire and interview.*

Questionnaire

A summary of the questionnaire results is presented in Table 3.2. The only domain which was statistically different between the two procedures was the pain median score (3 for FMs, 0 for Clarity). Perception of invasiveness varied with 46% reporting FMs more invasive than US and 49% considered the two procedures equivalent.

Table 3.2
Summary of questionnaire results – median (range)

	FMs *(n=40)*	**Clarity** *(n=40)*
Physical Discomfort	3 (0 - 8)	1 (0 - 6)
Psychological Discomfort	3 (0 - 9)	1 (0 – 8)
Pain*	3 (0 – 8)	0 (0 – 8)
Invasiveness	3 (0 – 10)	1 (0 – 10)
Information (*count*)		
Not informed	1 (2.5%)	0
Somewhat	0	3 (7.5%)
Well Informed	37 (92.5%)	34 (85.0%)
Not recorded	2 (5.0%)	3 (7.5%)

**indicates statistically significant difference ($p<0.05$)*

Interviews

The interviews ranged from 10 to 54 minutes (mean of 27) in length. The majority (18) were performed in person, with six choosing to have someone present (wife/partner = 4; daughter = 1; sister = 1). An additional three participants were invited to interview, however two did not wish to proceed, and one could not commit to several times suggested.

Analysis of the interviews revealed three major themes: Expectations versus experience; Preferences linked to priorities; and Motivations (Table 3.3).

Table 3.3
Summary of themes and categories

Major Theme	Subthemes
Expectations versus experience	Expectation based on past experiences Physical experiences Psychological experiences
Motivations	Desire to cure cancer Acceptance Resolve Resignation
Preferences linked to priorities	Doctor knows best Reasoning Understanding and Information

Expectations versus experience

Many men compared their biopsy experiences with the FM insertion and how the biopsy set up expectations for the insertion. This was particularly evident in those who had experienced a painful or negative biopsy experience and those who had multiple biopsies.

> *I'd had two biopsies before so I reckon they were worse. It would be different if I didn't have them first. It was better than the biopsies. (P32)*

Physical sensations were for the most part downplayed by participants, particularly when comparing the FM insertion to the biopsy. Two main physical factors were reported by men when describing the FM procedure: the sensation of the internal US probe, and the feeling of the 5 needles (2 for local anaesthetic and 3 for FM insertion). This was reported mostly as discomfort, or in fewer cases, pain.

> *There was probably a little bit of pain [with insertion] ... But nothing, you know, nothing you couldn't put up with sort of thing. (P03)*

In describing the experience of Clarity, most men described being aware that the external probe was there, but not causing any discomfort or pain.

All I felt there was when they pushed it [the Clarity probe] up it touched me, you know, pushed up. And when they got it in position, they just left it. Pretty sure I didn't even know it was there. (P01).

Many men reported on both the feeling of the cold ultrasound gel as well as the mess the gel made, requiring clean up.

The only other thing with the treatment, I've solved this myself actually, you've got so much gel down there right? Now when you stand up, to go and get changed, it runs down between your legs. So, I go to the toilet now and clean myself off. (P32)

Psychological discomfort was expressed as anxiety, apprehension and embarrassment. Many reported a generalised anxiousness in the lead up to the procedures, attributed mostly to not knowing what to expect.

I was very apprehensive at first. I sort of had a rough idea of what to expect, because when they inserted the seeds, I had previously had a biopsy done, so I was assured that the biopsy was more painful than planting the seeds. I was still apprehensive. (P19)

Most men stated that the desire to beat the cancer overcame any feelings of embarrassment.

I firmly believe that you leave your pride at the door and pick it up on your way out. So, I had no hassles. (P09)

It was recognised that both procedures can be a personally confronting experience, requiring access to the pelvis.

Maybe some blokes would be embarrassed, things like that. You are lying on the table, getting the gold seeds in, you are naked sort of thing, and there are a lot of folk about you. (P20)

Those who did report embarrassment indicated a willingness to endure the procedures in pursuit of cure.

There's no embarrassment. It's got to be done. I'm […] lucky that they are doing it, that I can get it done, you know? (P18)

Motivations (including acceptance, resolve or resignation)

The motivation to treat the cancer with the aim of cure was a strong theme amongst the men interviewed. “You gotta do what you’ve gotta do [to treat the cancer]” was an overarching sentiment, expressed by most participants. This motivation for treatment manifested as two mindsets: Resignation and Resolve, underpinned by a desire for a cure. While many men identified as being of one of these mindsets, some described their mindsets to vary at different points during their cancer diagnosis and treatment experiences.

> *Then you have to set your mind to it – ok, I’m going to beat this thing. Use a lot of mind over matter. (P12)*

Resolve was expressed by over half of the participants, with a desire and determination to “beat” the cancer and a pro-active approach to their own health and treatment.

> *You know you are sick; you know you have to get it cured. […] Aiming for a cure, so you take the best option, and to me, that is the best option at present. (P10)*

Resignation was expressed as an acceptance of the cancer and treatment requirements, with more of a submissive attitude to their treatment journey by six participants. These men were more likely to indicate a willingness to go along with health professional’s recommendations.

> *I wasn’t happy, well, it’s got to be done, it’s got to be done. […] Yeah, leave to the professionals, and just do what you’ve got to do. (P22)*

Linked with these mindsets were expressions of Acceptance and Stoicism, implying a pragmatic approach to do whatever was required to treat the cancer.

> *But you just accept this, if you want to get this treatment, and get over this cancer. That's the way I look at it. It's just one of those things. (P05)*

Some reflected on the disruption to their life, usually in retirement. Despite this, a positive outlook was expressed by many.

My attitude is, I'm not going to die of it, I'm going to die with it, maybe, and when the treatment is finished, hopefully I'm going to be free and clear. […] Once treatment is finished, I am going to live life to the fullest. I've got a second chance. (P14)

For others, the prostate cancer coincided with retirement and other health issues, leading to feelings of frustration.

I must admit it was a bit of a surprise... I had a stroke 5 years ago, so I'm thinking, why are all of these things rearing their head now, just as I'm retiring now, sort of thing. (P07)

Preferences linked to priorities

With the motivation of actively seeking treatment and a cure for the prostate cancer, many men discussed their priority was to be cured. This then influenced perceptions and preferences for image guidance.

When asked to identify a preference, 11 participants preferred Clarity, one preferred FMs, and the remainder could not define a preference, even when presented with a vignette of describing the procedures to a friend and identifying their preferred procedure in the process. In those who could not define a preference, three said that they were ambivalent with both procedures; while seven indicated confusion about the need for both procedures, that is "Gold seeds and the Clarity Probe. They are tied up together aren't they?" (P20) and "I thought they were both to do with the whole procedure." (P03)

The interviewer clarified they were receiving both methods only because of department policy but that clinically one or the other was necessary. Nevertheless, six still could not elicit a preference.

I think it just comes down to perception really. I don't think that any guy likes to be laid down and have things inserted in them. […] It's just if... you've got some thoughts about invasive procedures, as a lot of guys do, then go for the Clarity. But if you're quite happy to go for the gold seeds, well... do it! (P06)

Those who could identify Clarity as their preference in interview gave a variety of reasons, including it was less painful/most comfortable, and less embarrassing as it didn't require an internal probe.

> *The internal thing is just not pleasant. (P17)*

The one participant who identified FMs as their preference did so by relating it back to lived experience of increased accuracy.

> *I did a navigation course years ago and to pinpoint your exact position on the earth, you had to have... to be more accurate, you had to have 3 … sightings of something and then you can pinpoint. And that's why I think that gold seeding is really accurate. (P03)*

A subtheme of 'following health professionals' recommendations', or 'doctor knows best' arose. This subtheme was particularly evident when preference was discussed, with many participants expressing they will follow the recommendations of the doctors and health professionals, regardless of own personal preference: "I'll do what I'm told [by the health care staff]" (P17).

> *Main thing is to listen to those who are actually treating you, like the staff, and the doctor. (P19)*

The need for information and understanding about the procedures varied between the men.

> *Too much information is too much problem... it's a problem for some people. And not enough is another problem for other people. So, you have to pick that balance. (P05)*

> *And because it doesn't matter how much you read, you've still gotta go through with it. (P04)*

Discussion

Overall, low scores across the questionnaire domains (physical discomfort, psychological discomfort, pain and invasiveness) were supported by the "gotta do" attitude in the interviews. There was a statistically significant difference in the median pain score of the FMs and the Clarity procedures, however it is noted that both procedures scored low overall. The low scores indicated the resolve of this patient population to treat and "beat" the cancer. Robins et al (2018) similarly found low pain scores reported by patients who had undergone transrectal ultrasound-guided biopsies, with an overall median pain score of 3 (0-9).[14] The main themes emerging from interviews illustrated the variety of ways the men faced and processed their prostate cancer treatment.

Results from the questionnaire showed no statistically significant difference in physical discomfort between the procedures. However, during interviews most men only reported FM discomfort, with little mention of Clarity discomfort. Pang et al (2016) reported that patients found the Clarity positioning was acceptable.[15] However, this was a cohort of patients who only experienced the Clarity set up, with no other literature on the patient perspective of FMs and Clarity.

Reports of lack of embarrassment was at odds with clinical staff anecdotal observations of many patients expressing a fair degree of both verbal and non-verbal embarrassment during the FM procedure. Low embarrassment levels were also evident in the questionnaire's psychological discomfort score. It is possible that embarrassment is acutely felt at the time of the FM procedure, but quickly forgotten or brushed aside by the men, particularly with the pragmatic approach of getting the procedures "over and done with" to achieve cure. Chapple et al (2007) reported similar findings of downplaying of pain, discomfort and embarrassment in their qualitative study of patient experiences of prostate biopsies, a procedure similar to FMs.[16] Similarly, the participants accepted any embarrassment associated with the Clarity procedure in the pursuit of cure, although the reports of this embarrassment were low in both the questionnaires and interviews. Future studies in this population may benefit from data collection closer to the procedure to validate if there is acute embarrassment, or incorporating field observations into future studies.

Seemingly negative (Resignation) and positive (Resolve) mindsets were presented during interviews. Both mindsets led to the same outcome in this group of participants – the active pursuit of treatment with the desire to cure the cancer. The notion of proactivity in curing cancer was also identified in Saigal et al (2017) as an important attribute in prostate cancer treatment where undergoing treatment validated a proactive approach.[17]

The stoicism expressed by many participants is in keeping with hegemonic masculinity, reported in the broader male population and the prostate cancer specific population.[18–20] Kannan et al (2019) describes the "Australian masculinity" stereotype of stoicism, silent endurance and a reluctance for help-seeking behaviour.[19] Stoicism was also reflected in the overall low scores of the questionnaire domains. A number of strategies employed by prostate cancer patients have been identified in the literature, including positive mindsets, using humour to diffuse the emotional situation and believing the cancer was non-invasive and non-aggressive.[21]

The desire to beat the cancer was reported by most interviewees as their priority. To this end, they were willing to be guided to the most appropriate treatment choices recommended by their treating team of health professionals. This finding is consistent with Smith et al (2017) demonstrating trust in the radiation oncology professionals was such that that patients would agree with their treatment recommendations without much questioning.[22] Likewise, Scherr et al (2017) also found urology professionals opinions influenced prostate cancer patients treatment decisions.[23] Literature about prostate cancer preferences is currently focussed on prostate cancer screening and treatment modality decision-making, rather than specificities of a treatment modality such as image-guidance.[24–27]

The inability of many participants to separate the two procedures may have influenced the viewpoints expressed. In particular, the 7 participants who could not give a preference could not do so because they could not separate the two procedures in the interview. As participants received both procedures, asking them to hypothetically choose one over the other departed from their lived experience making the choice difficult. Indeed, many participants were surprised to be asked, suggesting patients are unfamiliar with health professionals asking them about their health preferences.

Of note, most participants indicated they were well informed about both procedures. However, this was not evident in the interviews where many could not separate the necessity of the two procedures suggesting the educational information about the reasoning of the two procedures was not understood or retained by participants, or indeed may not have been adequately given by the health professionals. Disparate information needs of participants were noted with some wanting to know everything, while others were satisfied to know only the basics. This dichotomy of information needs was also found by Kannan et al (2019) amongst undiagnosed men.[19] It is recognised that understanding the patient's health literacy level, their preference for both information and treatment decision-making should not be overlooked by the healthcare community.[28–30]

Strengths & limitations

This study was able to gain perspectives from patients who had undergone two image-guidance procedures. Our centre was in the unique position of using both procedures in routine care at the time of the study, giving the opportunity to directly compare both, which strengthens this study.

As the interviewer was a younger female, the male participants may have been reticent when discussing their prostate cancer experiences and preferences. To limit this influence and put them at ease as much as possible, the participants could choose to have a support person present. This may reflect the low reporting of embarrassment in interview, compared with clinical observations. Another limitation is ethnic homogeneity, with all participants of Caucasian decent.

Future directions

With a large proportion of participants (45%) unable to initially identify a preference at interview, a discrete choice experiment (DCE) will be undertaken. This qualitative work will inform the DCE development. The importance of patient perspectives in health technology assessments is recognised and this body of work will contribute to the assessment of the Clarity system.

Conclusion

Overall, both image-guidance procedures were well tolerated by patients, with low rates of pain, discomfort and embarrassment reported. Interviews revealed the majority were willing to follow the clinician's recommendations regardless of their own personal preference, with a large percentage (45%) not able to express a personal preference.

These results could potentially be extrapolated to insertion of other markers such as electromagnetic beacons done in the same procedure as FMs. For radiation oncology departments considering the implementation of either of these two procedures, these results will be reassuring that patients find both of the image-guidance procedures tolerable and patient reflections could be considered along with the clinical and technical data.

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Translation of Evidence Infographic

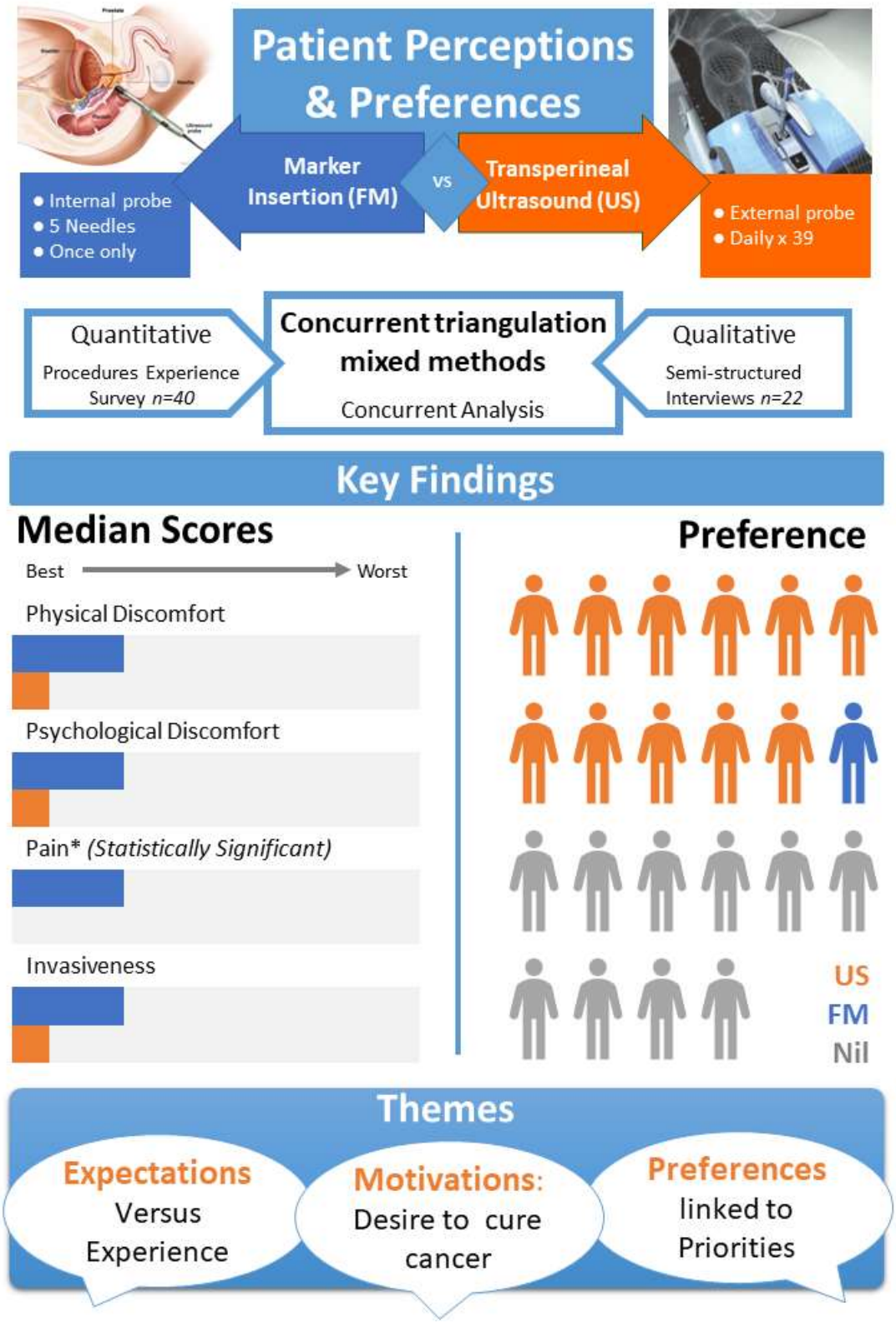


Figure 3.2: Translation of evidence infographic - Chapter 3

Link to Subsequent Chapter

The most significant finding of this sub-study was that 10 out of 22 participants could not elicit their preference for IGRT in the interview, despite having experienced both procedures.

This finding led to the development of the discrete choice experiment, to further elicit and understand preferences (Chapter 4).

This chapter addressed the research questions:

2) What are the patients' perceptions of pain and invasiveness using TPUS, compared with gold seed insertion?

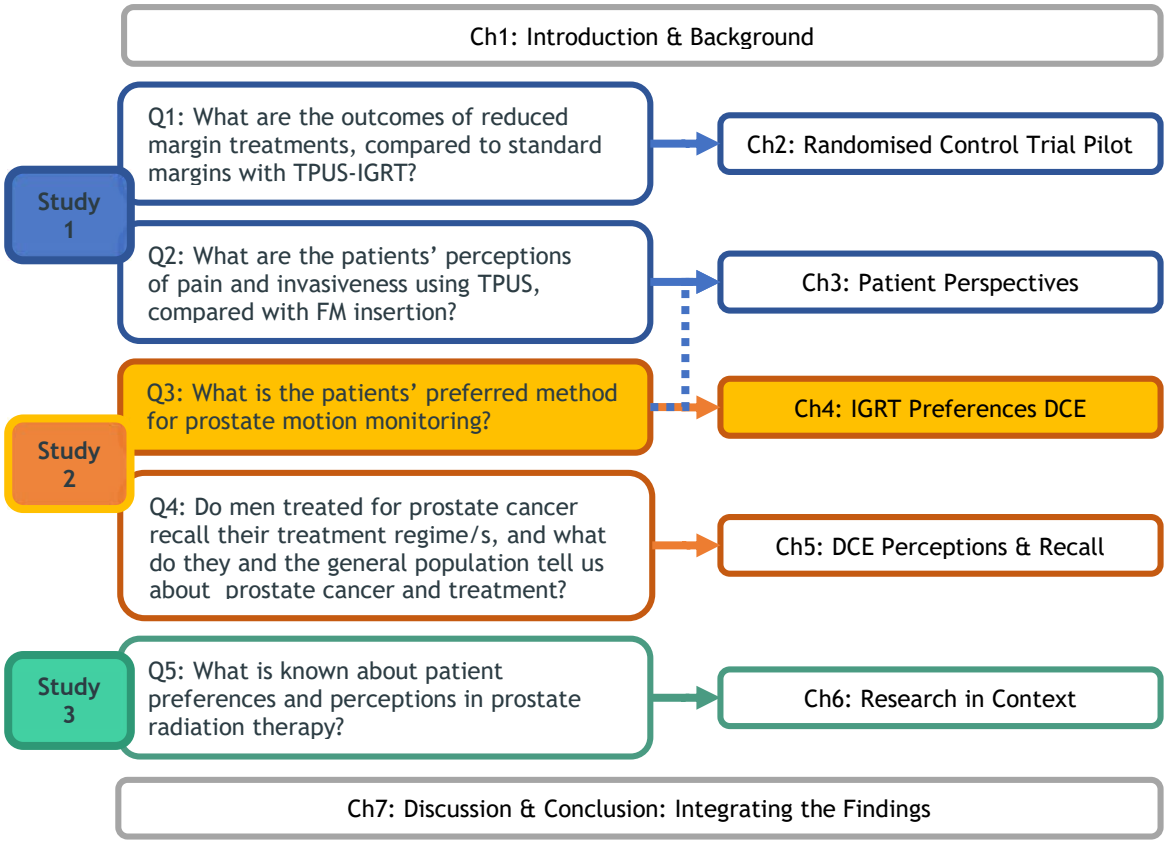
3) What is the patients' preferred method for prostate motion monitoring if both methods are presumed to achieve the same outcome? What factors do patients consider if choosing between different technologies and procedures?

Chapter 4 Image-Guidance Preferences Discrete Choice Experiment

Article: Men's preferences for image-guidance in prostate radiation therapy: A discrete choice experiment

Brown A, Pain T, Tan A, et al. Men's preferences for image-guidance in prostate radiation therapy: A discrete choice experiment. *Radiotherapy and Oncology*.2022;167(S1):49-56. doi:10.1016/j.radonc.2021.11.032

This chapter includes an exact copy of the published manuscript, except the formatting of section sub-headings, figure, table and reference numbers have been edited for the purpose of the thesis.



Note: TPUS: Transperineal Ultrasound; IGRT: Image-guided radiation therapy; FM: Fiducial Marker; DCE: Discrete Choice Experiment

Figure 4.1: Schematic overview of thesis: Study 2, Chapter 4

Context of study 2

This study was developed in order to elicit and understand patient preferences for image-guidance further, particularly given that 10 out of 22 participants in Sub-study 1 could not identify their preference for TPUS or FM in interview. A cohort of men within the general population of Australia was also surveyed, allowing for comparison to the men with prostate cancer population.

Abstract

Introduction

There are several options for real-time prostate monitoring during radiation therapy including fiducial markers (FMs) and transperineal ultrasound (TPUS). However, the patient experience for these procedures is very different. This study aimed to determine patient preferences around various aspects of prostate image-guidance, focusing on FMs and TPUS.

Methods

A discrete choice experiment (DCE) was conducted, describing the image-guidance approach by: pain, cost, accuracy, side effects, additional appointments, and additional time. Participants were males with prostate cancer (PCa) and from the general Australian population. A DCE survey required participants to make hypothetical choices in each of 8 choice sets. Multinomial logit modelling and Latent Class Analysis (LCA) were used to analyse the responses. Marginal willingness to pay (mWTP) was calculated.

Results

476 respondents completed the survey (236 PCa patients and 240 general population). The most important attributes for both cohorts were pain, cost and accuracy ($p<0.01$). PCa patients were willing to pay more to avoid the worst pain than the general population, and willing to pay more for increased accuracy. LCA revealed 3 groups: 2 were focused more on the process-related attributes of pain and cost, and the third was focused on the clinical efficacy attributes of accuracy and side effects.

Conclusion

Both cohorts preferred less cost and pain and improved accuracy, with men with PCa valuing accuracy more than the general population. In addition to the clinical and technical evidence, radiation oncology centres should consider the preferences of patients when considering choice of image-guidance techniques.

Background

Prostate cancer is in the three most prevalent male cancers globally.[1–3] Often, treatment for prostate cancer includes radiation therapy utilising different imaging methods to guide treatment delivery. The prostate is a mobile organ which can move during treatment, potentially increasing side effects and decreasing treatment efficacy.[4] Advances in technology now enable monitoring and correction for this motion, making the radiation therapy more accurate and safer.

There are currently a number of motion monitoring options available. One of the most common is insertion of fiducial markers (FMs) into the prostate in a surgical procedure prior to the treatment commencement. These markers can be identified on imaging prior to treatment delivery every day. Through new technology, implanted markers can be tracked in real-time, using kilovoltage imaging systems or an electromagnetic beacon system.[5–9] Transperineal ultrasound (TPUS) monitoring does not require a surgical implant, however requires the placement of an external ultrasound probe against the patient's perineum every day.[10–12] Clinical and technical data for these systems indicates equi-effectiveness.[5,13–15]

Patient experience of these image-guidance techniques varies given the differences in how they are applied; a once-off surgically invasive technique for the insertion of FMs compared to potentially "personally invasive" placement of the TPUS probe against the perineum daily for treatment. Previous work to gain insight into patient perspectives and preferences for the current image-guidance techniques (FMs and TPUS) found that 10 out of 22 patients could not express a preference between the two procedures.[16]

Gaining perspectives from patients is important in healthcare provision and is increasing in the prostate cancer and radiation oncology setting.[17–21] There are a wide variety of

technologies and techniques in radiation oncology, mostly with negligible differences in clinical outcomes. Therefore, it is important to incorporate patient preferences into decision-making about treatment options and infrastructure investments that may impact patient experiences.

Capturing these perspectives and experiences can be undertaken in several ways (surveys, interviews/focus groups). Discrete choice experiments (DCEs) are a quantitative methodology increasingly being utilised in health research to elicit preferences for healthcare products and programmes.[22,23] DCEs are used to elicit preferences by describing a health care scenario and asking respondents to choose between alternative, hypothetical treatment options presented to them. These options, or choice profiles, describe the treatment situation by its underlying characteristics (or attributes, e.g. whether there is pain), the levels of which (e.g. how great the pain is) vary between the alternatives shown and change between choice tasks. Analysis of the responses reveals how individuals trade-off between those attributes, thereby revealing the relative importance of each attribute in those trade-offs, and quantifying the strength of their preferences between the choices on offer.[23,24] This study reports on a DCE used to elicit preferences among men for image guidance in prostate radiation therapy.

Methods

Population and setting

The DCE was undertaken among two groups: Cohort 1 was patients with prostate cancer who presented to a regional tertiary cancer centre in Australia, and Cohort 2 was a male general population sample across Australia, aged 18 and over. These two cohorts ensured the perspectives and preferences of men with a lived experience of prostate cancer and the broader societal preferences were both captured. The broader societal preferences are relevant in that they reflect the views of tax-payers funding universal health care (as applies in Australia), but also the preferences of potential future prostate cancer patients, ensuring that health policy decisions incorporate these perspectives. Piloting occurred in February 2020 and the main survey was open from May to August 2020. A flowchart summarising the steps from development to analysis is provided (Figure 4.2 (supplementary).

Developing the DCE

The DCE was developed according to best-practice principles[24,25] drawing upon three key elements: literature review; a mixed methods study findings,[16] and expert opinion. Conduct of the mixed-methods study overlapped the development of the DCE and informed the initial candidate attribute set[16] allowing for this to be reviewed among men with prostate cancer. Five interviewees in the mixed-method study were provided the list of candidate attributes at the end of their interview and asked to identify any missing attributes or any which required updating.

The literature pertaining to FMs (and similar procedures such as beacons) and TPUS informed initial attribute and level development. While there was very little literature describing patient experiences with these procedures, the clinical literature available informed aspects such as side effects, appointments and costs of the procedures.

A panel comprising of radiation oncologists, nurses and radiation therapists, expert in the care of prostate cancer patients was convened to further discuss the attributes and levels proposed. Each attribute and corresponding levels were discussed with the panel to ensure congruency with their clinical experience and expertise. The main outcome was to increase the upper level of cost to reflect some patients' choice to undergo procedures such as FMs/beacons in the Australian private sector. The DCE was piloted (further details in Supplementary material; *and Appendix F*), with no changes made to the attributes/levels (Table 4.1).

Table 4.1
Attributes, levels and a priori expectations of the developed DCE

Attribute	Description (provided to respondents)	Levels ***NB: Base level in italics***	A priori expectations of impact on choice
Pain	The degree of pain associated with the procedure from a scale of 1 to 10, with 10 being the worst pain experienced.	Worst level of pain (10 out of 10) High levels (7 to 9) Medium levels (4 to 6) Low levels (1 to 3) *No pain*	A positive preference with low to no pain
Cost	Whether you have out-of-pocket costs not covered by Medicare (for example, for medication)	$2500 $150 $50 *Zero*	A negative preference for higher cost
Side effects	Whether you experience moderate bowel and bladder symptoms during and after treatment (e.g. moderate symptoms such as diarrhoea twice a day; or burning sensation on urination)	Decrease in overall side effects (1 in 10 experience moderate symptoms) *Same side effect likelihood (3 in 10 patients experience moderate symptoms)*	A positive preference for a decrease in side effects
Accuracy	Whether or not the radiation treatment delivery is more accurate	Increased accuracy in targeting the prostate (within 1mm) *Same accuracy (within 2mm)*	A positive preference for an increase in accuracy
Additional time	Whether or not additional time on the treatment couch is required for every day of treatment to achieve greater accuracy	30 mins per day 15 mins per day *5 mins per day*	A negative preference for additional time
Extra appointment	Whether or not you require an additional appointment at the hospital	Two additional appointments One additional appointment *No additional appointment*	A negative preference for additional appointments

Survey design and sample size

The design had 80 choice tasks, each with a size of 2, and was able to estimate the main effects of all attributes and the interaction between the attributes of pain and cost. It was a generator-developed design; further details in the supplementary material.[26] The 80 choice tasks were divided into 10 blocks and each respondent was randomly allocated to one block of 8 choice sets, with equal allocation (through both online and paper methods). With 20 respondents required to complete each block to provide sufficient power to analyse the underlying choice relationships, a sample size of 200 was required for each of Cohorts 1 and 2.[23,27]

The scenario provided to respondents and an example of a choice set is supplied in Supplementary Material (Figure 4.3 (supplementary) and 4.4 (supplementary) respectively). In addition to the DCE, demographics and follow-up questions pertaining to understanding of the DCE exercise were included (Figure 4.5 (supplementary and 4.5 (supplementary) respectively). Institutional ethics approval was granted (HREC/2019/QTHS/55905 and H7929, *Appendix D*). Implied consent was given by participants through completion of the survey.

Administration of the DCE

Cohort 1 was invited to participate through a mailout, utilising the oncology department's database (including radiation oncology and medical oncology) to identify patients with prostate cancer who attended between 2009 to 2019. An option to receive a paper copy of the survey was given to allow participation by those unable to complete the online survey. A follow-up reminder letter was sent to non-respondents after six weeks. The prostate cancer population were given the incentive of a small gift card, or donating the equal amount to a prostate cancer charity. Cohort 2 were recruited through an online panel (PureProfile), with a small monetary incentive awarded, as per usual practice by the panel. Quotas were set on key demographics, particularly age, to ensure a reasonable distribution for Cohort 2 respondents.

Analysis

All completed surveys were included in the analysis (that is, completed all choice sets and follow-up questions), with incomplete responses excluded from analysis. Where there was a clear indication that the respondent did not understand the choice tasks (e.g. a specific comment in the free text such as "Not understood at all. Just pressed right hand button to progress to next question."), a respondent was excluded from analysis. Two respondents from Cohort 1 were excluded for this reason.

Data were analysed to take account of the fact that we observed eight choices for each respondent. All attributes were expressed as categorical using dummy coding. Multinomial logit modelling (MNL) was used to analyse trade-offs made by respondents.[28,29] A p-value of <0.05 indicated attribute/level significance, with the sign of the choice coefficient indicating a positive or negative preference effect.

Marginal willingness to pay (mWTP) and relative attribute importance was calculated as a part of the trade-off analysis. The calculation of mWTP demonstrated how the respondents' value specific attributes and levels in relation to each other.[30] A negative mWTP value indicates the respondents would have to be paid to accept the particular attribute/level, whereas a positive mWTP indicates they would be willing to pay for the particular attribute/level. The method of means was used to calculate the mWTP.[31] Relative importance of each attribute was calculated as the ratio of the range of coefficents for a particular attribute over the total range for all attributes.

As two different cohorts were being surveyed, the assumption was made that there would be differences in respondent choice behaviour. Therefore, Latent Class Analysis (LCA) was used to analyse differences in preference behaviour. This model assumes there are latent classes with distinct preferences, allowing prediction of the probability of an individual belonging to each class. The class membership probabilities were calculated for each respondent. Bayesian information criterion was used to determine the optimal number of classes for LCA, with cohort membership as a determinant.[32] Membership probability was then used to investigate whether there was any alignment between socio-demographic characteristics and

respondent preferences through subsequent multivariate regression modelling, using class membership probability as the response.

Demographic data and responses to follow-up questions were summarised using descriptive statistics and compared across the two populations using t-tests and chi-square tests as appropriate (or nonparametric equivalent tests when assumptions were viloated). All analysis was undertaken in R version 3.6.1, using mlogit and gmnl packages.[33–35]

Results

1200 letters of invitation were mailed for Cohort 1 with a 16.7% response rate (n=236), including 81 (34.3%) completing the survey by paper. Twenty-four phone calls were fielded with specific survey questions, with 14 completing the survey following phone call clarification. Recruitment of Cohort 2 (n=240) was completed over 4 days through the online panel. The mean age of the respondents was 73.8 and 44.3 years for Cohorts 1 and 2 respectively. Characteristics of the two cohorts are summarised in Table 4.2, proportional to the Australian male population statistics.

Table 4.2

Survey completion and demographics of respondents

Survey Completion	**Cohort 1 PCa Patients n=236**		**Cohort 2 General Population n=240**		**ABS Australian Male Population**[39]
Median minutes to complete	27.6		9.8		
Non-completion rate (%)	44.9		52.7		
Demographics	*n*	*%*	*n*	*%*	*%*
Age (p< 0.001)					
18-29	0	0	44	18.3	21.9
30-39	0	0	61	25.4	18.9
40-49	0	0	48	20.0	16.6
50-59	1	0.4	36	15.0	15.5
60-69	45	19.1	27	11.3	13.3
70-79	121	51.3	19	7.9	9.3
80+	59	25.0	5	2.1	4.5
Did not answer	10	4.2	0	0.0	
Location (p< 0.001)					
QLD	229	97.0	42	17.5	20.1
NSW	0	0.0	68	28.3	31.8
VIC	0	0.0	60	25.0	26.0
TAS	0	0.0	16	6.7	2.1
SA	0	0.0	15	6.3	6.9
NT	0	0.0	3	1.3	1.0
ACT	0	0.0	12	5.0	1.7
WA	0	0.0	24	10.0	10.4
Did not answer	7	3.0	0	0.0	
Relationship status (p< 0.001)					
Single, never married	14	5.9	66	27.5	
Married or domestic partnership	169	71.6	141	58.8	
Widowed	21	8.9	3	1.3	
Divorced or separated	25	10.6	22	9.2	
Prefer not to say	1	0.4	0	0.0	
Did not answer	6	2.5	8	3.3	
Employment status (p< 0.001)					
Full-time employment	19	8.1	119	49.6	
Part-time employment	2	0.8	32	13.3	
Casual	2	0.8	11	4.6	
Retired	202	85.6	45	18.8	
Unemployed	4	1.7	30	12.5	
Prefer not to say	1	0.4	2	0.8	

Survey Completion	**Cohort 1 PCa Patients n=236**		**Cohort 2 General Population n=240**		**ABS Australian Male Population**[39]
Did not answer	6	2.5	1	0.4	
Level of education (p< 0.001)					
Less than high school	26	11.0	6	2.5	
High school (or equivalent)	85	36.0	55	22.9	
Apprenticeship, TAFE or tech school	83	35.2	68	28.3	
Undergraduate degree	28	11.9	74	30.8	
Postgraduate degree	3	1.3	33	13.8	
Prefer not to say	5	2.1	1	0.4	
Did not answer	6	2.5	3	1.3	
Annual household income (p< 0.001)					
≤ $39,999	116	49.2	58	24.2	
$40,000 - $79,999	53	22.5	69	28.8	
$80,000 - $149,999	19	8.1	74	30.8	
≥ $150,000	4	1.7	26	10.8	
Unknown	44	18.7	13	5.4	
Ethnicity† (p=0.076)					
Aboriginal and Torres Strait Islander	1	0.4	4	1.7	0.1
Aboriginal	2	0.8	8	3.3	3.0
Torres Strait Islander	0	0.0	2	0.8	0.2
Non-Indigenous	218	92.4	223	92.9	96.7
Did not answer	15	6.4	3	1.3	
Born (p=0.787)					
Australia	169	71.6	174	72.5	
Other	58	24.6	65	27.1	
Did not answer	9	3.8	1	0.4	
Language (p=0.029)					
English	221	93.6	220	91.7	
Other	6	2.5	18	7.5	
Did not answer	9	3.8	2	0.8	
Health State† (p< 0.001)					
Excellent	13	5.5	40	16.7	20.9
Very Good	52	22.0	91	37.9	35.5
Good	96	40.7	63	26.3	28.8
Fair	54	22.9	34	14.2	11.0
Poor	12	5.1	12	5.0	3.7
Did not answer	9	3.8	0	0.0	

Note: P-values are comparing Men with PCa and General Population, with Australian Bureau of Statistics (ABS) data supplied for reference only
†Combined Male and Female Data for ABS data

The MNL modelling results are presented in Table 4.3, including the preference coefficients for each attribute/level, the mWTP and relative attribute importance calculated. The most important attributes were pain, cost and accuracy for both cohorts ($p<0.01$), reflected in both the MNL coefficients and significance, and the relative attribute importance weightings. PCa patients were willing to pay more to avoid the worst pain attribute than the general population, and also willing to pay more for increased accuracy. Due to the age differences in the two cohorts, a sub-analysis was completed on responses from those in Cohort 2 greater than 50 years. While underpowered (with n=87, and some choice sets in this sub-analysis completed only 5 times), the results of this MNL showed a similar trend of preferring less pain and cost.

Table 4.3
MNL model of coefficients, marginal willingness to pay and relative attribute importance

		PCa			**Gen Pop**		
Attribute	**Level**	**Coefficient (SE)**	**mWTP ($)‡**	**Relative Attribute Importance†**	**Coefficient (SE)**	**mWTP ($)‡**	**Relative Attribute Importance†**
Pain *Base: No pain*	Low	-0.41 (0.13) **	-205.30	0.55	-0.22 (0.13) .	-66.93	0.49
	Medium	-0.61 (0.10) ***	-304.59		-0.76 (0.11) ***	-234.83	
	High	-1.19 (0.11) ***	-591.43		-1.05 (0.11) ***	-324.16	
	Worst	-1.71 (0.13) ***	-852.38		-1.54 (0.13) ***	-474.40	
Side Effects *Base: Decreased*	Same	-0.16 (0.05) **	-77.75	0.03	-0.21 (0.05) ***	-63.07	0.04
Accuracy *Base: Same*	Increased	0.55 (0.05) ***	272.05	0.11	0.37 (0.05) ***	113.15	0.07
Time *Base: 5 mins*	15 mins	0.08 (0.08)	40.30	0.01	0.00 (0.08)	-0.39	0.02
	30 mins	-0.05 (0.08)	-23.58		-0.23 (0.08) **	-71.74	
Appointments *Base: No appt*	One appt	-0.06 (0.08)	-27.97	0.03	-0.04 (0.08)	-11.29	0.02
	Two appts	-0.10 (0.07)	-47.49		-0.06 (0.07)	-19.46	
Cost *Base: Zero*	$50	-0.17 (0.09) .		0.27	-0.29 (0.09) **		0.36
	$150	-0.40 (0.09) ***			-0.65 (0.09) ***		
	$2500	-1.08 (0.09) ***			-1.42 (0.09) ***		
		Log-Likelihood: -1111.1 Wald: X2 = 446.2			Log-Likelihood: -1068 Wald: X2 = 454		

*Significance: *** = 0; ** = 0.001; *= 0.01; . = 0.05*
‡ A negative mWTP value indicates the respondents would have to be paid to accept the particular attribute/level. A positive mWTP indicates the respondents would be willing to pay for the particular attribute/level

† Relative Attribute Importance: A higher value indicates greater importance

LCA revealed 3 classes (Table 4.4), with up to 5 classes in total considered. Class 1 and 2 were focused more on the process-related attributes of pain and cost, with Class 1 considering side effects, and Class 2 also considering additional appointments. Class 3 was focused on the clinical efficacy attributes of accuracy and side effects. The proportion in each of the classes was 28.9%, 34.3% and 36.8% respectively for Classes 1, 2 and 3. There was a tendency for respondents in Class 2 to be younger, have a higher income and fewer had a previous prostate cancer diagnosis (Table 4.5). Those in Class 3 tended to be more highly educated.

Table 4.4
Latent class analysis

		Class 1	**Class 2**	**Class 3**
Attribute	Level	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Pain *Base: No pain*	Low	-0.06 (0.39)	-1.27 (0.48) **	-0.30 (0.15) .
	Medium	-1.51 (0.29) ***	-2.16 (0.60) ***	-0.19 (0.13)
	High	-2.63 (0.33) ***	-2.15 (0.38) ***	-0.35 (0.15) *
	Worst	-4.51 (0.85) ***	-3.87 (0.69) ***	-0.52 (0.18) **
Side Effects *Base: Decreased*	Same	-0.41 (0.18) *	-0.27 (0.23)	-0.21 (0.07) **
Accuracy *Base: Same*	Increased	0.37 (0.21) .	0.37 (0.24)	0.75 (0.09) ***
Time *Base: 5 mins*	15 mins	-0.00 (0.2)	-0.04 (0.28)	0.03 (0.10)
	30 mins	-0.13 (0.2)	-0.23 (0.27)	-0.11 (0.10)
Appointments *Base: No appt*	One appt	-0.05 (0.2)	-0.21 (0.29)	-0.04 (0.09)
	Two appts	-0.14 (0.19)	-0.52 (0.24) *	-0.10 (0.09)
Cost *Base: Zero*	$50	-0.17 (0.26)	-1.07 (0.33) **	0.05 (0.12)
	$150	-0.27 (0.29)	-2.82 (0.38) ***	0.08 (0.11)
	$2500	-1.51 (0.29) ***	-6.23 (0.94) ***	-0.15 (0.13)

Optimization of log-likelihood by BFGS maximization Log Likelihood: -1793.9 Number of observations: 3806 Number of iterations: 661
Significance: **** = 0; ** = 0.001; *= 0.01; . = 0.05*

The magnitude of the coefficients indicates the importance of particular attributes/levels for each class. A positive coefficient indicates a preference over the base level for that particular attribute/level.

Table 4.5
Multivariate regression on demographics for class membership

		Class 1	**Class 2**	**Class 3**
		Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
(Intercept)		0.28 (0.05) ***	0.66 (0.05) ***	0.06 (0.05) ***
Age		0.0007 (0.0005)	-0.0026 (0.0005) ***	0.0019 (0.0006) **
Previous PCa	*(1=Y; 2=N)*	0.04 (0.02) *	-0.07 (0.02) ***	0.03 (0.02) .
Income	*40,000-79,999*	-0.07 (0.02) ***	0.01 (0.02)	0.06 (0.02) ***
	80,000-149,999	0.04 (0.02) .	-0.01 (0.02)	-0.03 (0.02)
	>150,000	0.02 (0.03)	0.13 (0.03) ***	-0.16 (0.03) ***
Education	*High School*	-0.15 (0.03) ***	-0.12 (0.03) ***	0.26 (0.03) ***
	Apprenticeship	-0.04 (0.03)	-0.14 (0.03) ***	0.18 (0.03) ***
	Undergraduate	-0.09 (0.03) **	-0.17 (0.03) ***	0.26 (0.04) ***
	Postgraduate	-0.10 (0.04) *	-0.19 (0.04) ***	0.29 (0.04) ***
Relationship	*Married*	0.02 (0.02)	-0.04 (0.02) .	0.02 (0.02)
	Widowed	0.00 (0.04)	-0.08 (0.04) *	0.07 (0.04) .
	Separated	0.12 (0.03) ***	-0.16 (0.03) ***	0.04 (0.03)
Health	*Very Good*	-0.01 (0.02)	0.04 (0.02)	-0.04 (0.03)
	Good	0.00	0.04 (0.02)	-0.04 (0.03)
	Fair	0.05	0.01	-0.06
	Poor	0.05	0.09	-0.14

Significance: **** = 0; ** = 0.001; *= 0.01; . = 0.05*
The magnitude of the coefficients indicates the effectof the particular demographic/level on class membership probability.

The general population tended to rate their embarrassment levels greater than the PCa population in all scenarios given (Table 4.6). There was some variation in understanding and difficulty, with the majority indicating a good understanding and that the survey was easy to complete (Table 4.7 (supplementary)). Overall, the general population answered more

favourably, however there was also an increased drop-out rate in this cohort (Table 4.7 (supplementary)).

Table 4.6
Median scores for embarrassment

	Cohort 1 **PCa Patients** **Median (IQR)**	**Cohort 2** **General Population** **Median (IQR)**	**P value**
Overall Potential Embarrassment	0 (0-1)	2 (0-6)	< 0.001
Digital Rectal Exam	1 (0-3)	5 (2-7)	< 0.001
Internal US	1 (0-3)	5 (2-7)	< 0.001
External US	0 (0-2)	3 (0-6)	< 0.001

Rated on an Adjectival scale with 0 = No embarrassment to 10 = Extremely embarrassing.

Discussion

This study investigated the preferences of men in Australia regarding image-guidance for prostate cancer radiation therapy. The preferences in both cohorts were for image guidance with less pain, lower cost and greater accuracy. While intra-fraction monitoring using FMs or TPUS improves treatment accuracy, TPUS causes less pain and less ongoing consumable cost. Differences in sociodemographic data was expected due to the different age groups, and therefore different life stages. Nevertheless, there was preference homogeniety between the two cohorts regardless of differences in age. This was also supported by the preference trends noted in the age sub-analysis.

Our previous qualitative study indicated pain or discomfort as important considerations for men and this is supported by our results.[16] The attribute of accuracy was considered important in the population of both cohorts, but more so for the PCa cohort. Similarly, side effects were less important to the PCa cohort in this study, corroborating findings of willingness of patients with prostate cancer to undertake treatments with known side effects.[36] In a pilot study by Sigurdson *et al* (2019) to develop a DCE investigating preferences for hypofractionated prostate radiotherapy, respondents gave an unexpectedly high

weighting to avoiding FM.[37] However, this was not replicated in their larger DCE, instead risk of PSA recurrence followed by risks of late and acute toxicity were most important.[38,39] These findings mirror those of our own study.

When considering the levels for the cost attribute, an upper bound of $2,500 was selected to reflect potential costs in the private sector (for example, insertion of FMs). However, universal health care in Australia means that out-of-pocket costs to patients are minimal for these procedures through the public sector. The cost levels accounted only for direct costs associated with the image-guidance procedures such as prophylactic antibiotic cover and may not reflect other out-of-pocket costs such as travel and accommodation required to attend a radiation therapy centre.[40] Nevertheless, our results show that there was a preference for services associated with lower costs. With financial toxicity in patients with cancer increasingly recognised, it is important to consider the cost to the patient of any image-guidance procedure or indeed of any new technology.[41,42]

The class memberships identified in the LCA provides guidance to radiation oncologists in tailoring their discussions around image-guidance with patients. In particular, individuals in Class 3 tended to be more highly educated and were more focussed on side effects and accuracy. There is growing evidence around the importance of health literacy as a consideration in person-centred care and informed decision-making in oncology.[43–46] It is prudent for radiation oncologists to provide additional justification for treatment recommendations according to the patient's wishes and information requirements, while ensuring all patients are providing informed consent to the motion-monitoring procedure. Conversely, individuals in Class 2 were more concerned with pain, cost and additional appointments. Class 2 respondents were more likely to be in higher income brackets and of lower age, suggesting this group is at a different stage of life whereby the opportunity cost and inconvenience of additional appointments may impact their life more. Applying these class findings more broadly will depend upon the demographics of patient cohorts.

Recognition of individual preferences may allow radiation oncologists to better tailor treatments to respect their patients' preferences. This may be particularly relevant when patients are inclined to receive treatment based on clinician recommendations over their own personal preferences.[16,47,48] Treatment regret is commonly reported when worse than

expected side effects occur.[49–52] Having lived experience, the prostate cancer cohort is likely to have some experience of treatment regret suggesting a rationale for their willingness to pay a higher price for reduced side effects.

The motion monitoring preferences described in this study pertain more to policymakers, as most departments do not have multiple motion monitoring solutions. However, the results of this study may inform departments when choosing which solution to implement.

Limitations

DCEs collect stated versus actual preference. However, it would be very difficult to undertake a study to observe actual preference in practice, as most radiation oncology departments have one technology to offer patients.

Additionally, the cognitive burden of DCEs is understood and every attempt was made to reduce this burden during the design phase. However, there is a possibility some respondents randomly selected choices to proceed through the survey. Follow-up DCE comprehension and difficulty questions indicated a good level of self-reported understanding among participants suggesting the random selection was minimal. The non-completion rates between 44.9 and 52.7% for both populations indicates that some participants may have not completed due to the cognitive burden, among other reasons.

Comparison of responder and non-responder demographics of the PCa cohort is not possible, as data relating to education level and income was not collected at our institution. However, the characteristics of responders suggests men with a range of education and income levels completed the DCE. While there may have been participation by PCa patients with greater concern or anxiety, the results are comparable to the general population who do not have that lived experience and presumably less anxiety around a prostate cancer diagnosis and treatment.

The PCa cohort differed on most of the measured demograhpic characteristics from the general population. Sub-analysis was completed on responses from those in Cohort 2 (general population) with age greater than 50 years to address this, however the findings must be

interpreted within the context of the bias arising from the pre-existing differences in the cohorts.

Future Directions

To our knowledge, this is the first DCE comparing prostate image-guidance techniques in radiation therapy. With continuing advances in the radiation oncology field, such as the magnetic resonance linear accelerators (MRL), future DCE research could be undertaken to understand preferences when considering implementation of new technologies. The MRL has capabilities for real-time monitoring of the organ motion without marker insertion (and thereby reduced pain and associated IGRT cost to the patient), however with different factors to consider, such as noise and physical environment. As advancements are introduced, clinicians should be aware of the wishes of patients for increased information and shared decision-making.

Conclusion

Patients with prostate cancer and the general population preferred lower cost and pain, and improved accuracy. Given the considerable capital investment required for most image-guidance solutions, it is reassuring that men value the increased accuracy and benefits afforded. This DCE provides patient-preference data which can be considered by radiation oncology departments looking to implement or update their prostate IGRT. It is important to consider preferences of patients in considering the introduction of new treatments and technological advancements. Therefore, radiation oncology centres should consider patient preferences of image-guidance techniques in addition to the clinical and technical evidence for clinical decision making.

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Supplementary

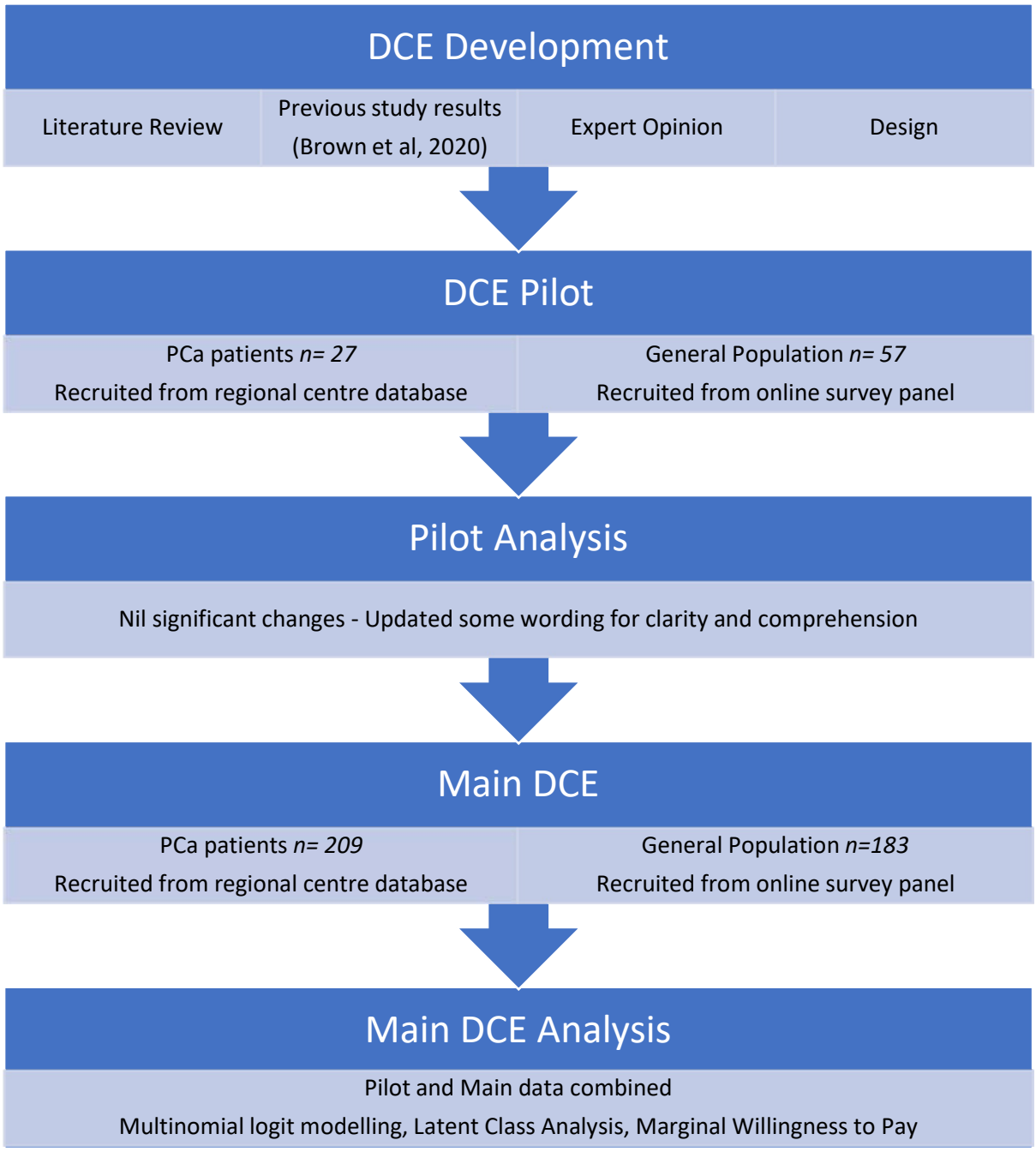


Figure 4.2 (supplementary) Development to analysis of DCE

DCE development

Piloting the DCE

For Cohort 1, 100 patients with prostate cancer were mailed a letter of invite, with 27 completing the survey (21 online and 6 paper). Fifty-seven men for Cohort 2 completed the pilot survey via the online panel. No changes needed to be made to the attributes or levels (**Error! Reference source not found.**) following the pilot, with only minor editing of wording and follow-up question order implemented prior to the main survey rollout. The pilot responses were incorporated with the responses from the main survey for analysis, and the combined data are presented.

DCE design details

The generator-developed construction approach for DCEs requires an initial orthogonal array and one or more generators. As we were interested in estimating the interaction between pain (with 5 levels) and cost (with 4 levels) we needed to have one attribute with 20 levels. The smallest suitable orthogonal array had 80 rows.[1] The other 4 attribute levels were obtained by collapsing the entries in the first 4 columns to give the two binary and two ternary attributes. The entries in columns 5 to 10 were discarded. The generator was (1,1,1,2,7). After construction of the choice tasks, the 20-level attribute was converted into pairs of levels representing pain and cost. Choice tasks were allocated into blocks randomly.

[1] Kuhfeld, WF (2006) Orthogonal arrays. Technical report, SAS Institute. Available at http://support.sas.com/techsup/technote/ts723_Designs.txt

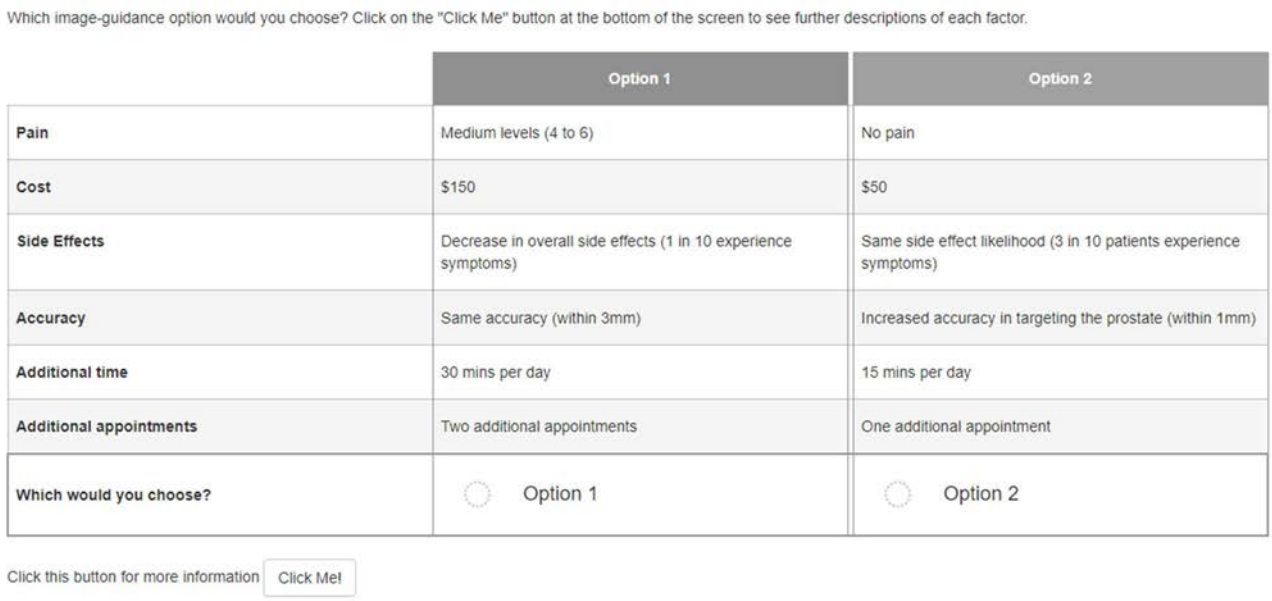
The questions in this survey are hypothetical. Imagine you've been diagnosed with early-stage prostate cancer and you've chosen to have radiation therapy treatment. Radiation therapy treatment involves coming into the radiation oncology department every day, Monday to Friday, for a treatment session that lasts approximately half an hour. Overall, prostate radiation therapy treatment ranges from 20 sessions over 4 weeks, up to 39 sessions over 8 weeks.

Your doctor has asked you to choose between 2 image-guidance options you have in conjunction with your radiation therapy treatment to increase the accuracy. Image-guidance allows the radiation therapists to locate your prostate and detect potential prostate motion during radiation delivery. These options differ based on factors like the pain you may experience, side effects, additional appointments required, additional daily time required, and costs.

You will now see 8 questions, and for each you will be asked to select your preferred option regarding imaging. You will be asked to choose across varying values of the factors in those options so that we can understand which factors are important to men when choosing one option over the other.

These options do not reflect your personal circumstances and in some cases are unlikely to occur in practice. As much as possible, please answer these questions as if you are facing the prostate cancer treatment options described. There are no right or wrong answers, and your answers will not influence your current, future or potential treatment options.

Figure 4.3 (supplementary) Vignette provided to participants


Which image-guidance option would you choose? Click on the "Click Me" button at the bottom of the screen to see further descriptions of each factor.

	Option 1	Option 2
Pain	Medium levels (4 to 6)	No pain
Cost	$150	$50
Side Effects	Decrease in overall side effects (1 in 10 experience symptoms)	Same side effect likelihood (3 in 10 patients experience symptoms)
Accuracy	Same accuracy (within 3mm)	Increased accuracy in targeting the prostate (within 1mm)
Additional time	30 mins per day	15 mins per day
Additional appointments	Two additional appointments	One additional appointment
Which would you choose?	○ Option 1	○ Option 2

Click this button for more information Click Me!

Figure 4.4 (supplementary) Example choice set

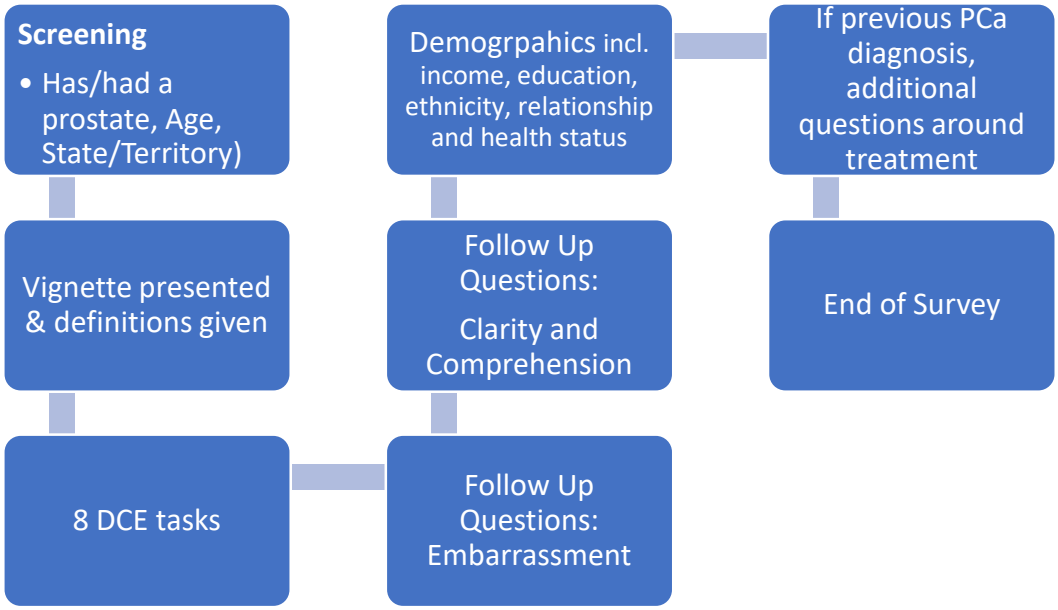


Figure 4.5 (supplementary) survey flow

(Note: formatting condensed)

The following questions ask how you were thinking when making the choices in the questions you have just completed.

- Reflect on how you made your decision when answering the question. Did potential embarrassment at having your genitals and anal area exposed to the health professionals factor into your thinking when making your choices? *(Please circle)*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

- Consider the following medical scenarios and rate your level of embarrassment *(Please circle)*:

    a. *A digital rectal exam, where the doctor inserts their finger into your back passage to feel your prostate*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

    b. *An internal ultrasound probe – where the probe is inserted into your back passage for the purpose of inserting markers into the prostate*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

    c. *An external ultrasound – where an ultrasound probe is placed externally against your perineum for the purpose of seeing your prostate on ultrasound and monitoring for motion. The perineum is the skin between your anus and scrotum (the part of you that would come into contact with a bicycle seat).*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

- Thinking about the questions you just answered, please fill out the following rating table *(Please tick)*.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
The language used in the questions was clear.	○	○	○	○	○
The questions were difficult to understand.	○	○	○	○	○
The task was difficult to complete.	○	○	○	○	○

Please provide any comments you wish to make.

_____

- Please fill out the following rating table about the survey.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
The instructions for the survey were clear.	○	○	○	○	○
The description of prostate cancer and the procedure was clear.	○	○	○	○	○
The description of prostate cancer and radiation therapy treatment was relevant to the task of answering the questions.	○	○	○	○	○

Please provide any comments you wish to make.

_____

- How much did each of the below factors influence your decision? (*please rate all the factors, selecting one from not at all to extremely)*

	Not at all	Slightly	Moderately	Very Much	Extremely
Being able to meet the costs of care	○	○	○	○	○
The rate and severity of side effects	○	○	○	○	○
The impact of additional appointments	○	○	○	○	○
Whether there would be pain, and its duration	○	○	○	○	○
The impact of additional daily time for treatment	○	○	○	○	○
Whether treatment was more accurate	○	○	○	○	○

- Thinking about the factors which varied in each of the questions, which one was the most important when choosing between the options? *(Please tick only one answer)*

○ The impact of additional daily time for treatment	○ Whether there would be pain, and its du
○ The rate and severity of side effects	○ Being able to meet the costs of care
○ Whether treatment was more accurate	○ The impact of additional appointments

7)

8) Are there any factors you would consider that we are missing?

_____

- Thinking about the factors which varied in each of the questions, which one was the least important when choosing between the options? *(Please tick only one answer)*

○ The impact of additional daily time for treatment	○ Whether there would be pain, and its du
○ The rate and severity of side effects	○ Being able to meet the costs of care
○ Whether treatment was more accurate	○ The impact of additional appointments

- Did you have a strategy, or decision rule, for how you made your choices? *(Please tick)*

○ I did not have a strategy

○ I focused only on the factors I thought were important

○ I considered most of the factors all the time.

○ I considered all the factors each time.

○ Other (please specify): _____

Please only answer this next question if you focused only on factors you thought were important:

a. In what order did you think about the factors when making your decision? Please number only those that you focused on, and in the order of importance to your decision making from most (starting with the number 1) to least important.

○ The impact of additional daily time for treatment	○ Whether there would be pain, and its du
○ The rate and severity of side effects	○ Being able to meet the costs of care
○ Whether treatment was more accurate	○ The impact of additional appointments

- Did the number of factors (rows) affect your ability to answer each question? (*Please tick only one*)

○ The number of factors did not affect how I answered

○ There were too many factors and it made it difficult to answer the questions

○ There were too many factors so I only focused on the ones I thought were important

Other_____

Figure 4.6 (supplementary) DCE follow-up questions

Table 4.7 (supplementary)
Comprehension and understanding follow up questions

	Cohort 1 PCa Patients n=236	%	Cohort 2 General Population n=240	%	p-value
The language used in the questions was clear.					
Strongly agree	49	20.8%	101	42.1%	< 0.001
Agree	141	59.7%	112	46.7%	
Neither	22	9.3%	21	8.8%	
Disagree	12	5.1%	3	1.3%	
Strongly disagree	6	2.5%	3	1.3%	
Missing	6	2.5%	0	0.0%	
The questions were difficult to understand.					
Strongly agree	10	4.2%	10	4.2%	0.085
Agree	33	14.0%	21	8.8%	
Neither	32	13.6%	50	20.8%	
Disagree	94	39.8%	89	37.1%	
Strongly disagree	55	23.3%	70	29.2%	
Missing	12	5.1%	0	0.0%	
The task was difficult to complete.					
Strongly agree	9	3.8%	11	4.6%	0.624
Agree	21	8.9%	24	10.0%	
Neither	36	15.3%	44	18.3%	
Disagree	100	42.4%	90	37.5%	
Strongly disagree	58	24.6%	71	29.6%	
Missing	12	5.1%	0	0.0%	
The instructions for the survey were clear.					
Strongly agree	45	19.1%	88	36.7%	0.002
Agree	138	58.5%	124	51.7%	
Neither	28	11.9%	19	7.9%	
Disagree	11	4.7%	7	2.9%	
Strongly disagree	4	1.7%	2	0.8%	
Missing	10	4.2%	0	0.0%	
The description of prostate cancer and the procedure was clear.					
Strongly agree	41	17.4%	76	31.7%	< 0.001
Agree	142	60.2%	118	49.2%	
Neither	25	10.6%	39	16.3%	
Disagree	13	5.5%	4	1.7%	
Strongly disagree	5	2.1%	3	1.3%	
Missing	10	4.2%	0	0.0%	
The description was relevant to the task.					

	Cohort 1 PCa Patients n=236	%	Cohort 2 General Population n=240	%	p-value
Strongly agree	45	19.1%	74	30.8%	0.002
Agree	148	62.7%	125	52.1%	
Neither	19	8.1%	35	14.6%	
Disagree	10	4.2%	4	1.7%	
Strongly disagree	5	2.1%	2	0.8%	
Missing	9	3.8%	0	0.0%	

Addendum

Additional information regarding the expert panel

There were 2 radiation oncologists, 3 radiation therapists and 1 prostate cancer nurse on the panel. This represented all of the radiation oncologists treating prostate cancer at our centre, the only prostate cancer nurse within the hospital and 50% of the radiation therapists who were assisting with both fiducial marker insertion and treating with Clarity within the department at the time of the study.

Additional information regarding the Latent Class Analysis (LCA)

It is also reasonable to expect different respondent behaviours and preferences in the same cohort, as different demographics and socio-economic factors may be noted in the same cohort which may impact choices. The LCA was undertaken by combining data from both cohorts.

Additional information regarding the General Population Inclusion/Exclusion Criteria and demographics

The inclusion criteria for the general population were: 1) over 18 years old in age, and 2) have or have had a prostate. Data was collected on if the respondents had personal lived experience of prostate cancer through the question “Have you ever had a prostate cancer diagnosis”, of which 27 (11.2%) responded “Yes”. No further sub-analysis was undertaken based on this personal lived experience.

Additional information regarding the non-completion rates

A completed survey was considered to be one which all choice sets and demographic questions were completed, with any drop-out prior to the completion of this minimum data excluded from analysis.

Translation of Evidence Infographic

Figure 4.7 Translation of evidence infographic - Chapter 4

Linking to Subsequent Chapter

The findings of this study led to developing a scoping review to contextualise and understand more about patient preferences in prostate radiation therapy (Chapter 6).

Additional results and analysis from the survey (specifically, content analysis of free-text comments, and analysis of the patient recall) are detailed in Chapter 5.

This chapter further addressed the research question:

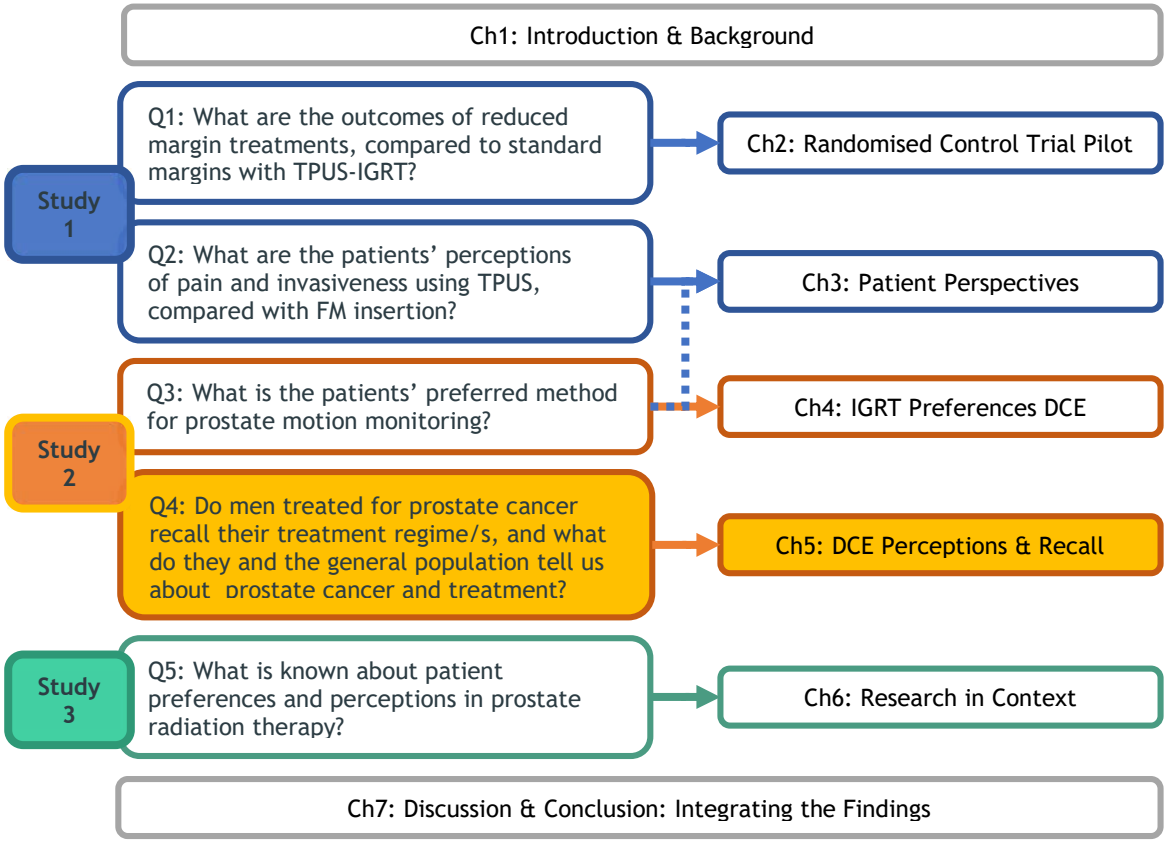
3) What is the patients' preferred method for prostate motion monitoring (if both methods are presumed to achieve the same outcome) and what factors do patients consider if choosing between different technologies and procedures?

Chapter 5 Perceptions from DCE and Patient Recall

Article: Perceptions and recall of treatment for prostate cancer: a survey of two populations

Brown A, Tan A, Anable L, Callander E, de Abreu Lourenco R, Pain T. Perceptions and recall of treatment for prostate cancer: A survey of two populations. Tech Innov Patient Support Radiat Oncol 2022;24:78–85. https://doi.org/10.1016/j.tipsro.2022.10.001.

This chapter includes an exact copy of the published manuscript, except the formatting of section sub-headings, figure, table and reference numbers have been edited for the purpose of the thesis.



Note: TPUS: Transperineal Ultrasound; IGRT: Image-guided radiation therapy; FM: Fiducial Marker; DCE: Discrete Choice Experiment

Figure 5.1: Schematic overview of thesis: study 2, Chapter 5

Context of sub-study 2

There were three questions in the DCE survey that allowed for free-text comments to be provided by the participants. We were surprised at the level of engagement both by the previous patients with prostate cancer and the general population. The free-text comments led to content analysis, which is presented in this chapter. In designing the DCE, I wanted to also understand if patients recalled their previous treatment, so the prostate patients were invited to indicate their treatment and image-guidance related procedures and optionally identify themselves (through initials and date-of-birth) to allow for comparison to their medical records. Patient recall is discussed further in the Discussion and Conclusion (Chapter 7).

Abstract

Background

The complexity of prostate cancer care can impact on patient understanding and participation in shared decision-making. This study used a survey-based approach to investigate patients' recall of their prostate cancer treatment, and more broadly, to understand the perceptions of patients and the general population of prostate cancer treatment.

Method

The survey was completed by 236 patients with prostate cancer (PCa cohort) and 240 participants from the general population of Australia (GenPop cohort). Free-text comments from both cohorts were analysed using content analysis. The PCa cohort reported which treatments and image-guidance related procedures they had received. These patient-reports were compared to medical records and analysed using proportion agreement, kappa statistics and regression analysis.

Results

135 (57%) PCa and 99 (41%) GenPop respondents provided at least one comment. Five major themes were identified by both cohorts: sharing experiences of treatment; preferences insights and reflections; mindsets; general commentary on the survey; and factors missing

from the survey. There was overall good treatment recall amongst the PCa cohort, with proportions of correct recall ranging from 97.3% for chemotherapy to 66.8% for hormone therapy. There was a tendency for younger patients (<70 years old) to recall their hormone treatment more correctly.

Conclusion

Participant comments suggest the complexity of prostate cancer diagnosis and treatment, and the varying perceptions and experiences of participants with prostate cancer. Patients' recall overall was good for both treatment and image-guidance related procedures/approaches, however the poorer recall of hormone therapy requires further investigation.

Introduction

Value-based healthcare is at the core of service delivery, with emphasis on appropriate care to achieve patients' personal goals.[1] Balancing clinically desirable outcomes with outcomes that matter to patients is recognised as critical.[2] Value-based frameworks within radiation oncology encourage the incorporation of patient-centred and safety-focused processes.[3,4] However, to achieve this patient-centred, value-based radiation oncology care, the perspectives of patients need to be understood.

A cancer diagnosis can be a fraught time for an individual as there is a great deal of information to digest and challenging treatment decisions to be made.[5] The move to patient-centred care is predicated on the clinician explaining complex treatments and procedures to an individual so they can understand. However, low health literacy is reported in 60% of adult Australians and 89% of US adults, making explanation a challenging task and affecting the patient's ability to make health decisions, potentially leading to poorer health outcomes.[6–9]

Ability to recall medical information is linked to greater health literacy.[10] Recall ability has implications for shared decision-making as patients must understand the clinical information to make an informed decision.[8] Radiation oncologists have reported employing many techniques to address the observed variation in health literacy of their patients, including tailoring the level of detail to the individual patient, using visual aids, repeating information,

and asking the patient to paraphrase information.[9] Patients' correct recall of health conditions and treatment is also important for patient-centred care, particularly when providing health history to new clinicians as the accuracy of recall may influence healthcare offered.[11,12] Furthermore, recall is important for researchers investigating patient-reported outcomes or experience as patients' recall ability may introduce variances.[13,14]

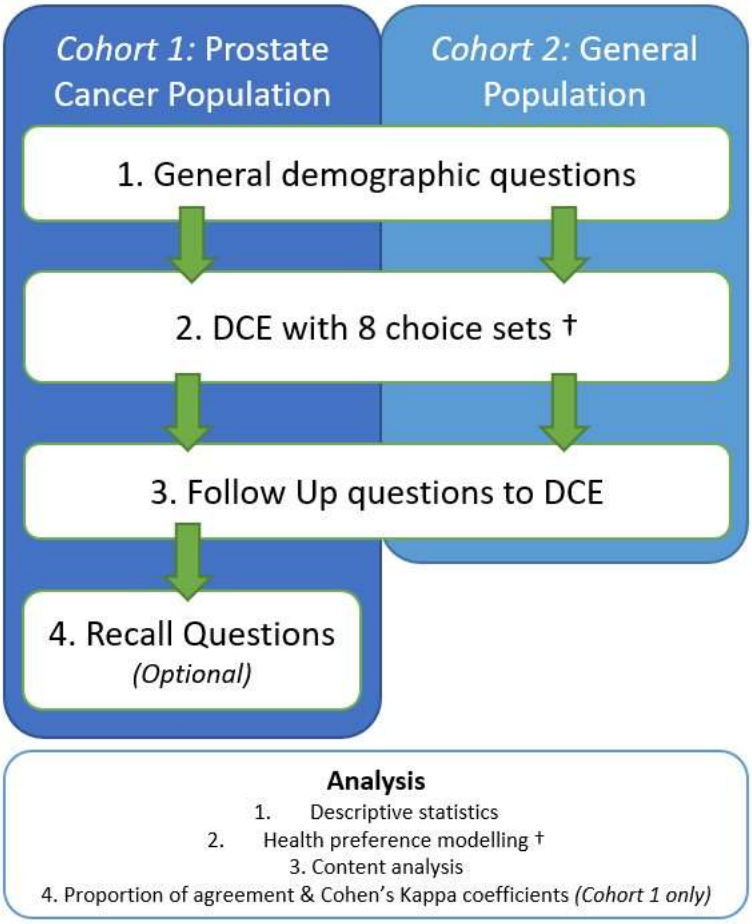
This present study builds upon two previous studies.[15,16] The first study captured the perspectives and preferences of 22 prostate cancer patients regarding image-guidance related procedures (fiducial markers versus transperineal ultrasound) via semi-structured interviews.[15] Participants reported image-guidance procedures were tolerable and recognised the importance for increased accuracy, however despite having experienced both fiducial marker insertion, and transperineal ultrasound prostate monitoring during radiation therapy, 45% of participants could not identify which image-guidance method they preferred. [15] The second study, a discrete choice experiment (DCE) survey, was undertaken to elicit preferences regarding image-guidance related procedures in the patient population and members of the Australian general population.[16] The DCE found that both patients and general population valued pain, cost, and accuracy, with differences in preferences in three groups of respondents: one group focussed on clinical efficacy in the attributes of accuracy and side effects, and two other groups focused more on process-related attributes of pain and cost. [16]

The aim of this study was to gain a better insight on participant's perspectives on treatment and image-guidance related procedures in prostate cancer radiation therapy by analysing free-text comments given on the larger survey. [16] This information will contribute to value-based radiation oncology by exploring patient and general population's insights around prostate image-guidance related procedures and radiation therapy. A secondary aim was to evaluate patients' recall of prior treatments they received for their prostate cancer, a separate component of the larger survey. This will provide information on potential improvements for information provision in prostate cancer radiation therapy.

Methods

The survey included a discrete choice experiment (DCE), free-text follow-up questions pertaining to the DCE, and treatment recall questions (as applicable) were purposively designed. 1200 patients presenting to a regional cancer centre with a prostate cancer diagnosis between 2009 to 2019 were invited to participate in the survey through a letter of invitation (from herein: "PCa cohort"). All invited patients had a consultation with a Radiation Oncologist, but not all underwent a radiation oncology treatment. This broad invitation was intended to maximise the range of perspectives captured from PCa cohort participants, not just limited to radiation oncology. Standardly, a patient was referred in the public setting to both a urologist and radiation oncologist to make an informed decision regarding their treatment options. No changes to standard information provision were made in the invitation period. Further contextual information about the treatment centre can be found in Supplementary materials.

A cohort from the Australian population completed the online survey, facilitated through an online survey panel (from herein: "GenPop cohort") in addition to the PCa cohort. A GenPop cohort allowed comparison with the target population (i.e. the PCa cohort) to establish if differences in preferences and perspectives existed from those with the lived experience of prostate cancer. Eligibility for participation included having or having had a prostate; and over the age of 18 years. Limits on participation numbers were placed on age groups and location (state or territory) to ensure a broad representative sample. The GenPop survey was open to participants until the target sample size (calculated at 200 to power the DCE) was reached. Further DCE methods and findings are reported elsewhere. [16] Figure 5.2 illustrates the overall survey, and which sections each cohort took part in. The survey was hosted online through SurveyEngine (Berlin, Germany), or a paper copy was available to the PCa cohort on request with the aim of maximising completion rate.



† *Note: Discrete Choice Experiment (DCE) results reported separately (16)*

Figure 5.2 Schematic overview of the survey, including which parts each cohort completed

In follow-up questions to the DCE portion of the survey, there were several questions allowing optional free-text responses, as summarised in Table 5.1. Non-meaningful free-text responses were removed including "no" responses (when asked if they wanted to provide any further information), or where a random string of characters was added.

The final part of the survey was presented to the PCa cohort only, and was optional. PCa cohort participants could choose to identify themselves for comparison of responses against their medical record, and provided treatment details, including details of image-guidance related procedures if they reported receiving EBRT. A short lay description was given for each item (Table 5.2). One investigator (AB) independently reviewed the medical records to retrieve participant's treatment details. Any unclear documentation in the medical record was discussed with another investigator (AT) for ratification. Retrieved medical record data

was then compared to the respondent's answers. Correct recall was defined as the correct identification by the patient of a particular treatment/procedure received, as verified by the medical record. No other recall factor (such as timing or order of treatment/s) was considered in this study.

Table 5.1
Free-text questions, context and number of responses

Free-text optional question	**Context of question in survey**	**Total number of comments**
Q1. Please provide any comments you wish to make	Followed Likert-type scales to rate clarity and understanding of the DCE	181
Q2. Are there any factors you would consider that we are missing?	Followed a question where participants rated the importance of the various DCE attributes for image-guidance preferences including: pain, cost, side effects, accuracy, additional time and additional appointments	115
Q3. Do you have anything else you would like to tell the researchers about the survey, or the imaging options presented?	Final question of the survey	103

DCE: Discrete Choice Experiment

Institutional ethics approval was granted (HREC/2019/QTHS/55905 and H7929, *Appendix D*). Consent was implied by participant completion of the survey. After extensive development through literature review, expert panel review and qualitative results, [15] the survey was piloted following ethics approval and prior to the main rollout, with only minor wording updates to improve clarity and comprehension. [16,17] Responses to the pilot and main survey were combined for analysis.

Table 5.2

Questions and descriptors for treatment and image-guidance related procedures

Question	Multiple Choice Answers	Descriptors provided
What treatment did you have for your prostate cancer? (*please select all that apply*)	Hormones	*Injections of hormones to help shrink the cancer, usually via a needle into abdomen but can also be through tablets*
	Surgery	*Usually to remove the prostate (prostatectomy)*
	Radiation therapy	*External radiation delivered by a specific machine at a dedicated Radiation Oncology clinic, usually involving a daily treatment session over a number of weeks*
	Brachytherapy	*Internal radiation, either through insertion of radioactive beads which remain in your prostate, or radioactive sources that are inserted to deliver the radiation for a few minutes then removed.*
	Chemotherapy	*Drug/s given to treat the cancer, most often in the case where the cancer has spread outside of the prostate*
	Other _____	
	Not sure	
As part of your radiation therapy preparation or treatment, did you have any of the following procedures. If unsure of the procedures, hover over to see a short description: (*please select all that apply*)	Gold seed fiducial markers	*Small gold beads (usually 3) are inserted into your prostate using ultrasound guidance, usually with the probe in your back passage. This may be while you were awake or asleep and occurs before your treatment course commences. These are used to locate your prostate every day for radiation therapy treatment.*
	Clarity ultrasound monitoring	*An external ultrasound probe sits against your skin during the radiation simulation/planning CT and every day for treatment, alerting treatment staff if your prostate moves*
	Other _____	
	Not sure	

Note: This portion of the survey was presented to the PCa cohort only. The survey utilised "Clarity" for TPUS, as this was the terminology commonly used with patients at the department

Analysis

Demographics were summarised using descriptive statistics. Summative content analysis of free-text survey comments was undertaken, with coding completed by two researchers (AB and LA), with discussion until consensus was reached. [18] Proportions of comments were calculated against the themes and subthemes, for both PCa and GenPop cohorts.

Concordance between the self-report by the PCa cohort and the medical record for each treatment modality and image-guidance related procedure was calculated through proportion of agreement and Cohen's Kappa coefficients. Level of agreement was categorised using Altman's method as: 0.75–1.0 = excellent; 0.60–0.74 = good; 0.40–0.59 = fair, and 0.0–0.39 = poor. [19] Following the initial concordance analysis, the cohort was stratified into two groups for sub-analysis, based on the number of years since treatment (Subgroup 1 : less than or equal to 5 years since treatment; Subgroup 2: greater than 5 years since treatment), allowing for a possible effect of time on recall.

A logistic regression model was used to analyse trends in the demographics of participants' recall. A-priori demographic and clinical characteristics of time since treatment, age at survey completion and education levels were included in the model. A separate model included all demographic categories except for ethnicity and language spoken, as these two demographic categories had insufficient numbers of responses. Odds ratios were calculated from model coefficients. All statistical analyses were performed using R 3.6.1. [20] A p-value of <0.05 was considered significant.

Results

Respondents and demographics

There were 236 respondents from the PCa cohort and 240 from the GenPop cohort. All participants identified as male. 135 (57%) PCa cohort and 99 (41%) GenPop cohort respondents provided comments in at least one of the free-text questions. 226 out of 236 from the PCa cohort (96%) voluntarily gave their ID, permitting comparison of their medical records to their recall survey responses. Of those, 221 respondents had sufficient details to allow for comparison. The mean age of respondents was 75.8 ± 7.1 years, and the mean time

from primary treatment in the PCa cohort was 6 years (range 0 to 18). Table 5.3 summarises the demographics of the cohorts.

Table 5.3
Demographics of respondents, including free-text and recall survey components

	GenPop Cohort		**PCa Cohort**			
	Free-text responders n=99		**Free-text responders n=135**		**Recall responders n=221**	
Demographics	*n*	*%*	*n*	*%*	*n*	*%*
Age						
18-29	20	20	-	-		
30-39	24	24	-	-		
40-49	14	14	-	-		
50-59	12	12	1	0.8	1	0.5
60-69	14	14	18	13.7	43	19.5
70-79	10	10	69	52.7	115	52.0
80+	3	3	45	34.4	59	26.7
Did not answer	2	2	2	1.5	3	1.4
Relationship status						
Single, never married	13	18.3	5	3.8	9	4.1
Married or domestic partnership	47	66.2	96	73.3	158	71.5
Widowed	2	2.8	12	9.2	24	10.9
Divorced or separated	4	5.6	16	12.2	28	12.7
Prefer not to say	-	-	-	-	1	0.5
Did not answer	5	7.0	2	1.5	**1**	0.5

	GenPop Cohort		PCa Cohort			
	Free-text responders n=99		Free-text responders n=135		Recall responders n=221	
Employment status						
Full-time employment	32	45.1	12	9.2	17	7.7
Part-time employment	11	15.5	1	0.8	2	0.9
Casual	6	8.5		0.0	1	0.5
Retired	18	25.4	115	87.8	195	88.2
Unemployed	2	2.8		0.0	3	1.4
Prefer not to say					2	0.9
Did not answer	2	2.8	3	2.3	1	0.5
Level of education						
Less than high school	32	45.1	12	9.2	26	11.8
High school (or equivalent)	11	15.5	1	0.8	82	37.1
Apprenticeship, TAFE or tech school	6	8.5	-	-	80	36.2
Undergraduate degree	18	25.4	115	87.8	26	11.8
Postgraduate degree	2	2.8		0.0	2	0.9
Prefer not to say	-	-	-	-	4	1.8
Did not answer	2	2.8	3	2.3	1	0.5
Annual household income						
≤ $39,999	16	22.5	58	44.3	114	51.6
$40,000 - $79,999	25	35.2	31	23.7	52	23.5
$80,000 - $149,999	15	21.1	14	10.7	17	7.7
≥ $150,000	9	12.7	2	1.5	4	1.8
Unknown	6	8.5	26	19.8	34	15.4

	GenPop Cohort		PCa Cohort			
	Free-text responders n=99		Free-text responders n=135		Recall responders n=221	
Ethnicity†						
Aboriginal and Torres Strait Islander	2	2.8	1	0.8	1	0.5
Aboriginal	2	2.8	1	0.8	2	0.9
Torres Strait Islander	0	0.0	0	0.0	0	0.0
Non-Indigenous	65	91.5	121	92.4	211	95.5
Did not answer	2	2.8	8	6.1	7	3.2
Born						
Australia	44	62.0	92	70.2	165	74.7
Other	24	33.8	34	26.0	52	23.5
Did not answer	3	4.2	5	3.8	4	1.8
Language						
English	64	90.1	126	96.2	214	96.8
Other	5	7.0	2	1.5	4	1.8
Did not answer	2	2.8	3	2.3	3	1.4
Health State†						
Excellent	15	21.1	8	6.1	12	5.4
Very Good	22	31.0	31	23.7	50	22.6
Good	20	28.2	51	38.9	91	41.2
Fair	7	9.9	32	24.4	53	24.0
Poor	5	7.0	4	3.1	12	5.4
Did not answer	2	2.8	5	3.8	3	1.4

	GenPop Cohort	PCa Cohort	
	Free-text responders n=99	**Free-text responders n=135**	**Recall responders n=221**
Year of primary treatment			
Prior to 2010		28	12.3
2010-2014		94	41.4
2015-2019		102	44.9
Currently on treatment		2	0.9
Refused any treatment		1	0.5
PCa Staging			
T1		44	19.4
T2		112	49.3
T3		58	25.5
T4		4	1.8
Tx		4	1.8
Not recorded		5	2.2

Content analysis

Five main themes were developed from content analysis of the free-text feedback: Factors considered by the respondents to be missing from the DCE attributes regarding image-guidance related preferences; patients sharing the experiences of treatment; insights and reflections pertaining to image-guidance related preferences; general commentary on the survey; and mindsets. Figure 5.3 summarises the major and sub-themes with illustrative quotes, with complete results of the content analysis in Supplementary material.

Factors missing from the DCE and general commentary on the survey comments were mostly in response to specific questions (i.e. Questions 2 and 3, Table 5.1). Respondents from both cohorts identified missing factors including treatment outcome and logistics such as travel , however the frequency of all suggested missing factors was low (1.4 to 5.6%). There was a mix of positive and negative feedback (as perceived by the coders) regarding the survey from both cohorts, with more positive responses provided by the GenPop cohort (39.4% vs 2.3% of PCa) and more negative responses provided by the PCa cohort (13% vs 9.9% of GenPop).

The majority of the PCa cohort (83.1%) provided comments on their experiences of treatment. This included reflections on their decision-making during the diagnosis phase (7.6%); their treatment experiences (13.7%) and reporting of side effects (28.3%) and outcomes (3%). Some respondents commented on specific aspects of their treatment journey including pain associated with gold seed insertion (1.5%) and the bladder/bowel filling requirements for EBRT (6.1%). Compliments regarding their treatment were given by 22.9% of the PCa cohort respondents.

12.3% of the PCa cohort and 22.4% of the GenPop cohort commented on the choices made in responding to the DCE. Comments were given about the DCE attributes of pain and cost (aggregated total 4.5% for PCa, 11% for GenPop), and other factors including treatment success (0.8% PCa, 2.8% GenPop), claustrophobia (0.8% PCa), specialist recommendations (1.5% PCa), avoiding insertion (2.3% PCa, 1.4% GenPop), and opting for no treatment (0.8% PCa, 1.4% GenPop). However, there were low frequencies for each of these suggested factors (0.8 to 7.0%).

Recall analysis

Overall, the PCa cohort could recall their treatment regimen with “fair” accuracy, with correct recall proportions ranging from 97.3% for chemotherapy to 66.8% for hormones. The proportion with correct recall for image-guidance related procedure was 87.3% for TPUS and 91.4% FMs. Table 5.4 summarises the proportions of correct and incorrect recall for each category with the corresponding Kappa statistic, including sub-analysis by year of treatment. The K indicated excellent agreement for surgery (0.81) and FMs (0.83), indicating correct recall; good agreement for brachytherapy (0.65), fair agreement for EBRT (0.41), chemotherapy (0.49) and TPUS (0.49), and poor agreement for hormones (0.35).

Sub-analysis showed recall rates were more correct for surgery and chemotherapy in the group treated less than 5 years previously. However, there were improved correct recall rates for FMs and TPUS for the group treated more than 5 years previously. There was no significant time-related difference in participants' recall for hormones and brachytherapy, however the group treated less than 5 years previously had better recall.

Table 5.4:

Proportions of observed recall, including treatment timing sub-analysis

		Patient Identification				**Comparison of Treatment timing**						
		All recall respondents n=221				≤5 years n=99			>5 years n=122			
Clinical Records		No %	Yes %	Accuracy (CI)	Cohen's Kappa	No %	Yes %	Cohen's Kappa	No %	Yes %	Cohen's Kappa	p-value
Hormones	No %	27.73	*6.36*	0.67 (0.60-0.73)	0.35 (0.23-0.47) p<0.001	24.24	*5.05*	0.39 (0.21-0.57) p<0.001	30.58	*7.44*	0.32 (0.15-0.48) P<0.001	0.11
	Yes %	*26.82*	39.09			*25.25*	45.45		*28.10*	33.88		
Surgery	No %	70.91	*6.36*	0.93 (0.89-0.96)	0.81 (0.72-0.90) p<0.001	66.67	*7.07*	0.83 (0.71-0.95) p<0.001	74.38	*5.79*	0.78 (0.65-0.92) P<0.001	<0.01
	Yes %	*0.91*	21.82			*0.00*	26.26		*1.65*	18.18		
EBRT	No %	1.82	*0.91*	0.94 (0.90-0.97)	0.41 (0.10-0.72) p=0.02	1.01	*1.01*	0.15 (-0.37-0.68) p=0.298	2.48	*0.83*	0.58 (0.18-0.98) P=0.03	0.09
	Yes %	*5.00*	92.27			*8.08*	89.90		*2.48*	94.21		
Brachytherapy	No %	93.64	*3.18*	0.97 (0.94-0.99)	0.65 (0.40-0.91) p=0.001	92.93	*4.04*	0.58 (0.18-0.98) p=0.03	94.21	*2.48*	0.71 (0.39-1.03) P=0.008	0.86
	Yes %	*0.00*	3.18			*0.00*	3.03		*0.00*	3.31		
Chemotherapy	No	95.91	*2.73*	0.97 (0.94-0.99)	0.49 (0.09-0.89) p=0.04	96.97	*1.01*	0.79 (0.39-1.19) p=0.036	95.04	*4.13*	0.28 (-0.34-0.89) P=0.228	0.01
	Yes	*0.00*	1.36			*0.00*	2.02		*0.00*	0.83		
Fiducial Markers	No %	51.82	*2.27*	0.91 (0.87-0.95)	0.83 (0.75-0.90) p<0.001	45.45	*0.00*	0.82 (0.71-0.93) p<0.001	57.02	*4.13*	0.83 (0.72-0.93) P<0.001	<0.01
	Yes %	*6.36*	39.55			*9.09*	45.45		*4.13*	34.71		
TPUS	No %	79.09	*7.27*	0.87 (0.82-0.91)	0.49 (0.31-0.67) p<0.001	62.63	*7.07*	0.52 (0.33-0.72) p<0.001	92.56	*7.44*	NA	<0.01
	Yes %	*5.45*	8.18			*12.12*	18.18		*0.00*	0.00		

Incorrect proportions are italicised. Cohen's Kappa: 0.75–1.0 = excellent; 0.60–0.74 = good; 0.40–0.59 = fair, and 0.0–0.39 = poor. (48)

Table 5.5
Odds ratios calculated through regression analysis

					OR (95% CI)
Demographic	***Hormones***	***Surgery***	***EBRT***	***Fiducial Markers***	***TPUS***
Age					
<70	*0.30*	*0.36*	*1.779*	*0.64*	*0.37*
***Base:* ≥70**	*(0.11-0.74)**	*(0.02-1.95)*	*(0.36-6.93)*	*(0.10-2.53)*	*(0.06-1.42)*
Time since treatment					
>5 years	*0.73*	*1.26*	*2.949*	*1.73*	*4.51*
***Base*: ≤5 years**	*(0.38-1.37)*	*(0.38-4.22)*	*(0.79-14.08)*	*(0.57-5.48)*	*(1.64-14.56)**
Level of education					
≥ Undergraduate	*0.49*	*0.682*	*0.781*	*1.30*	*1.54*
Base: < than Undergraduate	*(0.15- 1.37)*	*(0.04-3.85)*	*(0.04-4.65)*	*(0.19-5.33)*	*(0.32-5.56)*

**p<0.05*

In evaluating PCa cohort demographic trends (Table 5.5), only age was significantly associated with recall of hormones with younger respondents having better recall (OR = 0.3, 95%CI 0.11-0.74 for <70 years of age), and year of treatment was significantly associated with recall of TPUS, with treatment >5 years ago showing better recall (OR = 4.51, 95%CI 1.64-14.56).

The overall count of incorrect recall (i.e. counting each incorrectly identified treatment/procedure per respondent) and free-text comments was tabulated (Table 5.6 supplementary)). Overall, there was no significant difference with recall rates based and comments given.

Discussion

This study analysed free-text comments from participants in a larger study to understand the participants' perceptions of prostate cancer treatment. Additionally, recall by the PCa cohort of their prostate cancer treatment was analysed.

The free-text comments provided demonstrate the varied experiences of the PCa cohort, as well as the different perceptions and preferences in both the PCa cohort and GenPop cohort, with good engagement from both cohorts as demonstrated by the majority of respondents leaving at least one comment. Apart from direct responses specific to the survey (that is, missing factors and specific feedback relating to the survey), most free-text comments from both cohorts were un-prompted. This engagement indicates both a willingness of the PCa cohort to share their experiences and an interest from the general population, and serves to further contextualise the DCE survey. [16] There is an increasing emphasis on analysing free-text responses given by survey participants. [21-23] Two studies in the oncology setting analysing free-text comments provided additional information on aspects including side effects, treatment outcomes, needs, emotions and experiences. [24,25] These aspects were mirrored in our study from both cohorts, but particularly the PCa cohort.

The PCa cohort in our study recounted experiences associated with EBRT including fiducial insertion and preparation. The comments regarding bladder and bowel filling treatment requirements suggests that preparation makes an impression on the patient. This impression may reflect that this preparation is the most active participation required of the patient during treatment delivery, thereby making it more memorable. The necessity of preparation is reported as a significant cause of distress, with the timing of preparations and lack of instructions contributing to distress, and lack of understanding of the purpose leading to non-compliance. [26,27] With adaptive radiation therapy developments, further evaluation of the necessity of strict preparations when adapting to daily anatomy would be of benefit, given the negative impact reported by respondents.[28]

PCa cohort compliments to the staff were more numerous than any other aspect recounted of their treatment (22.9%). This suggests a high level of rapport with the treating team, implying the way patients are treated by staff is just as important to the patient, if not more so, than the treatment/ procedures. Previous radiation therapy studies corroborate the importance of rapport and trust with the health care providers, including oncologists, therapists, and nurses. [28-30]

The recounting of side effects (ranging from nil to long-term side effects impacting quality of life) indicates the varied and lasting impact of treatment toxicity on patients. Geographical

differences in patient perceptions around prostate radiation therapy side effects have been reported, with regional/remote patients expressing an acceptance of side effects rather than a process to improve as expressed by metropolitan men. [31] This difference was reflected in our study, with regional PCa cohort reporting on the presence of side effects more so than a desire for improvement of the side effects, however some respondents did express regret at the side effects experienced. Previous studies indicate not all patients feel informed about the possible severity of side effects, highlighting a further opportunity for improvement. [30] The GenPop cohort provided comments around possible side effects in both factors missing and in preference insights, suggesting that even without the lived experience of prostate cancer and treatment, the hypothetical impact of treatment is of importance.

The desire to follow doctor recommendations found in the present study supports our earlier finding that patients utilise the clinician agency to guide their treatment decisions. [15] The decision to undergo radiation therapy was reported to be "agreeing with the radiation oncologists' recommendation" rather than a personal choice, recognising the trust in the medical professional. [30] Of note, the pragmatic "gotta do" sentiment was reflected in both cohorts in this study, confirming previous findings of a pragmatic approach to treating the prostate cancer. [15] Additionally, the necessity of treatment and procedures overriding potential associated embarrassment was commented on by both PCa and GenPop cohorts. A positive frame of mind in approaching radiation therapy has also been reported, mirroring our results. [29]

Good recall of their treatment/s was indicated in the majority of the PCa cohort. However, the recall of hormone treatment was incorrect in 33.2% of respondents, including 26% stating they had not received hormone therapy where the clinical records indicated they had. The Kappa statistic for EBRT and chemotherapy indicated fair agreement. However, the overall proportion of incorrect recall was lower: EBRT and chemotherapy at 5.9% and 2.7% respectively, whereas it was 7.3% for surgery. Kappa's limitations are recognised where observed proportions are high, making it a conservative measure. [32,33] Differences in levels of recall amongst cancer populations has been reported previously.[34-38] Recall agreement for patients with prostate cancer was good to excellent for surgery, brachytherapy, and radiation therapy but only fair for hormone treatment. [38] As with our present study, there was no

specific change in information provided to the prostate cancer population, thus capturing general recall. [38]

The PCa cohort overall had high recall receiving radiation therapy (including EBRT and brachytherapy), however were less accurate recalling specific image-guidance related procedures. Lower accuracy in the recall of image-guidance related procedure may indicate that patients focus on the overall treatment rather than individual components or aspects of treatment. While it may not be as crucial that patients recall their image-guidance related procedures compared to their treatment/s, less recall of image-guidance related procedures may suggest the purpose of these procedures may not be understood by all patients.

Time may introduce additional recall bias for patients treated more than 5 years previously. Unsurprisingly, treatment recency sub-analysis (<5 and >5 years) demonstrated patients treated more recently were more accurate in their recall. Patients treated more recently, however, tended to recall TPUS incorrectly, indicating they had TPUS when they had not. However, this recall value was associated with a wide confidence interval indicating large variances. Patients' recall of TPUS may be confused by the term “ultrasound” which is used during both biopsy and treatment as suggested in our previous study which found that patients often confused the external probe of TPUS with the internal probe of the biopsy and insertion procedures.[15]

Younger patients tended to recall their hormone treatment more accurately, suggesting age is a contributor to the poorer recall of hormone treatment in older patients. There is a known link between hormonal therapy and mild cognitive impairment, however exploring this further was beyond the scope of this study. [39,40] There may also be an element of older patients choosing to take a more passive role in their health care, as found in the study investigating decision-making in choosing active surveillance for prostate cancer.[41] Patient education levels have also been demonstrated to influence certainty in prostate cancer patients, showing patients with a lower level of education tending to report higher levels of uncertainty.[42] However, our results did not find a significant recall difference based on education.

Lower levels of recall agreement for hormone treatment have been previously reported. Level of agreement increased when limiting to patients who only had hormone treatment, as opposed to when used alongside radiation therapy and/or surgery.[38] This may be due to hormone treatment being a more "passive" treatment, and the hormone injection not recognised as a separate treatment in their whole treatment regimen. Hormone terminology has been found to be confusing, with "chemical castration", "hormonal therapy" and "androgen deprivation therapy" incorrectly described and not recognised as synonymous by study participants.[43] Additionally, the side effects of hormone therapy were not known by a majority of PCa patients and their partners.[44] This may explain the low recall findings of our study, with some patients not understanding they were on hormones.

Our results indicate that overall, recall of PCa treatment was reasonable. However, as recall is indicative of patient understanding, our results suggest there is opportunity for further improvement, particularly in the areas of hormone treatment. Improvements could be facilitated through use of decision aides which have demonstrated decreased treatment regret, however these aides need the flexibility to accommodate the differences in information needs.[45-47] Further work is required to understand the patient's decision-making processes at the time of initial consultations with specialists, including the immediate recall of treatment option details. While not all radiation oncology departments have multiple image-guidance procedures/techniques to offer an individual choice to a patient, it is ultimately up to the patient to consent to procedures such as fiducial marker insertion.

Conclusion

Overall, our recall and free-text findings further illuminate the complexities of PCa treatment pathways, with individuals having different experiences and reporting various levels of needs and satisfaction with treatment and related procedures. Incorporating the patient perspective and preferences into future research and clinical developments can ensure increased agency and participation by the patients. Our findings inform areas for improvement to improve patient experience. Further education and research into hormone therapy understanding is recommended.

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Supplementary Materials

Treatment centre setting

The regional cancer centre was treating external beam radiation therapy (EBRT) all throughout the invitation period of 2009 to 2019; and had implemented fiducial markers (FMs) in 2010, and transperineal ultrasound (TPUS) motion monitoring in 2016 for EBRT prostate treatment. Low-dose rate brachytherapy was available in the private sector. Hormone therapy was prescribed by either the treating radiation oncologist or urologist as required. Surgery was available in either the public or private sector. When required for advanced cases, chemotherapy was available in either the public or private setting.

Table 5.6 (supplementary)
Major and sub-themes developed from free-text content analysis

Major Theme	Sub Theme	Illustrative Quotes	PCa (n= 135)		Gen Pop (n= 99)	
			n	%	n	%
Factors Missing	***Total***		21	12.7	18	25.4
	Outcome	"Probability of a better outcome of therapy." P65 "Overall impact the diagnosis has versus these factors. Is a person able to withstand the pain, are they coping and how much accuracy could make a difference in treatment outcomes?" G36	6	4.5	3	4.2
	Logistics: travel/time away	"As I have mentioned, the need for travel. AND the need for accommodation when in the location of the Hospital. Daily visits for 8 weeks nearly broke me." P93 "If it was a public or private oncology unit and how far away this centre was from where I lived." G53	5	3.8	4	5.6
	Side effects (incl long term)	"Is there any, on going affects after treatments?" G65	4	3.1	3	4.2
	Preparation incl. communication and Information Needs, and bladder and bowel filling requirements	"I think the communication to the patient of the importance of the preparation before treatment is extremely important to the success of the procedure" P76 "I just wonder how much time a GP or specialist would allow for a detailed explanation of the procedure? Given the complexity of the treatment the patient should be able to have ALL their queries answered."G39	4	3.1	1	1.4
	Other factors (*n*): Prevention (1), General anaesthetic requirements (1), Health insurance cover (2), recovery time (2), mental health impact (1), embarrassment (1) and disability considerations (1)					
	Total		**109**	**83.1**	-	-

Sharing Experiences of Treatment		"Having experienced an internal prostate punch biopsy and the mess it made of the rectal area (not been the same since) I don't think I would agree to another one" P127				
	Diagnosis, Work-up and Decision-making	"It would be good if doctors would discuss all the treatments for prostate cancer and i might not have the side effects i have now after 6yrs and still having to have procedures and op to stop my incontinence." P116	10	7.6	-	-
	Treatment modalities and/or treatment experiences	"I had my prostate surgically removed and had follow up radiation" P101 "I have 6 month injections" P15 "The accuracy was good because of the markers." P44	18	13.7	-	-
	Reporting side effects	"A few years since radiation treatment I have encountered a couple of (probably minor) side effects." P114 "Most side effects were after treatments but settled after time" P121	25	19.1	-	-
	None	"I did not experience any pain or side effects for radiation" P01	8	6.1	-	-
	Acute	"I finished my eight weeks of radiation treatment for prostate cancer on the [date],[…] and all side effects have subsided." P48	1	0.8	-	-
	Late	"My treatment was 10 years ago and I don't know if manageable difficulties I am having now are related to the radiotherapy." P78	3	2.3	-	-

	Outcomes				-	-
	"Success"	"This is my 10th year since treatment & I am still free of cancer. I have PSA test every 6 months." P34	2	1.5	-	-
	"Failure"	"Radiation failed" P85	2	1.5	-	-
	Other				-	-
	Pain - Gold seeds	"I had 4 gold seeds implanted.. It was, I think, the most painful physical experience I have ever had, any embarrassment I had previously, was completely eradicated, for fear of what was to come." P29	2	1.5	-	-
	Bladder and Bowel Filling	"A full bladder for each radiation session is a discomfort and sometimes embarrassment that reaches a critical point after 33 treatments." P75				
		"The worst part by far, at least to my mind, was retaining the great quantity of water that had to be taken before each radiation session; thinking back, I don't know how I managed!" P120	8	6.1	-	-
	Complimentary	"I am one very happy patient and can not thank all the wonderful people at the [hospital] enough." P48	30	22.9	-	-
		"The technicians and nurses were excellent during my successful treatment" P76				
Preferences Insights and Reflections	***Total***		**16**	**12.3**	**16**	**22.4**
	Accuracy	"While I might be slightly embarrassed at having the Clarity ultrasound technique applied the most important aspect was the accuracy of the radiation beam in relation to the invading cancer." P49				
		"In most cases I chose the increased accuracy option" G46	3	2.3	3	4.2
	Cost	"It's all about the money" G04	2	1.5	2	2.8

	"Costs for me was not a consideration as I am a Gold Card holder." P89 "Outcome is the most important thing. Pain, cost, time or embarrassment are short term issues. The outcome is for the rest of your life. I will always choose the option likely to give the best outcome or 'cure.'" P72 "My first preference would be the one that is more effective in treating prostate cancer not the procedure." G15				
Outcome/Success		1	0.8	2	2.8
Claustrophobia	"Severe claustrophobia and the mitigation of it's effects during the procedure would be a primary factor in my choice of treatment." P55	1	0.8	-	-
Pain	"the pain levels and experiencing them daily is a big consideration after seeing how daily painful treatment can affect people long term." G07 "I regarded the potential pain as a more important consideration than the potential embarrassment." G01 "Pain/discomfort should be kept to a minimum for such a small gain in accuracy." P75 "I would be asking how long the pain levels last.....I could tolerate extreme pain for a short while, or very low level for a longer time." G05	2	1.5	5	7.0
Pain and Cost	"I hate to admit it but my decisions were pretty well all driven by the level of pain likely to be experienced. […] A far more difficult decision would have been to choose high pain if it would guarantee significantly better outcomes from the therapy." P65 "Level of pain and cost are the two biggest factors in my view." G69	2	1.5	2	2.8

	Specialist recommendation	"My decisions would be strongly influenced by a Doctor recommendation." P38 "Did what doctors wanted (they're the doctors)." P24	2	1.5		
	No Insertion	"Option overall better with no insertion" G17	3	2.3	1	1.4
	No treatment	"I'd prefer to die WITH prostate cancer than have intervention. Few people die OF prostate cancer" G59	1	0.8	1	1.4
Survey Feedback: General commentary on the survey	***Total***		**23**	**17.6**	**35**	**49.3**
	Positive (incl. ease, clarity and interest)	"survey was well presented and easy to navigate and understand "P61 "The questions were very easy to understand and it's an important topic for male health. The description was very clear in layman terms to make it as easy to understand as possible" G51	3	2.3	28	39.4
	Negative (incl. difficulty, confusion, repetitive)	"With reference to the previous page regarding how we felt when answering question, i found a little confusing , how can anyone relate to answers given unless they've experienced it , or have been given a detailed description of what expect" P128	17	13.0	7	9.9
	Required assistance	"My wife helped to explain to me what the questions went and clarified my answers without influencing my answers" P99	3	2.3	-	-
Mindsets			**16**	**12.2**	**9**	**12.7**
	Embarrassment & Masculinity	"When you are sick though, your embarrassment levels with these types of things would likely reduce due to the situation." G47 "I do not feel any embarrassment in any of the procedures sure the probe or finger up the anus is uncomfortable but necessary." G03	8	6.1	3	4.2

		"My embarrassment level would be low because I would know whatever is being done is helping me. The medical person do their job and therefore helping me in the long term." P04 "most men are scare about losing their manhood by having their prostate removed, if it means saving your life & leaving a few more years go ahead & have it done, too many of my friends have died because of prostate cancer" P11				
	Pragmatic: "Gotta do what you gotta do"	"if there is a problem you need to get it fixed you either get it fixed or suffer" P07 "For me it was a case of do it or suffer the consequences so i believe that you leave your pride at the door and pick it up on the way out" P107 "Very invasive ..if it needs to be done don't have much choice" G23 "just made me think of the cancer and how I would feel during the process, if I had it I would want to do everything that is required of me to help me battle the problem" G62 "I noticed with all my answers upon reflection, that Cost of treatment to me mattered, time did not particularly matter at all , the level of discomfort to when I am receiving life saving Life Saving treatment is barely, or hardly a factor, nor is embarrassment in those same circumstances a great consideration to me, if it means getting the job done." P81 "It must be done to prevent cancer spread" G70	6	4.6	6	8.5
	Compliance	"From initial diagnosis to this day I resolved to adopt & maintain a positive, optimistic & cooperative attitude at all times. To comply with	2	1.5	-	-

	every directive from treatment team." P41
	"When having treatment for prostate cancer I was more than happy to comply with the instructions given by the medical staff." P83

For illustrative quotes, P indicates respondent from men with prostate cancer cohort, G indicates respondent from general population cohort.

Table 5.7 (supplementary*)*
Count of incorrect recall per PCa respondent and free-text comments

Count of Incorrect Recall	Treatment & IGRP		Treatment only		IGRP only	
	Free-text (n=109)	No free-text (n=112)	Free-text (n=109)	No free-text (n=112)	Free-text (n=109)	No free-text (n=112)
0	51 (45.5%)	51 (46.8%)	66 (58.9%)	60 (55.0%)	91 (81.2%)	89 (81.6%)
1	44 (39.3%)	42 (38.5%)	36 (32.1%)	43 (39.4%)	15 (13.4%)	20 (18.4%)
2	12 (10.7%)	13 (11.9%)	8 (7.1%)	4 (3.7%)	6 (5.4%)	-
3	3 (2.7%)	2 (1.8%)	2 (1.8%)	1 (0.9%)	-	-
4	2 (1.8%)	1 (0.9%)	-	1 (0.9%)		

Where n = number of participants; IGRP - image-guidance related procedure

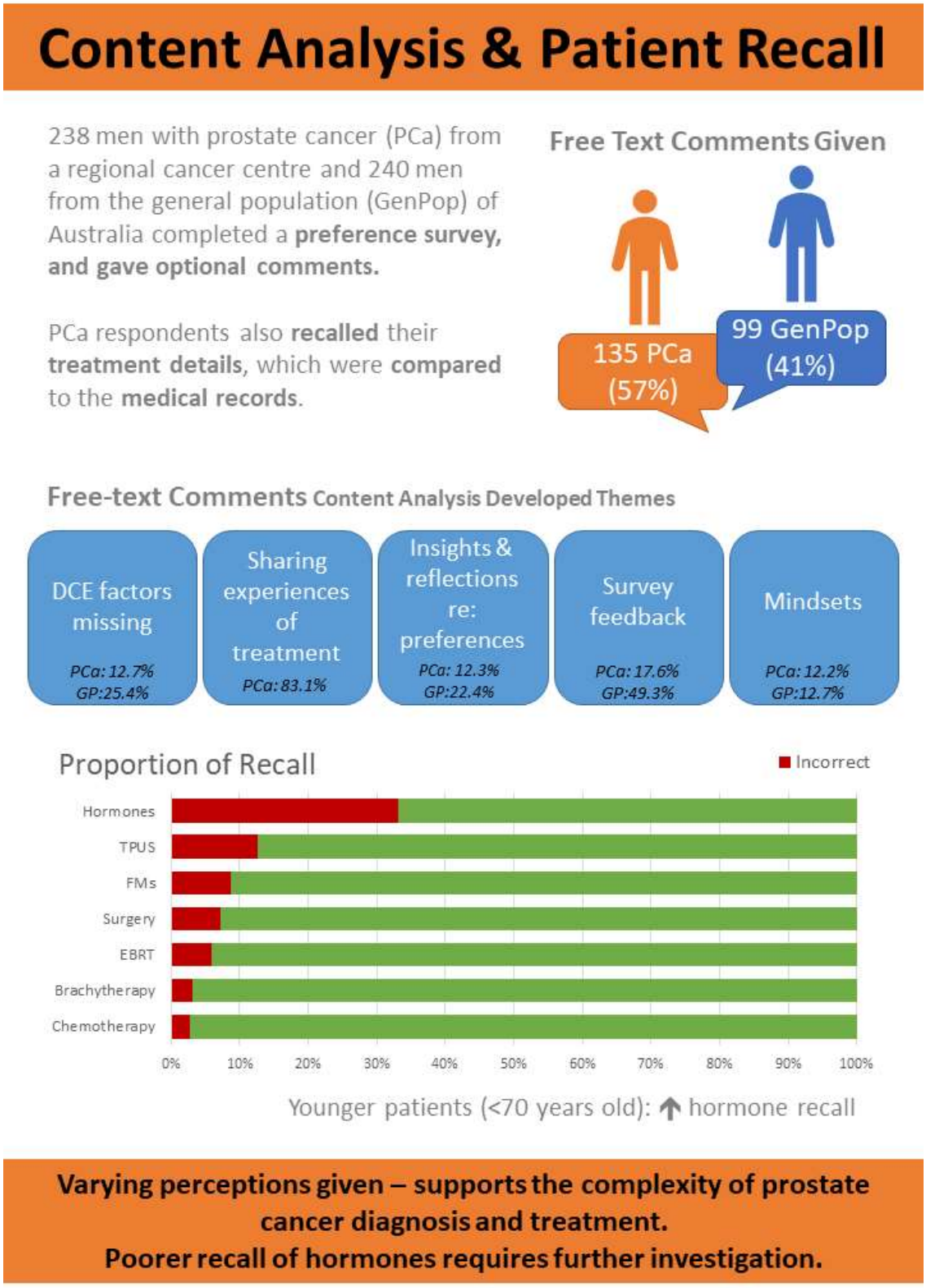


Figure 5.3 Translation of evidence infographic - Chapter 5

Linking to Subsequent Chapter

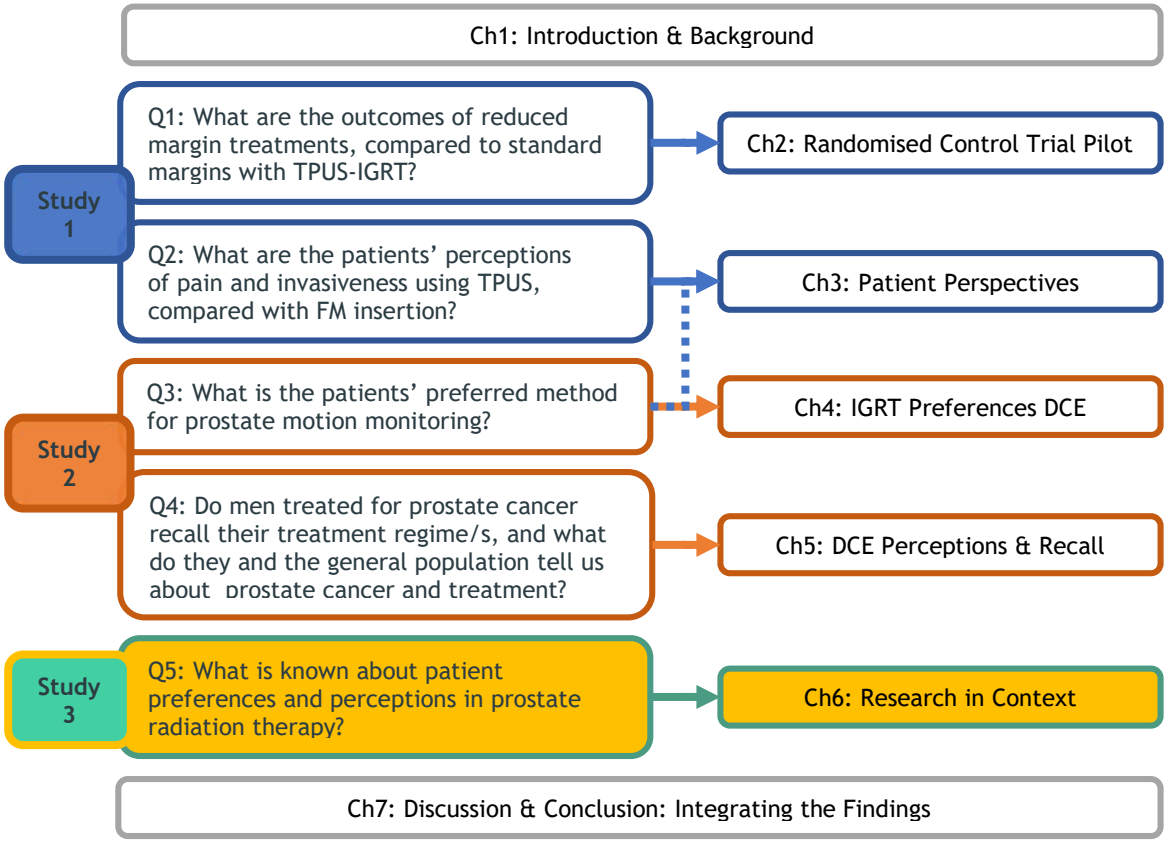
The most significant findings of this sub-study were: 1) there were many and varied comments given by both populations, indicating the complex nature of prostate cancer care and 2) overall, recall of treatment and image-guidance related procedures were good, however hormones recall was poorer. **The findings of this study led to the development of the scoping review to situate these findings further in current literature (Chapter 6).**	This chapter addressed research question 4: Do men treated for prostate cancer recall their treatment regime/s, and what do they and the general population tell us about prostate cancer and treatment?

Chapter 6 Research in Context

Article: Men's perceptions and preferences regarding prostate cancer radiation therapy: a systematic scoping review

Brown A, Yim J, Jones S, Tan A, Callander E, Watt K, et al. Men's perceptions and preferences regarding prostate cancer radiation therapy: A systematic scoping review. Clin Transl Radiat Oncol 2023;38:28–42. https://doi.org/10.1016/j.ctro.2022.10.007.

This chapter includes an exact copy of the published manuscript, except the formatting of section sub-headings, figure, table and reference numbers have been edited for the purpose of the thesis.



Note: TPUS: Transperineal Ultrasound; IGRT: Image-guided radiation therapy; FM: Fiducial Marker; DCE: Discrete Choice Experiment

Figure 6.1: Schematic overview of thesis: study 3, Chapter 6

Context of study 3

This scoping review was developed to situate the findings of both focus areas (clinical considerations and patient perceptions and preferences) to the current literature. While a systematic literature review (Appendix G) was undertaken in developing the RCT (Chapter 2), and a literature review regarding image-guidance procedures was conducted to inform the DCE attributes and levels (Chapter 4), this scoping review was more broadly to investigate preferences and perceptions in prostate cancer radiation therapy.

Abstract

Purpose

To assess the literature on men's preferences and perceptions regarding prostate cancer radiation therapy.

Methods

A scoping review was undertaken as per JBI guidelines. Searches were conducted in PubMed, CINAHL, Scopus and Science Direct with search terms including "prostate cancer," "radiotherapy," "radiation therapy," "radiation oncology," "patient preferences," "patient perceptions" and "patient experience." The resultant studies were mapped and grouped according to the emergent themes and pathway stages.

Results

A total of 779 titles and abstracts were screened by two independent reviewers. Fifty-two full-text studies were reviewed, with 27 eligible for inclusion. There were 4 pre-treatment, 13 during treatment and 10 post-treatment studies covering broad themes of information needs (n=3), preferences and decisions (n=6), general experiences (n=8), side effects (n=6), and support (n=4). There were a mix of methodologies, including 11 qualitative, 14 quantitative (including four preference studies), one mixed methods and one narrative review.

Conclusion

There were only four preference studies, with the remaining 23 reporting on perceptions. Overall, there is a paucity of literature regarding patient preferences and perceptions of prostate cancer radiation therapy, particularly when considering how many clinical and technical studies are published in the area. This highlights opportunities for future research.

Background

Primary treatment for prostate cancer can include surgery (prostatectomy), hormones and radiation therapy, or a combination of these. Active surveillance is a further option for patients diagnosed with low-risk disease. The clinical efficacy and patient-reported outcomes of these primary treatments are well documented.[1–6]

The treatment options and pathway for each individual is negotiated between the patient and their health professional and is influenced by numerous factors. As reported in previous studies and systematic reviews, patients' choices of primary treatment(s) are influenced by both health and non-health related factors.[7–9] Perceptions of efficacy, side effects and clinician recommendations influenced preference for primary treatment and management of localised prostate cancer.[7] Personal beliefs and the beliefs of others (such as clinicians, family and friends) about cancer, treatment efficacy and the severity of possible side effects have also been shown to influence treatment choice.[8] Even though treatment efficacy and side effects are influential factors, it has been reported that there are large variations in how men considered the importance of these two factors in relation to their treatment choice.[9] Systematic reviews on both decision aides and shared-decision making (SDM) demonstrate the complexity of the decision-making process following a prostate cancer diagnosis.[10–12] The existing systematic reviews on patient perceptions and preferences regarding prostate cancer radiation therapy treatment focus solely on the primary treatment choice, rather than the more nuanced aspects of radiation therapy.[7–9]

Choosing primary treatment is one of the most significant decisions for a man with prostate cancer. However, it is just one of many decisions and experiences in the prostate cancer treatment pathway. Even when a patient chooses radiation therapy as their primary treatment, there are a number of aspects to the delivery of care where patient perception and preference are important. The radiation therapy treatment pathway is defined by three

distinct phases: pre-treatment preparation, treatment and follow-up post-treatment. Pre-treatment preparation includes information needs, shared decision making and preparatory procedures such as fiducial marker insertion for image guidance. Treatment may include daily treatment preparation (such as bowel/bladder filling protocols) and fractionation schedules. Post-treatment follow-up may include decisions about who provides follow-up care (e.g. nurse or radiation therapist-led models), frequency of follow-up appointments and survivorship aspects. While most active decision-making occurs when choosing primary treatment, there are various points during the three following phases where patients have choices: for example, an individual may choose not to have fiducial markers inserted, a radiation oncologist may give the patient a choice on the fractionation schedule or a choice between in-person or telehealth follow-up appointments).

Our scoping review aims to answer the following question, "What is known about patients' perceptions of prostate cancer radiation therapy from preparation to treatment and follow-up?." This review seeks to identify patient perception and preference knowledge gaps so that future research can be undertaken to inform prostate cancer radiation therapy service delivery.

Methods

A scoping review, with supporting protocol,[13] was conducted as per JBI methodology.[14] The review question was developed using the Participants, Concept and Context (PCC) framework (Table 6.1). [14] Eligible sources included peer-reviewed studies, theses and grey literature such as professional guidelines. Inclusion and exclusion criteria are outlined in Table 6.1.

Search strategy, sources and screening

Electronic databases of PubMed, CINAHL, Scopus and Science Direct were searched using combinations, synonyms and truncations of the following key search terms: "prostate cancer," "radiotherapy," "radiation therapy," "radiation oncology," "patient preferences," "patient perceptions" and "patient experience" (Supplementary). Grey literature sources and government, policy and college websites (including the American Society for Radiation Oncology (ASTRO), the European Society for Radiation Oncology (ESTRO), and the Royal

Australian and New Zealand College of Radiologists (RANZCR)) were also searched. No date limits were applied.

Each title and abstract were screened independently by two reviewers (AB, and SJ or JY) for eligibility in abstrackr.[15] Full-text review was undertaken by two reviewers (AB, and SJ or JY) of all eligible studies, with any uncertainty discussed with the third reviewer until consensus was reached.

Table 6.1
Participants, concept and context of scoping review; with inclusion and exclusion criteria

Scoping Review		Inclusion	Exclusion
Participants	Men / Individuals with or who have had prostate cancer	Prostate cancer patients' perceptions OR general population hypothetical perceptions (e.g. preferences) relevant to prostate cancer	Comparisons/Contrasts of primary treatments (e.g. surgery versus radiation therapy)
			No clear indication of prostate cancer sub-population (i.e. general oncology perceptions)
		Perceptions relevant to any stage and aspect of prostate cancer radiation therapy, including pre-treatment preparation, treatment, and follow-up aspects	Perceptions of carers, families, or other proxies (with no report of patient perceptions)
		Post-prostatectomy evidence included providing focus is on radiation therapy treatment	Perceptions of health professionals (with no report of patient perceptions)
		Original research (including systematic literature review)	Opinion pieces/editorials
			Language other than English

Data extraction

A data extraction form was initially developed and tested on 3 studies, with all co-authors agreeing on the data inclusion. Data from all eligible studies were extracted by one author (AB) and verified by at least one other author (SJ or JY). Data extraction included: year of

publication, country, major theme addressed, stage of radiation therapy described/studied (pre-treatment, during treatment, post-treatment pathway), aim/s, population and sample size, key findings, and limitations and/or biases presented in the record. The results are presented grouped by major theme, across the treatment pathways.

Results

After removing duplicates, the initial search yielded 779 records with 727 excluded after title and abstract screening. No records were included from the grey literature. One record eligible in title/abstract screening could not be retrieved as it did not have an English translation. Of the 51 full-text records assessed, a total of 27 studies covering 25 study populations were eligible and were included in this review. Reasons for exclusion are detailed in the PRISMA flow diagram (Figure 6.2).

The data extraction is presented in Table 6.2, grouped according to theme. The broad themes of information needs (n=3)[16–18] preferences and decisions (n=6)[19–24] general experiences (n=8)[25–32] side effects (n=6)[33–38] and support (n=4)[39–42] are detailed in a matrix mapping the themes of each pathway (Figure 6.3). Collectively, the three major stages of the prostate cancer pathway were described, with four addressing pre-treatment aspects;[16–19] 13 addressing during-treatment aspects;[20–22,25–28,33–35,39–41] and ten addressing post-treatment aspects.[23,24,29–32,36–38,42]

A range of methodologies were reported: 11 using qualitative methods,[16,27,30–32,34–37,40,41] 14 using quantitative survey-based methods,[18–24,26,28,29,33,38,39,42] one mixed-methods study[25] and one narrative review.[17] Of the studies using quantitative methods four were preferences studies (including three discrete choice experiments and one best-worst scaling survey).[20–22,24]

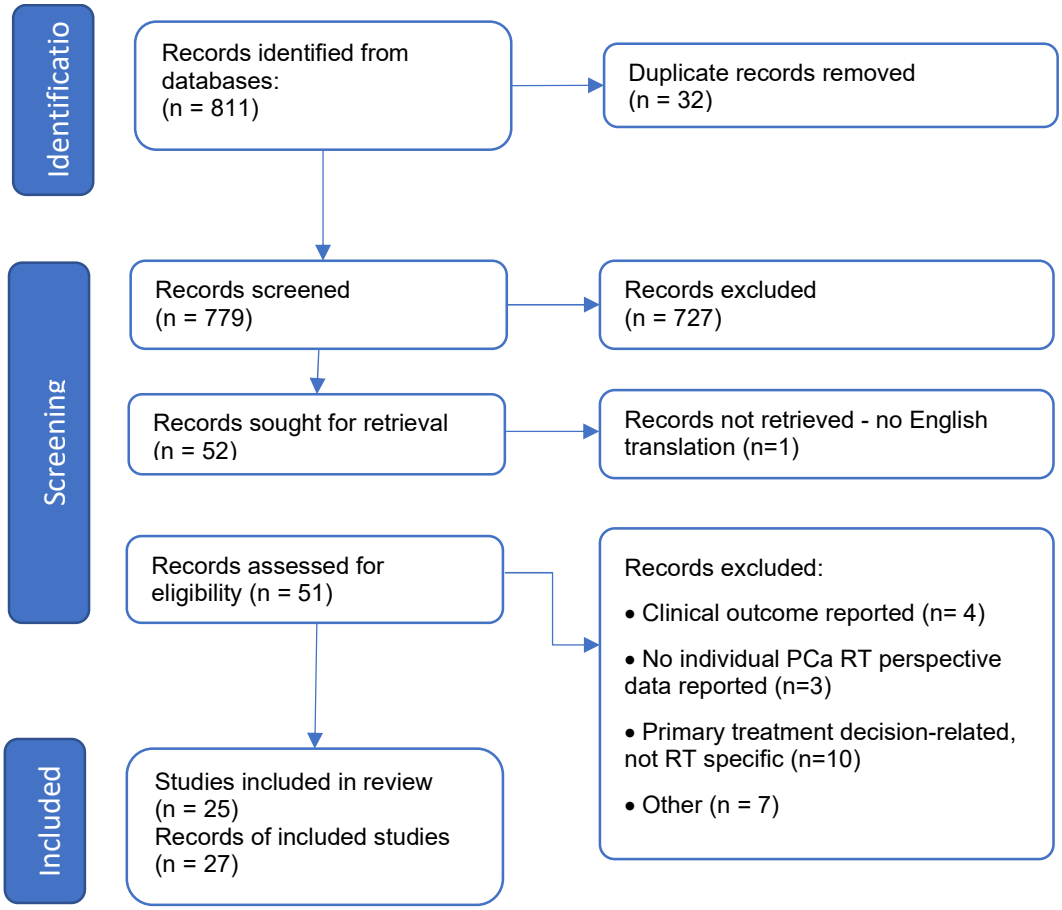


Figure 6.2: PRISMA flow diagram; PCa: Prostate Cancer; RT: Radiation Therapy

Note: coloured squares indicate primary focus of the study, with coloured bordered squares indicating a secondary focus. Numbers denote the references.

Figure 6.3 Mapped matrix of major themes addressed across the treatment pathway continuum.

Table 6.2 Summary of included literature

Reference	Country & Pathway Stage	Aim/s	Population and Sample Size	Methods	Key Findings	Considerations†
Information Needs						
Chen et al (2021)[16]	United Kingdom Pre-treatment	To gain an understanding of men's experience of and specific needs for information and communication	Prostate cancer men in United Kingdom Interviews: 19 patients and 6 carers *Interviewees invited from survey population of Johnson et al (2021)	*Study Design:* Qualitative descriptive Semi-structured interviews Framework analysis, with deductive and inductive approach	Four themes emerged: • Information gaps • Professional communication skills • Individualisation of information • Alternative information sources These were important not just at time of making a treatment decision, but throughout the cancer journey – e.g. understanding side effects of radiation therapy and what to do about them – the "real-life" implications of treatment.	Not clear how many participants had radiation – however the sampling frame indicates aiming for 3-4 patients. It is recognised that those who participated may be self-advocates and able to seek/engage with support
Gordon et al (2019)[17]	United Kingdom	To identify, synthesise and analyse literature	33 articles from 2000-2017 were identified	*Study Design:* Systematic literature review	Many articles included radiation therapy patients	Many qualitative studies did not

	Pre-treatment	reporting the experiences of men with PCa related to information in radiotherapy		Quality assessment to assess validity and reliability Synthesis and thematic reporting	more broadly than only focusing on PCa. Themes identified • information needs • information regarding adverse effects • information and time • information preferences • satisfaction with information related to radiotherapy patient experience related to radiotherapy information	report on validity and reliability
Thavaraiah et al (2015)[18]	Canada Pre-treatment	To investigate patient opinions about information that should be discussed/provided to patients requiring radiation therapy post- prostatectomy.	New and follow-up patients who were referred for consultation N=31 78% accrual rate Time of Survey Completion (to RT): • Prior: 10 (32.3%)	*Study Design:* Quantitative Once-off survey Included domains of: • understanding situation & diagnosis • making a decision • radiotherapy procedures • potential benefits • side effects • supportive network during radiation therapy	Variability between respondents with every question essential to at least some patients, and majority of questions were rated as either essential or important. However, no domains were deemed essential by 100% of respondents.	Generalisability as only one centre

			• During: 12 (38.7%) • After: 9 (29.0%)	Likert-type scale rating importance, ranging from essential to avoid.	
Preferences & Decisions					
Stalmeier et al (2007)[19]	Netherlands Pre-treatment	To evaluate if radiation oncologists know what patient preferences are regarding two radiation dose options	150 patients from two different centres scheduled to undergo RT (50 did not consent)	*Study Design:* Qualitative Interview with Decision Aid (on 2nd visit to clinic having been provided with general radiation therapy information on 1st visit), with preferred treatment followed up by telephone 2 days later. Patients also indicated their decision-making preference. Choice between two radiation doses of 70Gy or 74Gy (trade-off between disease-free survival and adverse side effects). Compared to radiation oncologist's substitute preferences, gauged at first clinic.	79% of patients preferred an active participation role. 71% of patients favoured the less toxic treatment, whereas the radiation oncologist predicted only 51%. Overall agreement was 60% (k = 0.20) 31 patients did not want to choose, and 25 ROs did not provide substitute treatment preferences. Agreement between patient preference and radiation oncologist prediction improved when patient was more hopeful and with RO experience

				Analysis: K statistic for agreement, with bivariate and multivariate analysis.		
Sigurdson et al (2022)[20]	Canada During Treatment	To quantify patient preferences for toxicity and convenience of regimens of EBRT, to contribute to clinician counselling of treatment options with PCa patients	Prostate Cancer Patients who had either recently completed or were completing EBRT for PCa n = 58	*Study Design:* Quantitative DCE – completed with interviewer 12 choice tasks completed 24 total choice sets Pilot: 6 patients Attributes/Levels: 1. Length of EBRT: 2 weeks (5#) / 4 weeks (20#) / 8 weeks (40#) 2. Marker implant Yes / No 3. PSA recurrence risk: 6% / 12% / 18% 4. Acute GI or GU toxicity risk: 20% / 35% / 50% 5. Late GI or GU toxicity risk: 10% / 15% / 20% Analysis: • Multinomial logit and Mixed multinomial logit	Overall preference: • Lower recurrence risk • Lower side effects risk • No marker implantation • Shorter treatment time >70 years old preferred shorter EBRT Those living further away preferred shorter EBRT Reduction in risk of PSA recurrence – respondents more likely to be working Individuals were willing to increase length of EBRT to avoid fiducial markers and risk of worse efficacy or toxicity	Status quo bias / cognitive discordance recognised – i.e. that patients may "defend" their own treatment experience, particularly as partway through (43.1%) or recently completed treatment (56.9%)

				Latent Class analysis		
Brown et al (2022)[21]	Australia During Treatment	To elicit preferences of men for IGRT techniques used in prostate radiation therapy	238 men with previous prostate cancer diagnosis 240 men from general population	*Study Design:* Quantitative DCE completed online or via paper Pilot: 27 men with PCa, 57 general population men Attributes/Levels: 1. Pain: No Pain / Low / Medium / High / Worst 2. Side Effects: Decreased / Same 3. Accuracy: Same / Increased 4. Additional Time: 5 / 15 / 30 minutes 5. Additional Appointments: No / One / Two Appointments 6. Cost: 0 / $50 / $150 / $2500 Analysis: Multinomial logit modelling Latent Class Analysis (LCA)	Overall preference: • Less cost • Less pain • Improved accuracy PCa men valued accuracy more than general population PCa patients willing to pay more to avoid the worst pain than the general population, and willing to pay more for increased accuracy 3 sub-groups identified in LCA, concerned with: 1: Process-related attributes of pain, cost, as well as side effects 2. Process-related attributes of pain, cost as well as additional appointments 3. Clinical efficacy attributes of accuracy and side effects.	Different demographic characteristics between the two cohorts – differences between preferences of two cohorts must be interpreted with this in mind

				Marginal willingness to pay (mWTP)		
Mishra et al (2020)[22]	USA During Treatment	Determined which bowel side effects prostate cancer patients find to be most impactful	174 PCa respondents – varied primary treatments EBRT: 81 ADT: 53 Proton: 51 Prostatectomy: 27 Brachytherapy: 24 AS: 15 Recruited from 2 institutions	*Study Design:* Quantitative Best-Worst scaling Orthogonal design – 18 tasks Attributes (with Levels of Moderate, Small and Very small for all): • Urgency • Pain • Control • Bloody stools • Frequency Attributes/levels based on bowel subscale of the EPIC-26 short-form.	Most bothersome: Control Least bothersome: Frequency Proposed attribute bother weights: • Urgency 20.8% • Pain 18.7% • Control 29.5% • Bloody stools 17.6% • Frequency 13.4%	Demographics reporting was voluntary therefore a lot of missing data. Preference heterogeneity may be lacking as predominately Caucasian respondents Only 12 from one site, compared to 169 from other site.
Eade et al (2021)[23]	Australia Post Treatment	To evaluate patient's treatment decision and decision regret in stereotactic body radiation therapy (SBRT)	112 out of 120 eligible patients consented and completed the survey Recruited from two centres, however treated	*Study Design:* Quantitative Survey – patient reported outcome measures Treatment decision: How much did the option of having 5 stereotactic treatments (as compared	74% reported the SBRT regime was a significant factor in their decision making. Decision regret associated with toxicity, particularly urinary bother	Note: this article also evaluates treatment outcomes not presented here.

			under the same radiation oncologists	to 20 to 40 visits of standard radiation) influence your decision to receive radiation treatment for your prostate cancer? Decision regret: Do you regret the choice of treatment (5 fraction stereotactic radiotherapy) for your prostate cancer compared to other treatment options?	5 patients (4%) reported "quite a lot" of regret. 1 patient had biochemical control and no reported bother (bowel, bladder or sexual) – appeared to regret not having surgery.	An aim was not specified in the article.
King et al (2012)[24]	Australia Post Treatment	To quantify the patient preferences of relative tolerability of adverse side effects or survival gains needed to make side effects worthwhile in the treatment of localised prostate cancer	422 total • Active surveillance (n=64) • Radical prostatectomy (n=66) • External beam radiotherapy (EBRT) (n=29) • Androgen deprivation therapy (ADT) (n=31)	*Study Design:* Quantitative Discrete choice experiment, with survival gains needed to justify persistent side effects estimated. Attributes: (Levels: No, Mild, Severe) • Erectile dysfunction • Loss of libido • Urinary leakage • Urinary blockage • Bowel symptoms	Median survival benefit in months (with 2.5-97.5 percentiles): Severe erectile dysfunction: 4.0 (3.4, 4.6) Severe loss of libido: 5.0 (4.9, 5.2) Mild urinary leakage: 4.2 (4.1, 4.3) Severe urinary leakage: 27.7 (26.9, 28.5) Mild bowel problems: 6.2 (6.1, 6.4)	

			• EBRT + ADT (n=37) • LDR brachytherapy (n=63) • HDR brachytherapy (n=66) Controls without PCa (n=65).	• Fatigue • Hormonal effects	Severe urinary and bowel symptoms were the least tolerable. Mild bowel problems were most prevalent after EBRT (30%)	
General Experiences						
Brown et al (2021)[25]	Australia During Treatment	Explored experiences and preferences of patients undergoing IGRT - both fiducial marker (FM) insertion and Clarity ultrasound (US) procedures.	Prostate Cancer Patients from single centre Survey = 40 Interviews = 22	*Study Design:* Sequential explanatory mixed methods: • Quantitative Surveys • Qualitative Interviews Surveys – investigator-developed; descriptive analysis Interviews – semi-structured with thematic analysis	Perceptions of invasiveness varied with 46% reporting FMs more invasive than US and 49% the same for the two procedures. Survey: • 46% FMs more invasive than US; 49% same invasiveness • Mean scores for pain, physical & psychological discomfort were higher for FMs, only pain achieved significance ($P < 0.05$). Three themes: Expectations versus Experience; Preferences	Generalisability as only one centre

					linked to Priorities; and Motivations. Eleven patients (50%) preferred US; however, 10 (45%) could not elicit a preference.	
Foley et al (2018)[26]		To describe the quality of personal care delivered to patient PCa undergoing radiation therapy, to identify areas for improvement		*Study Design:* Quantitative Questionnaire as for Foley et al (2016), this article reporting on how quality of care was perceived	Top ranked elements included professionalism of ROs/RTs/Nurses to patients (including care, politeness, honesty and respect); knowledge of ROs/RTs, explaining and answering questions in a clear way, and taking the time to do so. Lowest ranked elements included: Environment and facilities such as waiting room, food/drink availability, parking etc; Additional information including second opinions and support groups.	Timing of questionnaires may reflect different timing in respondents' trajectories Generalisability as only one centre
Renzi et al (2017)[27]	Italy During Treatment	Assessed the experiences of prostate cancer men during radiation	10 patients undergoing radiation therapy	*Study Design:* Qualitative	5/10 reported the possibility to share information and questions with at least one health care provider, and	Generalisability as only one centre.

		therapy treatment, with a particular focus on patient empowerment.	• Radical: 3 • Adjuvant: 3 • Salvage: 4 (21 patients in total approached)	Semi-structured interviews, with thematic analysis Semi-structured interview guide was structured following explorative phase, examining department procedures/pathways and interpersonal dynamics experienced by the patients. 4 key theme areas identified: patient-healthcare providers' communication, decision-making, needs, and resources.	identified as having an active role in communication Burdens associated with radiation therapy were identified, including: travelling for treatment, being away from home, practical challenges with managing work around appointments, and preparation for radiation therapy including bladder and bowel. Resources which assisted included family and social support, economic resources, flexible appointment schedules around work commitments, supportive care including physiotherapists and case-managers.	While interviewing patients undergoing radiation therapy, a lot was focused on diagnosis or pre-prostatectomy stages.
Hruby et al (2011)[28]	Australia During Treatment	To determine patient's ratings of physical and psychological discomforts associated with the brachytherapy procedure	58 men undergoing in-patient brachytherapy boost	*Study Design:* Quantitative Survey - adapted from a validated questionnaire for urodynamic and prostate biopsy "Prostate Brachytherapy Questionnaire" completed on consecutive days for 3 days during in-patient stay	"Being stuck in bed" and "discomfort" were rated as most troublesome. Actual experience was rated better than expected by 60% of respondents. "Fear of opening my bowels" was rated to be worse than expected.	Generalisability as only one centre

				(during which, were bed-bound with brachytherapy template and catheter in place).	These findings contributed to a change in protocol of 2 fractions delivered over 2 weeks, without the need for in-patient stay	
Shaverdian et al (2017)[29]	USA Post Treatment	Evaluation of treatment regret and patient perceptions of treatment experience between radiation modalities, including IMRT, SBRT and HDR.	276 prostate cancer patients (329 approached, 86% response) (IMRT, n=74; SBRT, n=108; HDR, n=94) Single institution	*Study Design:* Quantitative Survey study, including domains of: treatment decision-making experience, original expectations of toxicities versus realities, and treatment decision regret Analysis: chi-square or Wilcoxon test for comparing toxicity expectation with experience	87% - fully informed about possible side effects Actual short term side effects less than originally anticipated: • IMRT: 56% • SBRT: 55% • HDR: 25% Actual long term side effects less than originally anticipated: • IMRT: 20% • SBRT: 43% • HDR: 10% Long term side effects significantly more than expected in HDR and IMRT: self-reported problems with urinary, bowel and sexual functions. Regret: 13% in total (19% IMRT, 18% HDR and 5% SBRT),	A wide range of follow up: 12-93 months. Generalisability as only one centre

Hackshaw-McGeagh et al (2017)[30]	England Post Treatment	To explore opinions, experiences and perceived acceptability of taking part in nutritional and physical activity interventions	16 men with PCa (4: Radiation therapy; 12: Surgery) 7 partners (4: Radiation therapy; 3: Surgery)	*Study Design:* Qualitative Semi-structured interviews Thematic analysis 6-month lifestyle intervention was described (30-min brisk walk, 5 days a week; and dietary changes or supplement).	Motivation for change: • Diagnosis shock led to many taking stock of current lifestyle • Motivated to reduce mortality and suffering, not specifically improving health/wellbeing. Facilitators of change • Family support • Health gains and clinical advice • Rationale for change • Anticipated enjoyment of lifestyle • Barriers to change • Poor weather • Urinary incontinence (more so for post-prostatectomy patients) • Time pressure • Overall health Research considerations including participation, group versus individual interventions, data collection methods

					including digital etc were also explored.	
Appleton et al (2015)[31]	United Kingdom Post Treatment	To explore how men receiving radiation therapy for PCa managed; and what aided/hindered their ability to adjust throughout	27 men in total n = 9 men prior to EBRT n = 8 men 6-8 months post EBRT n = 10 men 12-18 months post EBRT	*Study Design:* Qualitative Grounded theory approach Semi-structured interview	Themes: • Pathway to diagnosis • Diagnosis • Impact of PCa and its treatment on daily life • Living with PCa in the long term Painful biopsies were considered the worst part of the experience Radiation therapy preparation regimes caused discomfort and inconvenience. Side effects were often traded off against the benefits of radiation therapy.	Cross-sectional sample – may have been different views if longitudinal
Dieperink et al (2013)[32]	Denmark Post Treatment	Exploration of experiences with radiation therapy and ADT, and participation in a rehabilitation programme	Focus Groups x 2 Group 1 – spouse actively involved (n=6 patients) Group 2 – alone (n = 7 patients)	*Study Design:* Qualitative Rehab programme – 2 nursing counsel sessions; two sessions of physio within 6 months post treatment Analysis of FG data:	Influence on treatment on everyday life (including driving >100km per day for some) EBRT less complicated then expected. Handled mostly by themselves, but welcomed advice from health professionals. Rehabilitation	

				Phenomenological approach, with descriptive and meaning condensation analysis.	was viewed as a way to return to normal life particularly after the months of treatment. Side effects – bother to bowel/bladder significantly decreased after EBRT "Accept things as they come" – particularly when told cured. Humour as coping strategy.
Side Effects					
Devlin et al (2019)[33]	Australia During Treatment	To investigate the association between patient response expectancies of side effects and subsequent toxicity experienced after prostate radiation therapy.	35 patients from two hospitals	*Study Design:* Quantitative Completed pre-treatment expectations survey; and repeated survey at 2 to 7 weeks during treatment Assessed 18 treatment-related side effects, health and hormonal status, emotional state and coping style Hierarchical multiple linear regression analysis	Men felt they had adequate information on side effects prior to commencing treatment Baseline expectancies predicted 6/18 toxicities at week 2 Week 2 expectancies predicted 7/17 toxicities at week 7 Sexual side effects expectancies had greater prediction, particularly "inability to reach orgasm" Some side effects were predicted and reported to occur at 2 weeks, prior to

					when medically expected, suggesting a psychological component.	
Halleberg Nyman et al (2017)[34]	Sweden During Treatment	Explored PCa patient's perceptions of participation during radiation therapy, with or without a smartphone app to manage symptoms and give self-care advice.	28 patients interviewed n = 17 app use group n = 11 standard care Two university hospitals (one rural, one suburban) n= 8 EBRT n = 20 Brachytherapy + EBRT	*Study Design:* Qualitative Open-ended interviews Analysed: "directed qualitative content analysis" utilising a analysis scheme developed for an emergency context	Four participation dimensions confirmed: • Mutual participation • Fight for participation • Requirement for participation • Participation in getting basic needs satisfied The app increased patient participation in their care in managing symptoms. It was seen as a point of contact, facilitating question/answers. Some participants reported frustration with unanswered questions, with radiation therapy staff only able to answer questions relating to radiation therapy rather than more broader questions around their illness or care. While the information received regarding radiation therapy was clear and provided in	It is noted that "participation in their care" was a difficult concept for some men.

					multiple forms, it was perceived that the health care staff set the conditions for when and how participation could take place.	
Blomberg et al (2016)[35]	Sweden During Treatment	To map and describe the symptoms and self-care strategies of patients undergoing prostate cancer radiation therapy	8 patients Recruited from a rural and urban centre 3 individual interviews, 1 focus group with 5 participants	*Study Design:* Qualitative Individual interviews (n=3) and one focus group (n=5) Open-ended question: • "Can you describe your symptoms and concerns during and after radiotherapy?" • Followed by questions about how they managed the symptoms they had, and how they felt about the support they had received. Qualitative content analysis	Symptom categories identified: urinary symptoms, bowel problems, pain, sexual problems, fatigue, and anxiety, depression and cognitive impairment, and irregular symptoms (incl weight gain, numbness, sweating, swollen feet, shivers, cyanosis). Self-care strategies rarely described but two identified: • Urinary urgency – empty bladder prior to leaving the house • Fatigue – trying to remain active Uncertainty reported by patients from around waiting to see health professionals; incomplete or limited information received and	Sample size – although a breadth of EBRT modalities covered, and rural and urban centre included. Note: This was a mixed-methods study including professionals interviews and a scoping review, however the data extracted focuses solely on the patient qualitative interviews.

					feeling unsure of information received.	
Kinnaird and Stewart-Lord (2021) [36]	England Post Treatment	To investigate men's perceptions of sexual dysfunction caused by EBRT and ADT, and the impact of this on their life.	8 patients who were 18-24 months post treatment	*Study Design:* Qualitative Phenomenological study Semi-structured interviews Thematic analysis	Three themes: 1) Priorities when making treatment decisions – with a strong focus on survival rather than side effects 2) Information and support received about sexual side effects 3) Perceptions and experiences of sexual dysfunction	Selection bias recognised as those participating willing to discuss a sensitive issue
Schultze et al (2020) [37]	Germany Post Treatment	To capture the diverse range of experiences of having and having had prostate cancer Part of a larger project to add narratives to a website	44 men Recruited from health centres, support groups and consumer organisations 17 had radiation therapy and/or brachytherapy	*Study Design:* Qualitative Narrative interviews Thematic analysis	Life-disrupting side effects: urinary leakage, potency and libido loss Attributing losses to ageing and/or cancer – intertwining of ageing and cancer.	Recognised that because interviews were also going to be used online, there may have been a more positive prognosis consented.

Dyer et al (2019)[38]	United Kingdom Post Treatment	To explore how erectile dysfunction is experienced by patients, and assessed and managed.	546 men, 137 (25%) received EBRT	*Study Design:* Quantitative Cross-sectional survey Recruited through Prostate Cancer UK's communication channels Analysis: Proportions	*Results presented here represent the radiation therapy + ADT cohort only: 54% of men reported that no one asked about erections prior to treatment. 74% of men reported information regarding potential erectile dysfunction was given 41% reported not being offered treatment to help get or keep an erection	Also included health professional perspective, not presented here Survey was co-produced with PCa patients Higher proportion of younger men than the prostate cancer population.
Support						
Foley et al (2016)[39]	Canada During Treatment	To identify the elements of nontechnical (personal) care that are most important to prostate cancer radiation therapy patients	108 patients undergoing prostate EBRT Exclusion: Nodes, prostatectomy or brachytherapy Inclusion: ADT	*Study Design:* Quantitative Questionnaires developed via cognitive interviews with 8 patients and 4 health professionals Aspect of care: • Patient centeredness • Empathy and respectfulness of caregivers	Most important: perceived competence of their caregivers, the empathy and respectfulness of caregivers, and the adequacy of information sharing. Differences in patient's different priorities were not predictable by age, education or health status.	Timing of questionnaires may reflect different timing in respondents' trajectories Generalisability as only one centre

				• Perceived competence of caregivers • Adequacy of information sharing • Accessibility of caregivers • Continuity of care • Comprehensiveness of services • Treatment environment • Privacy • Convenience		
Clarke & Burke (2016) [40]	United Kingdom During Treatment	To ascertain PCa patient perceptions of support received during radiotherapy treatment course	13 patients, interviewed within last week of radiation therapy treatment (fractions 32 to 37)	*Study Design:* Qualitative Qualitative phenomenological approach, with Giorgi analysis Qualitative interviews	Quality of support overall positive. Many felt well supported during treatment sessions, not requiring additional on-treatment reviews Peer support found in the waiting room, building relationships with other men going through treatment. Mixed views regarding information and support prior to treatment commencement.	Generalisability as only one centre. No patient demographics are reported.

					Uncertainty around bladder and bowel preparation reported by 31% of participants. Requested to know why, not just instructions.	
Ormerod & Jessop (2015) [41]	UK During Treatment	To evaluate if on-treatment review clinics were meeting patients needs during and at the completion of radiation therapy.	7 prostate cancer patients Convenience sample of all PCa patients completing treatment within 1 month	*Study Design:* Qualitative Phenomenology using semi-structured interviews	Two main themes emerged: 1) Information giving 2) Clinical assessment of symptoms Information was important to patients, with some specifics reported: • 2/7 felt there had been information omissions at planning and treatment commencement, causing unnecessary anxiety • However 6/7 were satisfied with information giving during and end of treatment • 2/7 did not understand purposes of daily imaging • All patients reported being aware of possible side effects	Generalisability as only one centre Note: Two health professionals were also interviewed, however their specific insights are not included here

					• 6/7 did not experience any that necessitated medication or required referral All patients' priority at the end of treatment was "to know how it's [the treatment] gone" with quality of life not commonly raised.	
Johnson et al (2021) [42]	United Kingdom Post Treatment	To identify unmet supportive, palliative care and informational needs of people living with prostate cancer (patient and carers).	Prostate cancer men in United Kingdom Survey: 216 men, 97 carers Previous treatment: ADT: 42% RT: 39% Surgery: 37% AS: 28% Chemotherapy: 9% Palliative care: 1% Interviews: 19 patients and 6 carers	*Study Design:* Quantitative Survey including: • Patient Supportive Care Needs Survey • Carer Support Needs Assessment Tool • Health Status (EQ-VAS) Free-text analysed thematically	Patients: • 62% reported moderate-high needs • Locally advanced/advanced cancer diagnoses were associated with higher unmet needs. Carers: • Chronic illness significantly predicted supportive care needs. • Free-text analysis: • Poor communication led to frustration • High burden of symptoms, particularly hormone therapy	Cancer stage was self-reported, with 40.7% as "don't know/not to say"

			• Symptoms were “inevitable, to be borne stoically” Busyness of hospitals meant person-centred care was not always delivered, with some poor coordination or management noted

†***including limitations or biases;*** **Abbreviations:** ADT: Androgen Deprivation Therapy; AS: Active Surveillance; DCE: Discrete Choice Experiment; EBRT: External Beam Radiation Therapy; GI: Gastrointestinal; GU: Genitourinary; HDR: High dose rate brachytherapy; IMRT: Intensity Modulate Radiation Therapy; LCA: Latent Class Analysis; LDR: Low dose rate brachytherapy; mWTP: Marginal Willingness to Pay; PCa: Prostate Cancer; RO: Radiation Oncologist; RT: Radiation Therapy; SBRT: Stereotactic Body Radiation Therapy

Many studies included perspectives of men who underwent a range of treatments including surgery and hormonal therapy. The majority of studies involved men who underwent external beam radiation therapy to the intact prostate,[18,19,29,32,35,36,42] and three of these studies also investigated stereotactic body radiation therapy (SBRT) and/or hypofractionation.[19,29,35] Six of these studies included other modalities such as brachytherapy[18,29,32,36,42] and one also included proton therapy.[29] One study focused on radiation therapy in the post-prostatectomy setting. [29] A number of studies included a range of treatments/modalities.[18,27,29,33] The complete details of treatment regimens were not specified[33] or were unclear in some studies,[18,27] usually when different treatment modalities were undertaken.

One study reported in two manuscripts included the perspective of the carer in addition to the patient,[16,42] and another included patients' partners at the patient's invitation.[30] Two studies each resulted in two separate records: Foley et al (2016, 2018) reported on 108 patients undergoing radiation therapy in Canada;[26,39] and Johnson et al (2021) and Chen et al (2021) reported on 216 men and 97 carers in the United Kingdom,[42] with a subset of 19 men and 6 carers interviewed.[16]

Countries represented in the studies included Australia,[21,23–25,28,33] Canada,[18,20,26,39] Denmark,[32] Germany,[37] Italy,[27] Netherlands,[19] Sweden,[34,35] United Kingdom[16,17,30,31,36,38,40–42] and United States of America.[22,29] The studies were published in a range of journals. Eleven were published in radiation therapy/radiation oncology specific journals and the remainder in varying oncology or other medical or supportive care journals. The earliest study was published in 2007,[19] with a noted increase in recent years.

Information needs

Information needs were an important factor for patients undergoing radiation therapy. Three studies were focused on the pre-treatment phase (n=3).[16–18] Across the studies, 247 men[16,18] and 97 carers[16] were surveyed and 25 men interviewed.[16] Additionally, two studies covered information needs during treatment as a secondary focus with one in the post-treatment phase.[40–42]

Tailored information and the manner in which it was delivered was identified as important, not just at time of diagnosis but throughout the treatment journey. [16] The information needs of post-prostatectomy patients referred for radiation therapy were varied, with all domains presented (including diagnosis, decision making, radiation therapy procedures, benefits, side effects, and support network) in the survey deemed as essential by at least some participants.[18] These results were corroborated by the narrative review investigating information needs around radiation therapy for prostate cancer patients. In this review the authors argued that information needs, preferences and satisfaction varied, and noted that few records focussed only on prostate cancer. [17]

Patients reported they needed more information about radiation therapy processes such as bowel and bladder preparation as a secondary focus when discussing support. For example, some participants requested instructions in addition to the reasoning behind these requirements, however it is noted that while this information may be provided to patients, it may not be retained by all.[40,41] The information needs following treatment reflected the different phase of the treatment pathway, with a need for improved communication/information around survivorship and palliative care reported by both patients and carers.[42]

Preferences / decisions

Preferences and decisions covered specific aspects of radiation therapy including fractionation and image-guidance, as well as understanding values and trade-offs made by participants. The preferences and decisions/decision making of participants were reported in six studies, with one focussing on pre-treatment,[19] three focussing on during-treatment[20,21] and two post-treatment.[23,24] 1055 participants were surveyed across the studies (survey population ranging from n=58[20] to n=478[21]).

Results from a study utilising a decision aide to help patients decide on radiation treatment schedule (between 70Gy and 74Gy) found that 79% of men preferred active participation in the decision, with 71% favouring the less toxic treatment.[19]

Other treatment studies covered preferences of patients including: hypofractionation schedule preferences,[20] IGRT preferences[21] and bothersome bowel side effects.[22] Two studies

elicited preferences through discrete choice experiments,[20,21] and one through best-worst scaling.[22] One of these preference studies included a general population cohort in addition to a patient cohort,[21] and the other two focused on patient cohorts only. [20,22] Overall, men preferred shorter treatment regimens associated with lower recurrence risk, lower side effects risk and no FM implantation; [20] preferred IGRT with less cost, less pain and improved accuracy; [21] and perceived that bowel side effects of loss of control is most bothersome, and frequency least bothersome. [22]

When quantifying the trade-offs between side effect tolerability and survival gains, respondents were least willing to tolerate severe bowel and bladder symptoms after EBRT, with a trade-off of 27.7 median months survival benefit required for severe effects.[24] Decision regret in choosing SBRT over other treatment options was evaluated in 112 men, and found that 4% of men reported regret associated with side effects.[23]

General experiences

General experiences related to any aspect of treatment interaction not covered by the other major themes. The experiences of participants were reported in five studies, with three focussing on during-treatment experiences,[25–28] and two focussing on post-treatment.[29,30] Across the studies, 36 men[25,27,30] and 7 partners[30] were included in interviews and 482 men surveyed[25,26,28,29] (survey population ranging from n=40[25] to n=276[29]).

During treatment, the experiences of image guided radiation therapy (IGRT) procedures were explored, with participants describing fiducial marker insertion as more invasive compared to transperineal ultrasound monitoring.[25] The practical challenges of radiation therapy including time away from home/work were identified as a burden.[27] Following a high-dose brachytherapy (HDR) procedure, the most troublesome factors reported were “being stuck in bed” and “discomfort” by participants.[28] Men undergoing brachytherapy rated discomfort as most troublesome, however 60% rated their experience as better than expected.[28]

Treatment regret in choosing radiation therapy over other treatments and associated side effects was evaluated. Regret regarding their specific treatment was reported by a total of 13% of men surveyed (specific modality incidence: 19% intensity modulated radiation therapy (IMRT), 18% HDR and 5% stereotactic body radiation therapy (SBRT)), with SBRT and IMRT

patients reporting short-term side effects less than expected, and SBRT patients reporting long-term side effects less than expected.[29] Of those reporting regret, 71% regretted their decision for radiation therapy treatment, and instead wished they chose active surveillance.[29]

The acceptability of a proposed lifestyle intervention (dietary changes and physical activity) post-treatment was evaluated in interviews with patients and their partners. The main motivation identified was to participate in such interventions to reduce mortality and suffering rather than improve health and wellbeing.[30]

The care given by the multidisciplinary team (radiation oncologists, nurses and radiation therapists) during treatment was recognised by participants, with factors including politeness, respect, care and collaboration rated as important.[26]

Side effects

Side effects included the experience of various symptoms, the impact of side effects and symptom management. Side effects were reported in seven studies, with three focussing on during-treatment side effects,[33–35] and four focussing on post-treatment.[36–38] 88 men were included in interview[34–37] and 172 men surveyed[33,38] (survey population ranging from n=35[33] to n=137[38]) across the studies. Additionally, two studies in the during-treatment phase[22,28] and two studies in the post-treatment phase[31,32] covered side effects as a secondary focus.

Urinary and bowel symptoms were identified in one study, as well as sexual problems and psychosocial problems such as anxiety and depression.[35] Life-disrupting side effects were described by some men including urinary leakage, lack of potency and libido loss.[37] Men reported the side effects were less than expected, with bowel/bladder bother significantly decreasing after treatment, and there was a willingness to accept side effects for cure.[32] Similarly, side effects were found to be traded off for the benefits of radiation therapy.[31]

Men identified self-care strategies in managing their symptoms, including practical measures such as emptying their bladder prior to leaving their house.[35] In one study, a smartphone app utilised during treatment increased the patient participation in managing their symptoms.[34] One study compared pre-treatment side effect expectancies to the experienced side effects in 35 men; the participant's expectancies predicted seven out of 18 side effects near the

completion of radiation therapy, that is, they experienced seven side effects that they expected.[33]

Erectile dysfunction (ED) is a known common side effect of prostate cancer treatment for men receiving EBRT. Almost three-quarters of respondents (74%) reported being given information on ED prior to treatment, but 41% reported they were not offered treatment for ED.[38] Similarly, some men in interview reported a lack of information or overly optimistic outlooks were given by health professionals regarding sexual function.[36]

Support

Support included that provided by health professionals, peer support and unmet needs of patients and carers. The support needs of participants were reported in three studies in the during-treatment phase, [39–41] and one in the post-treatment phase.[42] Across the studies, 45 men were included in interview[40–42] and 324 men[39,42] and 97 carers[42] surveyed. Additionally, one study included support as a secondary focus in the treatment phase.[26]

The perceived competence, empathy and respectfulness of healthcare professionals was indicated as most important during treatment.[39] Support provided during the treatment phase and information (including access, type and volume) was considered important, with one study showing 28% of men did not understand the reason for imaging during radiation treatment.[41] Another study found men felt well supported during treatment, and aspects such as peer-support through meeting other men in the radiation therapy waiting room added to this feeling of support.[40]

The support needs in the post-treatment phase reflected the changed needs of patients and carers, higher needs were associated with more advanced prostate cancer diagnoses and chronic illness.42 Poor coordination was a reported frustration and attributed to the demands of the health service, meaning patient-centred care was not always delivered.42

Discussion

This scoping review explored the literature pertaining to perceptions and preferences of prostate cancer radiation therapy. Overall, the 27 studies included in this review covered five

themes: information needs, preferences and decisions, general experiences, side effects and support, spanning three stages of treatment (pre-, during-, and post-treatment stages). These themes align with several of the domains of patient-centred care first described by the Picker institute and adopted by many international health services and systems, most notably: respect for preferences and values; emotional support; physical comfort; information, communication and education; and continuity and transition. [43]

The studies were categorised into five themes and pathway stage for this review. However, it is recognised that some studies may have addressed multiple pathway stages or themes. For example, two studies categorised as general experiences in post-treatment also covered side effects as part of those experiences.[31,32] The multiple categorisations reflect the interlinked nature of patient experience, perception and preference. The most overarching theme and pathway stage for mapping was determined through data extraction to keep the scoping results as clear and concise as possible, with secondary focus indicated as applicable.

The initial search revealed a number of pre-treatment studies focused on modalities (such as surgery versus radiation), but these were excluded during title and abstract screening as they were not radiation therapy specific. Of the full-text records assessed, an additional 19.6% of records were excluded as the focus was on primary treatment decisions. While the decision of treatment modality is a critical decision already well described in existing studies and systematic reviews,[7–9] there are many other factors for patients to consider once a particular treatment modality such as radiation therapy has been decided.

The focus on information particularly in the pre-treatment stage highlights the different information needs between patients at this pathway stage and the challenges faced by radiation oncology professionals in meeting these needs. The unknown environs of radiation therapy are documented, and help explain this “unknown” phenomenon often reported by patients about to start radiation therapy, influencing their need for information.[44] It is important for future research to recognise that “one size does not fit all” in meeting patient information needs, as there was a variance in information provision reported by men from ”not enough” to ”too much”.[16–18,41] There is a need for robust information at the time of diagnosis to guide overall treatment decisions as reported by treatment decision literature,[10–12,45] however information needs continue throughout the whole treatment pathway.[42]

In analysing general experiences, valuable perspectives are gained from the patients highlighting areas that could be immediately improved such as targeted information provision.[40] Additionally, preference studies highlight where patients place value, which may be different to the healthcare professional, such as preferring lower risk.[20] General experiences also provide insight into person-centred care aspects important to the patient – insights which can only be captured directly from the patient.[26,39]

The side effects and their management experienced by men were the focus of during-treatment studies and included other aspects such as support and logistics, unsurprising as these aspects are the most pressing during treatment. While shorter fractionation was found to be a preference by Sigurdson et al (2022), [20] so was lower side effect risk. This may reflect the increased advances in treatment since Stalmeier et al (2007) reported findings of patients opting for the less toxic (i.e. the lower dose of 70Gy compared to 74Gy) treatment.[19] The predominant theme of studies in the post-treatment phase was continued management of longer-term side effects, as well as treatment regret and survivorship with lifestyle modifications.

The importance of competence, empathy and respectfulness indicates the vital supportive roles expected of healthcare professionals in the prostate treatment pathways in providing patient-centred care.[39] Additional supports identified included peer-support and informational support.[40,41] Of note, while carers were included in some studies, none were included in studies around support, indicating this as a knowledge gap.

The paucity of radiation therapy specific literature suggests future potential areas for patient preferences research, particularly as the radiation oncology community seeks to increase and improve patient-centred care for men with prostate cancer. It is recognised that some records not included in this review may have relevant details, particularly studies about broad cancer populations that include a prostate cancer sub-cohort. Every effort was made to identify these studies, but where these sub-cohorts were not easily identifiable, studies may have been inadvertently excluded. This is a limitation of this review.

This review highlights that many factors influence the preferences and perceptions of prostate cancer patients receiving radiation therapy. More broadly, we believe the findings

identify opportunities for radiation therapy services to further develop patient-centred practices, particularly around information needs, treatment procedures and the management of side effects. Delivering patient-centred care improves treatment adherence, better patient satisfaction and overall health system efficiency.[46,47]

Conclusion

This scoping review highlights the paucity of literature currently available describing the perceptions and preferences of men with prostate cancer regarding radiation therapy and related aspects. The varied perceptions reported in the literature demonstrates the complexity of delivering person-centred care in a healthcare setting such as radiation oncology. Continued research in the areas of pre-treatment, treatment and post-treatment patient needs will further improve patient-centred care delivery in prostate cancer.

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Supplementary

Supplementary I: search strategy

1. ((("Radiotherapy"[MeSH Terms] OR "Radiation Oncology"[MeSH Terms]) AND "prostatic neoplasms"[MeSH Terms])) AND ("perception"[MeSH Terms])
2. ((("Radiotherapy"[MeSH Terms] OR "Radiation Oncology"[MeSH Terms]) AND "prostatic neoplasms"[MeSH Terms])) AND ("Patient Preference "[MeSH Terms])
3. ((("Radiotherapy"[MeSH Terms] OR "Radiation Oncology"[MeSH Terms]) AND "prostatic neoplasms"[MeSH Terms])) AND ("choice behaviour"[MeSH Terms])
4. ((("Radiotherapy"[MeSH Terms] OR "Radiation Oncology"[MeSH Terms]) AND "prostatic neoplasms"[MeSH Terms])) AND (patient perception)
5. ((("Radiotherapy"[MeSH Terms] OR "Radiation Oncology"[MeSH Terms]) AND "prostatic neoplasms"[MeSH Terms])) AND (patient experience)

Translation of Evidence Infographic

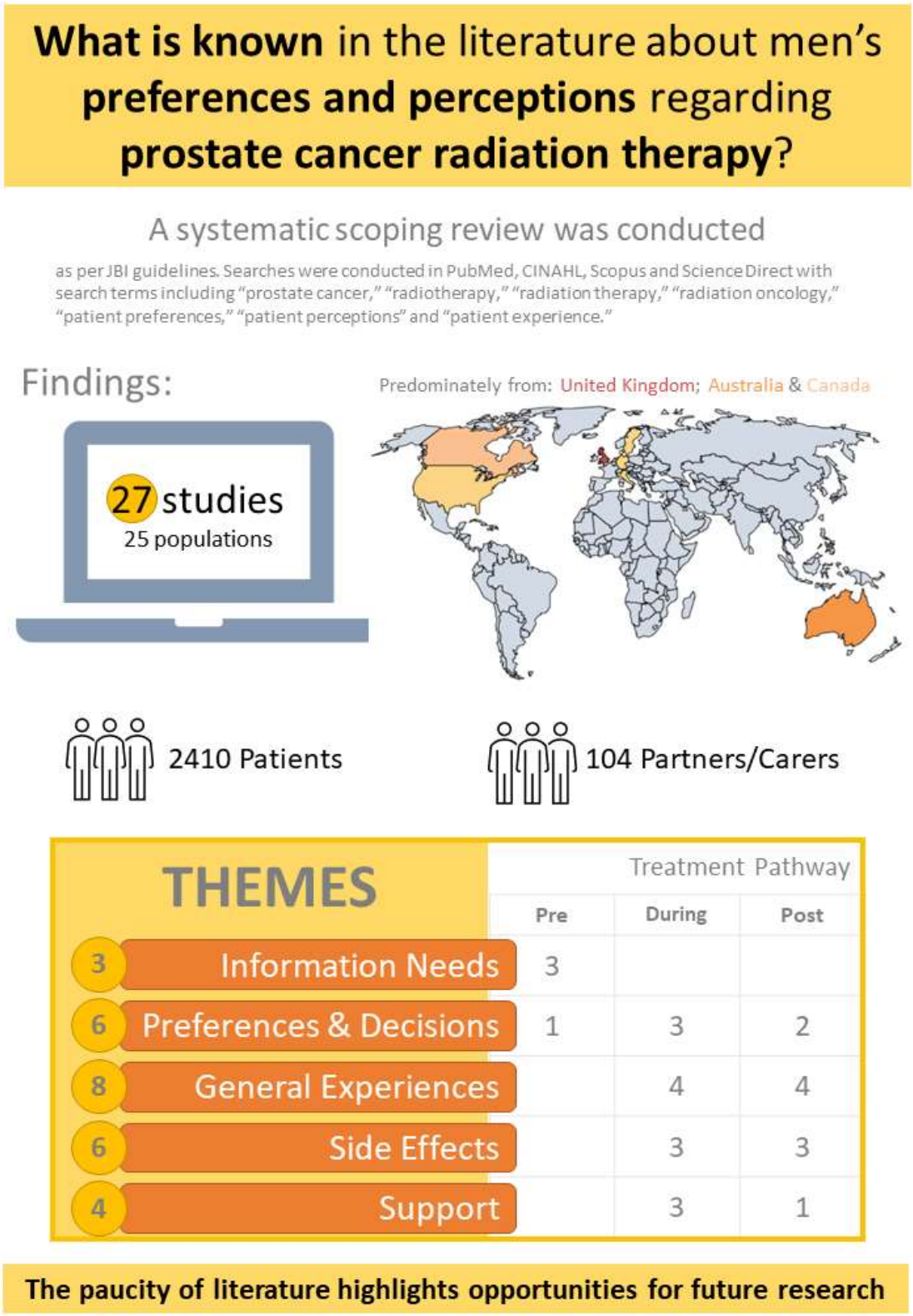


Figure 6.4 Translation of evidence infographic - Chapter 6

Linking to Subsequent Chapter

The findings of this study situate this thesis within the literature, and point to further knowledge gaps for future research. Specifically, further work regarding patient preferences in radiation therapy treatment of prostate cancer are recommended.	*This chapter addressed research question 5:* *What is known in the literature about patients' perceptions of prostate cancer radiation therapy?*

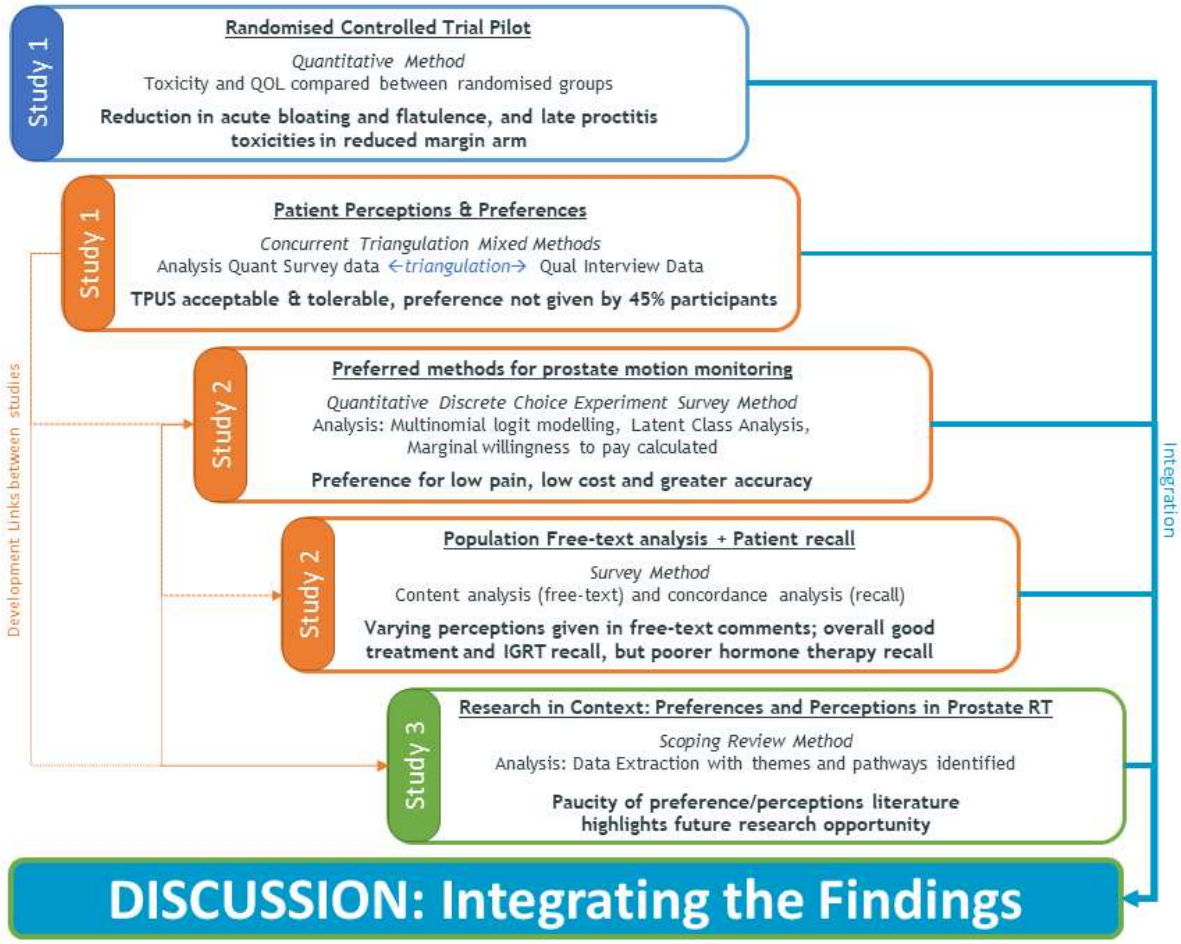
Chapter 7 Discussion and Conclusion

The overarching aim of this PhD was to use a patient-centred approach to improve prostate cancer radiation therapy. The clinical outcomes of reducing prostate margins in conjunction with intrafraction motion monitoring were analysed. In addition, patient experiences, perceptions and preferences regarding prostate IGRT were studied. These two focus areas have been largely addressed separately throughout the thesis, yet they are inextricably linked: clinical outcomes research informs clinical practice, however clinical practice needs to be acceptable to the patient. This final chapter brings these two focus areas together, identifies future research opportunities and describes the impact of this research to date.

Impact of Work

At the Townsville Cancer Centre (TCC), two changes in practice have been initiated by this research. Firstly, fiducial marker insertion has been disinvested, based on 1) the perspectives of the patients included in this PhD (Chapters 3 and 4) and 2) the increased experience and capability of treating radiation therapists to align radiotherapy treatment using the prostate as seen on CBCT, without FMs present.[1,2]

Secondly, TCC has implemented reduced margins for prostate cancer radiation therapy, when treated with TPUS motion monitoring, as standard practice from September 2022. The decision was based on the pilot RCT results (Chapter 2), further departmental technical analysis, and additional emerging evidence. [3–7]



Blue indicates clinical outcome focus area, orange indicates patient perspectives focus area and green indicates bringing both focus areas together

Figure 7.1 Integration of PhD findings, with key findings of each study in bold.

To understand the clinical outcomes and patient perspectives of image-guided prostate cancer radiation therapy, a multi-study approach was adopted for this PhD program (as visualised in Figure 7.1), using multiple methods. Using multiple methods allowed for greater understanding of the two focus areas of clinical outcomes and patient perspectives, and research context integration.

Clinical Considerations

An initial literature review found a lack of high-level evidence regarding reduced margins with image guidance (Appendix F), leading to the development of the RCT (Chapter 2, Study 1, Research Q1). The pilot RCT provided encouraging results to reduce margins with TPUS. The

statistically significant reduction in long-term proctitis in the reduced margins group demonstrates the potential for improved patient outcomes through the reduction in margins. These results are mirrored in the literature, however, to date there remains a lack of high-level evidence regarding patient outcomes, with the majority of the literature regarding both IGRT and reduced margins being drawn from technical and dosimetric analyses, or observational studies.[8–10] Additionally, measures of more complicated patient outcomes such as radiation proctitis have only relatively recently been developed and validated, with previous clinician toxicity scores historically focusing solely on rectal bleeding, and not other symptoms associated with proctitis such as bowel urgency and/or faecal incontinence.[11] Further research into radiation proctitis, including prevalence, quality of life impacts and the potential reduction through measures such as reduced margins should be undertaken.

A randomised controlled trial is considered a high level of evidence in health research, allowing for the testing of efficacy of treatments and/or technologies against the 'standard'.[12,13] Indeed, it is often the case that radiation oncology innovations outpace evidence generation and at times, innovations are implemented prior to high-level evidence.[14] Radiation oncology differs from many other health fields because 1) clinical practice is largely technology driven, and 2) individual patient outcomes are modelled in a process known as dosimetry, where the radiation treatment plan is custom generated for each individual patient. [13] The dosimetry may predict improvement in outcomes such as tumour control or toxicity however, this is difficult to demonstrate through RCTs because of the time required to recruit large sample sizes and the duration of follow up required to record sufficient events.[13-15]

Many RCTs of prostate cancer treatment compare primary treatments (such as radiation therapy, brachytherapy, radical prostatectomy or active surveillance) rather than the treatment-specific factor of treatment margins with prostate-motion monitoring evaluated in this PhD. However, as demonstrated in a recent systematic review of 36 prostate cancer treatment RCTs, the sample sizes are often small indicating further larger RCTs are recommended.[16] Of note, more pragmatic approaches are being adopted in the global radiation oncology community with the implementation and uptake of MRL technology, including the R-IDEAL framework (Stages: Radiotherapy-predicate studies; Idea, Development, Exploration, Assessment, Long-term evaluation),[17] and evaluating

interventions through 'trials within cohorts' models, whereby patients presenting to radiation oncology departments provide informed consent for the collection of clinical, technical and patient-reported outcome data, and may opt-in to future randomisation for experimental-interventional trials (such as MRL versus standard linear accelerator treatment).[18] There is also an increasing interest and uptake in "learning health systems" in radiation oncology, with supporting infrastructure to rapidly learn from real-world patient data, which may serve radiation oncology well in implementing and evaluating technological advances.[19]

The pilot RCT undertaken as part of this PhD program recruited less participants than anticipated due to various factors. These are discussed in Chapter 2 but briefly include: lower referral numbers, greater than anticipated refusal rates and a fractionation change. While results were promising, the trial is ultimately underpowered. However, as per the principles above, the theoretical dosimetric gains afforded by reduced margins with real-time monitoring and correction as required have supported the adoption of reduced margins into clinical practice at TCC, the largest tertiary cancer centre within North Queensland. Continued evaluation of PTV margins through quality improvement at individual department level is recommended.[20,21] Locally, the adoption of reduced margins is in addition to the adoption of hypofractionation as standard in 2020, and thus further outcomes research to investigate these additional changes is warranted. With the higher dose delivered per treatment with hypofractionation, reducing margins is even more vital to reduce toxicity.

Patient Perspectives

The patient perspective is an important consideration in patient-centred care.[22] This PhD was the first to explore patients' experiences with, perceptions about, and preferences for image-guidance in prostate radiation therapy.

The sequential explanatory mixed methods study to obtain patient perspective of IGRT enabled further understanding of the patient experience and perceptions of both TPUS and FM (Chapter 3, Study 1, Research Question 2). The concurrent triangulation of surveys and interviews allowed exploration of the way participants responded to concepts in the survey through the semi-structured interviews.

Both patient and general population preferences for IGRT were evaluated in Chapter 4 (Study 2, Research Question 3). These built upon the findings in Study 1 and further identified that the most important attributes to both populations were pain, cost and accuracy. However, patients valued pain and accuracy over cost compared to the general population. Health preference research methods, including DCEs, are increasingly utilised in health research. Patient preferences are a key domain of patient-centred care. Clinical outcomes rely on the patient's uptake of desired treatments/healthcare, thus the patient's perspective and preferences are important considerations to improve outcomes.

Findings from Study 1 (Mixed methods) filled the knowledge gap regarding patient perceptions of the TPUS system, particularly tolerability and acceptability. Findings from Study 2 (DCE) provide important preference information for radiation oncology departments who are considering options for monitoring prostate motion, with patient preference adding to clinical, technical and policy considerations.

Capturing patient's recall illuminated the fact that recall is overall good, except with respect to hormonal therapy (Chapter 5, Study 2, Research Question 4). Evaluating recall was intended as a proxy for patient understanding of their treatment. Patient health preferences can be heavily influenced by their understanding of the healthcare or treatments on offer.[23] However, it was found that men with prostate cancer and men from the general population preferred lower cost, less pain and greater accuracy, suggesting that lived experience and understanding did not influence preference differently, except for willingness to pay.

Low individual health literacy is associated with poorer health outcomes.[24] This study does not reveal why recall may be low, however in triangulating with the unpublished data from Study 1 (Chapter 3) potential reasons for the poorer recall of hormone therapy are suggested, with one participant explaining "*But I didn't really fully understand when he said a needle, I didn't really fully understand it was a hormone needle (P37)*". The hormone therapy recall rate may explain the low tolerability of hormone therapy reported in literature and observed in our clinical practice.[25-27] The poorer recall of hormone therapy may reflect a poor understanding of the treatment self, including rationale and associated toxicities. Improving patient understanding of hormone treatment may also improve the patient compliance when understanding the rationale and importance of hormone therapy.

Bringing Together Clinical Considerations and Patient Perspectives

The scoping review linked the focus areas of clinical outcomes and patient perspectives by situating Study 1 and 2 findings within the literature (Chapter 6, Study 3, Research Question 5). The review demonstrated a paucity of literature on the perceptions and preferences of patients with prostate cancer regarding radiation therapy, suggesting these areas for future research. Patient perceptions and preferences will remain important to understand as clinical technologies and techniques within radiation oncology continue to emerge, particularly as different technologies may be experienced differently by individual patients. Respecting patient's perceptions, preferences and values ensures patient-centred care principles are enacted in health care, alongside the clinical considerations.[28]

Implications for Clinical Practice and Policy

It was the original intent for this PhD to culminate in an HTA of the TPUS system, as there is no published evidence to date. HTAs are an analysis of safety, efficacy and cost-effectiveness of technologies and interventions, providing information to health policy makers at a local health service level or more broadly.[29-30]

Two domains to conduct a Health Technology Assessment (HTA) have been addressed in this PhD: Evidence regarding the patient perspective and preference for TPUS and pilot data on clinical outcomes afforded by TPUS prostate monitoring.[29-31] Health utilisation data to inform an assessment of costs was collected as part of the RCT, however owing to the slow recruitment, more economic evidence is required to enable an economic evaluation. The TPUS system does come at a significant up-front capital cost and therefore robust economic analysis is required to support continued investment in such technologies. A cost-utility analysis in the United States of America compared electromagnetic beacon correction with other correction methods (electronic portal imaging, CT or transabdominal ultrasound), and reported an incremental cost effectiveness ratio of $14,053 per Quality Adjusted Life Year (QALY), within the stated willingness to pay threshold of $50,000 per QALY.[32] However, this cost-utility analysis was based on interfraction correction only due to the lack of available intrafraction outcome data available at the time. Indeed, there are no health economic analyses of prostate cancer intrafraction guidance, with current data focusing on

interfraction.[33-34] The intrafraction correction studied in this PhD provides further evidence on the number of pauses/corrections required, as well as pilot outcome data.

Strengths

The greatest strength of this PhD is the range of research methods used to understand clinical and patient focus areas. Both focus areas are necessary when investigating TPUS, and image-guidance more broadly, to improve prostate cancer radiation therapy for both patients and health services. This research has also captured perspectives of men within the general population of Australia, in addition to men with prostate cancer, providing the preferences of both a population with the lived experience, and of the taxpayer and potential future patients.

This PhD has been conducted with the support of a comprehensive research team (including clinicians, researchers, academics and a consumer investigator). These investigators bring expertise and interest in key areas of clinical considerations and patient perspectives, and more broadly in health services research, including health economics and policy. The expertise and interest of the research team has particularly strengthened the development and interpretation of each study.

Insights into patient preference were gained via two methods - concurrent triangulation mixed methods followed by a DCE - which is a strength of this PhD. The preferences of males in the general population were elicited in the DCE, in addition to men with a prostate cancer diagnosis. Both perspectives were sought to establish what is important to potential future patients, to inform policy and decision makers at radiation oncology departments for future planning. In a taxpayer funded public health system such as Australia, the general population analysis also provides information about the tax-payers willingness to pay through health preferences research.[35-36]

Limitations

The pilot RCT represents a single institution's experience and further research is warranted. Additionally, the pilot results are underpowered, and instead provide information for future power calculations. The adoption of reduced margins, however, highlights the willingness of clinicians to adopt practice change based on modelled dosimetric benefit but limited outcome

evidence. Additionally, there are challenges with systematically and robustly collecting toxicity and patient-reported outcomes, as evidenced by the lack of baseline toxicity data collected in the pilot RCT, and the missing data throughout (as demonstrated in Table 2.4 (supplementary)).

As discussed in Chapter 3, there are potential limitations in a younger female interviewing older men about prostate cancer treatment experiences. This was mitigated as much as possible by allowing a partner/carer to be present for the interview at the participants preference, however, it is still a recognised limitation. It is interesting to note however, that similar sentiments were captured within the free text of the DCE survey suggesting this limitation was minimal. Lastly, the perspectives given were from participants who had experienced both TPUS and FM which, while invaluable for the study, would not often happen in other departments/settings as most departments would invest in one IGRT technology only – however, this also makes revealed preferences challenging to measure.

The preferences captured in Study 2 are stated and not revealed preferences. The impact of cognitive burden may have influenced some responders in randomly choosing within the choice sets to progress to the next question, however the follow-up question responses suggest a good level of self-reported understanding. Additionally, the influence on time since treatment may have impacted on the recall ability of men with PCa. Finally, while an extensive search of the literature was undertaken in the scoping review, it is possible that not all articles, particularly those with a prostate cancer sub-population, were retrieved.

Future Directions for Clinical Practice, Policy and Research

Clinical practice

For health professionals, these results highlight aspects for consideration as they care for prostate cancer patients in the radiation therapy department. Firstly, as both the pilot RCT QOL data and the DCE free-text comments given by patients demonstrated, each patient's journey through treatment and in follow-up is different. This serves as a reminder that though counselling of side effects and QOL impacts can be guided by outcomes research, the clinician needs to consider and tailor information provision to the individual patient in front of them. Secondly, some patients may need further information regarding their treatment or aspects

of it (such as specifics of treatment including image-guidance), as identified for the different subgroups in the latent class analysis of the DCE, and also highlighted in scoping review findings. The additional time required to provide this advice can be challenging in the busy clinical setting. However, it is vital for patient satisfaction, understanding and overall wellbeing, and an important aspect in providing patient centred care.[37,38]

Policy

Currently there is no health technology assessment published on TPUS, as previously discussed. Knowing that patients prefer a less invasive IGRT method, a health technology assessment would provide evidence on the clinical and technical benefits of ultrasound, especially when compared to fiducial markers while accounting for cost of capital, implementation, training and consumables. To date, little evaluation of the cost-benefit of intrafraction motion monitoring has been undertaken, with interfraction evaluations finding that IGRT should be leveraged through further exploitation of IGRT technologies, including reduced margins.[33,34]

Future research should be undertaken into hypofractionated schedules in prostate cancer radiation therapy to inform policy, such as Medicare rebates in Australia. Despite the demonstration of patient preference for hypofractionation,[39] and the clinical data supporting the safe delivery of more hypofractionated schedules enabled with motion monitoring,[40-42] there remains variance in the uptake of these schedules within Australia.[43-45] Current Medicare rebates are based on number of fractions delivered, which could financially disadvantage departments implementing hypofractionation schedules.[43,45] There are increased resourcing commitments (particularly capital and staffing) to deliver advanced techniques which further enable the safe and effective delivery of greater hypofractionation, such as adaptive radiation therapy.[43] TPUS is one of the image-guidance technologies that can ensure accuracy for hypofractionated delivery on standard linear accelerators, and as demonstrated in the pilot RCT, the reduction of margins and improved accuracy afforded through the prostate motion monitoring and correction may further improve outcomes with hypofractionated schedules.

Research

The scoping review demonstrated a number of aspects of radiotherapy treatment for prostate cancer which lack evidence, including but not limited to: pre-treatment education and support, radiation therapy modalities (such as VMAT vs MRL), follow-up schedules and logistics, and survivorship care. Further patient preference research to fill these knowledge gaps is vital to informing patient-centred care. As the results of patient perceptions in Study 2 suggest that health locus of control may be varied in this population, with a large proportion of the participants in interview indicating a deference to the health professional, evaluating preference and personal health locus of control would be of benefit.[23] Further research into the links between preferences, lived experience and understanding, and potential treatment regret is warranted.

A body of future research could be to further explore recall of hormone therapy treatment as 27% of this cohort failed to recall their hormone therapy treatment. It is important to understand this poor level of recall, whether this corresponds to a lack of understanding of the purpose of hormones, and to evaluate methods to improve it. Future research is recommended.

Conclusion

This PhD investigated real-time monitoring of prostate motion during radiation therapy, including both clinical considerations and patient perspectives. This PhD has demonstrated the potential for reducing margins with the use of TPUS for prostate motion monitoring during prostate radiation therapy, with a promising decrease in toxicity in a pilot RCT. As a result, reduced margins have been implemented locally, when treating prostate cancer patients with TPUS-guided radiation therapy. The patient perspectives and preferences of prostate-image guidance were explored. TPUS was acceptable and tolerable to patients, and there was a preference for low pain, low cost and greater accuracy. Participants were engaged in the DCE, with comments given that reflected the varied nature of perspectives and experiences. While patients previously treated for prostate cancer with radiation therapy demonstrated overall good recall, there was less recall for hormone therapy which requires further research. The scoping review evaluating patient perceptions and preferences in prostate radiation therapy

demonstrated the paucity of literature in this area, indicating an exciting opportunity for further work. The findings of this novel, multi-methods research have been directly translated into local clinical practice changes to inform patient-centred, high-quality care, and to ultimately improve lives of men with prostate cancer.

Patient preference research alongside clinical outcomes research will continue to advance quality patient-centred radiation oncology care.

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Appendices

Appendix A: Ethics Approvals – RCT & Patient Perceptions

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Procedures Experience Questionnaire

Patient Initials: _____
Date: _____

Your time to fill in this short questionnaire is appreciated. When we say "Gold Seed Insertion Procedure" we are referring to the first procedure where you were lying on your left side, with the internal ultrasound probe in your back passage. When we say "Clarity Probe Procedure" we are referring to the second procedure where you were lying on your back, with the external ultrasound probe placed at your perineum.

Question 1.
How would you rate the physical and psychological/emotional **discomfort** experienced during the Gold Seed Insertion procedure? *Please circle from 0 to 10, with 0 being no discomfort at all and 10 being the worst discomfort you have ever experienced.*

Gold Seed Insertion Procedure										
No ***PHYSICAL*** discomfort										Worst ***PHYSICAL*** discomfort
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Gold Seed Insertion Procedure										
No ***PSYCHOLOGICAL*** discomfort									***PSYCHOLOGICAL***	Worst discomfort
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Question 2.
How would you rate the physical and psychological/emotional **discomfort** experienced during the Clarity Probe procedure ? *Please circle from 0 to 10, with 0 being no discomfort at all and 10 being the worst discomfort you have ever experienced.*

Clarity Probe Procedure										
No ***PHYSICAL*** discomfort									***PHYSICAL***	Worst discomfort
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Clarity Probe Procedure										
No ***PSYCHOLOGICAL*** discomfort									***PSYCHOLOGICAL***	Worst discomfort
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Question 3.

a) How would you rate the **pain** experienced during the Gold Seed Insertion procedure? *Please circle from 0 to 10, with 0 being no pain at all and 10 being the worst pain you have ever experienced.*

Gold Seed Insertion Procedure										
No Pain										Worst Pain
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

b) How would you rate the **pain** experienced during the Clarity Probe procedure? *Please circle from 0 to 10, with 0 being no pain at all and 10 being the worst pain you have ever experienced.*

Clarity Probe Procedure										
No Pain										Worst Pain
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Question 4.
If you experienced pain or physical/psychological discomfort, can you describe the cause during each procedure (such as the hard couch you were laying on, the pressure of the probe, the positioning of your legs/hips, the feeling of embarrassment etc)?

Question 4.

When we say "invasive" other words to use might be intrusive, offensive or encroachment

a) How would you rate the **invasiveness** experienced during each procedure? *Please circle from 0 to 10, with 0 being not invasive at all and 10 being the most invasive.*

Gold Seed Insertion Procedure										
Not invasive at all										Invasive
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

b) How would you rate the **<u>invasiveness</u>** experienced during each procedure? *Please circle from 0 to 10, with 0 being not invasive at all and 10 being the most invasive.*

9)

Clarity Probe Procedure										
Not invasive at all										Invasive
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Question 5.
How informed about each procedure did you feel? *Please circle*

Gold Seed Insertion Procedure		
Not informed	Somewhat informed	Well informed

Clarity Probe Procedure		
Not informed	Somewhat informed	Well informed

What would help you feel more informed?

Thank you for your time. Please hand this questionnaire back to your treating radiation therapist, or return in the included postage-paid self-addressed envelope.

Appendix C: Interview Guide for Chapter 3 - Patient Perceptions and Preferences

Semi Structured Interview Questions

Intro: Clarify the different procedures:

When I say “Gold Seed Insertion Procedure” I am referring to the first procedure where you were lying on your left side, with the internal ultrasound probe in your back passage.

When I say “Clarity Probe Procedure” I am referring to the second procedure where you were lying on your back, with the external ultrasound probe placed at your perineum.

1. Tell me about your experience with the Gold Seed Insertion procedure?
    a. Was it what you expected?
    b. Were there any negative aspects/experiences (e.g. pain, discomfort, embarrassment)?

2. Tell me about your experience with the Clarity Probe procedure?
    a. Was it what you expected?
    b. Were there any negative aspects/experiences (e.g. pain, discomfort, embarrassment)?

3. From what you’ve just described, it sounds to me like you found the ____ procedure the worse of the two? Is that right?
    a. What made it worse (e.g. pain, discomfort, embarrassment)?

4. If both procedures had the same result (for us to monitor your prostate motion and make treatment more accurate) is there one procedure you would pick over the other? Why would that be your choice?
    a. Do you understand that with the gold seed insertion, it’s a once-off procedure, whereas with the Clarity probe procedure, it’s put in place for every day of treatment? Does that change your choice at all?

5. Imagine you have a friend who has just been diagnosed with prostate cancer and is coming for radiation therapy treatment. You are discussing treatment with them – what would you tell them about the 2 different procedures?
    a. If you were to recommend just one procedure to your friend, which would it be?

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Appendix E: Survey Questions for Chapter 4 & 5

A note of explanation: This appendix contains a copy of the DCE survey provided as a paper copy to PCa patients who requested it. The choice sets represent that of Block Set 1 only, with the remaining block sets changing as appropriate. Font size and white space/pagination has been reduced for the purposes of this Appendix.

Participant Information Sheet

Thank you for making time to complete this survey. The aim of this survey is to ask men about different ways of undergoing imaging currently used as part of radiation therapy treatment for prostate cancer.

This survey may take approximately 20 to 30 minutes to complete. We will also ask some questions about you. Your participation is voluntary, and you can choose to withdraw or stop answering questions at any point during the survey by closing the browser.

You may find some of the questions personal in nature, and some of them may cause emotional distress. If this arises for you, further support can be accessed by contacting the Cancer Council on 13 11 20 or https://www.cancer.org.au/about-cancer/patient-support/ or Beyond Blue on 1300 22 4636 or https://www.beyondblue.org.au.

Your responses will be kept completely confidential. You will not be identified in the survey, unless you have had treatment at the Townsville Cancer Centre and give details so that we can look at your treatment specifics (this is optional). Once we have looked up your treatment specifics, we will then delete the identifying details provided.

The answers will be stored on a password-protected computer drive, accessible only to the research team members. The data will be stored and retained in a manner where you will not be identified in any way. No personally identifiable data will be stored alongside the collection of the survey data. The de-identified data may be used in future methodological studies within the field of preference research, however this is not anticipated. The de-identified data will be kept for a minimum of 5 years after the publishing of the study results, at which time it will be deleted.

This study has been reviewed by the ethics committees of Townsville Hospital and Health Service (THHS) and James Cook University (JCU). The study adheres to the National Statement on Ethical Conduct in Human Research. You are welcome to discuss your participation in this study with the research investigator (contact Amy Brown amy.brown@health.qld.gov.au or 07 4433 5046, or Tilley Pain on 07 4433 4154). If you would like to speak to someone regarding the conduct of this study, please contact THHS Ethics TSV-Ethics-Committee@health.qld.gov.au or 07 4433 1440).

It is not expected that you will personally benefit from taking part in this survey, however, the results of the survey will help us understand what patients and the community values and prefers, guiding technology investment decisions and may help us to improve patient care.

This project will contribute to the PhD of Amy Brown. To find out the overall findings of this project, please be following the Australian Institute of Tropical Health and Medicine (https://www.facebook.com/AITropHealthMed/) or visit www.amybrown.org for a post in the final quarter of 2020.

Do you agree to take part in this survey?

○ **Yes** – thank you, please complete the following questions

○ **No** – thank you for your consideration

About this survey:

The questions in this survey are hypothetical. **Imagine you've been diagnosed with early stage prostate cancer and you've chosen to have radiation therapy treatment.** Radiation therapy treatment involves coming in to the radiation oncology department every day, Monday to Friday, for a treatment session that lasts approximately half an hour. Overall, prostate radiation therapy treatment ranges from 20 sessions over 4 weeks, up to 39 sessions over 8 weeks.

Your doctor has asked you to choose between 2 image-guidance options you have in conjunction with your radiation therapy treatment to increase the accuracy. Image-guidance allows the radiation therapists to locate your prostate and detect potential prostate motion during radiation delivery. These options differ based on factors like the pain you may experience, side effects, additional appointments required, additional daily time required, and costs.

You will now see 8 questions, and for each you will be asked to select your preferred option regarding imaging. You will be asked to choose across varying values of the factors in those options so that we can understand which factors are important to men when choosing one option over the other.

These options do not reflect your personal circumstances and in some cases are unlikely to occur in practice. As much as possible, please answer these questions as if you are facing the prostate cancer treatment options described. There are no right or wrong answers, and your answers will not influence your current, future or potential treatment options.

Section 1: Choice Questions

From the following treatment options, please select the choice you would make.

Descriptions for your information:

- *Pain: This describes the degree of pain associated with the procedure from a scale of 1 to 10, with 10 being the worst pain experienced.*
- *Cost: Whether you have out-of-pocket costs not covered by Medicare (for example, for medication)*
- *Side Effects: Whether you experience moderate bowel and bladder symptoms during and after treatment (e.g. moderate symptoms such as diarrhoea twice a day; or burning sensation on urination)*
- *Accuracy: Whether the radiation treatment delivery is more accurate*
- *Additional time: Whether additional time on the treatment couch is required for every day of treatment to achieve greater accuracy*
- *Extra Appointment: Whether you require an additional appointment at the hospital*

Choice 1

Choice Set 1	**Option 1**	**Option 2**
Pain	Worst level of pain (10 out of 10)	Medium levels (4 to 6)
Cost	2500	150
Side Effects	Decrease in overall side effects (1 in 10 experience moderate symptoms)	Same side effect likelihood (3 in 10 patients experience moderate symptoms)
Accuracy	Increased accuracy in targeting the prostate (within 1mm)	Same accuracy (within 2mm)
Additional time	30 mins per day	15 mins per day
Additional Appointments	No additional appointment	Two additional appointments
Which would you choose (Tick only one option)	○	○

Choice 2

Choice Set 19	**Option 1**	**Option 2**
Pain	Low levels (1 to 3)	Worst level of pain (10 out of 10)
Cost	0	150
Side Effects	Decrease in overall side effects (1 in 10 experience moderate symptoms)	Same side effect likelihood (3 in 10 patients experience moderate symptoms)
Accuracy	Same accuracy (within 2mm)	Increased accuracy in targeting the prostate (within 1mm)
Additional time	30 mins per day	15 mins per day
Additional Appointments	One additional appointment	No additional appointment
Which would you choose (Tick only one option)	○	○

Choice 3

Choice Set 28	**Option 1**	**Option 2**
Pain	High levels (7 to 9)	Low levels (1 to 3)
Cost	2500	150
Side Effects	Same side effect likelihood (3 in 10 patients experience moderate symptoms)	Decrease in overall side effects (1 in 10 experience moderate symptoms)
Accuracy	Same accuracy (within 2mm)	Increased accuracy in targeting the prostate (within 1mm)
Additional time	15 mins per day	5 mins per day
Additional Appointments	Two additional appointments	One additional appointment
Which would you choose (Tick only one option)	○	○

Choice 4

Choice Set 38	**Option 1**	**Option 2**
Pain	Worst level of pain (10 out of 10)	Medium levels (4 to 6)
Cost	50	0
Side Effects	Same side effect likelihood (3 in 10 patients experience moderate symptoms)	Decrease in overall side effects (1 in 10 experience moderate symptoms)
Accuracy	Same accuracy (within 2mm)	Increased accuracy in targeting the prostate (within 1mm)
Additional time	15 mins per day	5 mins per day
Additional Appointments	Two additional appointments	One additional appointment
Which would you choose (Tick only one option)	○	○

Choice 5

Choice Set 42	**Option 1**	**Option 2**
Pain	No pain	High levels (7 to 9)
Cost	50	2500
Side Effects	Decrease in overall side effects (1 in 10 experience moderate symptoms)	Same side effect likelihood (3 in 10 patients experience moderate symptoms)
Accuracy	Increased accuracy in targeting the prostate (within 1mm)	Same accuracy (within 2mm)
Additional time	15 mins per day	5 mins per day
Additional Appointments	One additional appointment	No additional appointment
Which would you choose (Tick only one option)	○	○

Choice 6

Choice Set 59	**Option 1**	**Option 2**
Pain	High levels (7 to 9)	Low levels (1 to 3)
Cost	150	50
Side Effects	Decrease in overall side effects (1 in 10 experience moderate symptoms)	Same side effect likelihood (3 in 10 patients experience moderate symptoms)
Accuracy	Same accuracy (within 2mm)	Increased accuracy in targeting the prostate (within 1mm)
Additional time	5 mins per day	30 mins per day
Additional Appointments	No additional appointment	Two additional appointments
Which would you choose (Tick only one option)	○	○

Choice 7

Choice Set 67	**Option 1**	**Option 2**
Pain	Low levels (1 to 3)	Worst level of pain (10 out of 10)
Cost	50	2500
Side Effects	Same side effect likelihood (3 in 10 patients experience moderate symptoms)	Decrease in overall side effects (1 in 10 experience moderate symptoms)
Accuracy	Same accuracy (within 2mm)	Increased accuracy in targeting the prostate (within 1mm)
Additional time	15 mins per day	5 mins per day
Additional Appointments	No additional appointment	Two additional appointments
Which would you choose (Tick only one option)	○	○

Choice 8

Choice Set 71	**Option 1**	**Option 2**
Pain	No pain	High levels (7 to 9)
Cost	150	0
Side Effects	Same side effect likelihood (3 in 10 patients experience moderate symptoms)	Decrease in overall side effects (1 in 10 experience moderate symptoms)
Accuracy	Increased accuracy in targeting the prostate (within 1mm)	Same accuracy (within 2mm)
Additional time	30 mins per day	15 mins per day
Additional Appointments	Two additional appointments	One additional appointment
Which would you choose (Tick only one option)	○	○

Section 2: Follow Up Questions

The following questions ask how you were thinking when making the choices in the questions you have just completed.

- Reflect on how you made your decision when answering the question. Did potential embarrassment at having your genitals and anal area exposed to the health professionals factor into your thinking when making your choices? *(Please circle)*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

10)

11)

- Consider the following medical scenarios and rate your level of embarrassment *(Please circle)*:

12)

a. *A digital rectal exam, where the doctor inserts their finger into your back passage to feel your prostate*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

b. *An internal ultrasound probe – where the probe is inserted into your back passage for the purpose of inserting markers into the prostate*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

13)

14)

c. *An external ultrasound – where an ultrasound probe is placed externally against your perineum for the purpose of seeing your prostate on ultrasound and monitoring for motion. The perineum is the skin between your anus and scrotum (the part of you that would come into contact with a bicycle seat).*

No embarrassment										Extremely embarrassing
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

- Thinking about the questions you just answered, please fill out the following rating table *(Please tick)*.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
The language used in the questions was clear.	○	○	○	○	○
The questions were difficult to understand.	○	○	○	○	○
The task was difficult to complete.	○	○	○	○	○

Please provide any comments you wish to make.

15) _____

_____

_____

16)

- Please fill out the following rating table about the survey.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
The instructions for the survey were clear.	○	○	○	○	○
The description of prostate cancer and the procedure was clear.	○	○	○	○	○
The description of prostate cancer and radiation therapy treatment was relevant to the task of answering the questions.	○	○	○	○	○

Please provide any comments you wish to make.

17) _____

_____

_____

18)

19)

- How much did each of the below factors influence your decision? (*please rate all the factors, selecting one from not at all to extremely)*

	Not at all	Slightly	Moderately	Very Much	Extremely
Being able to meet the costs of care	○	○	○	○	○
The rate and severity of side effects	○	○	○	○	○
The impact of additional appointments	○	○	○	○	○
Whether there would be pain, and its duration	○	○	○	○	○
The impact of additional daily time for treatment	○	○	○	○	○
Whether treatment was more accurate	○	○	○	○	○

- Thinking about the factors which varied in each of the questions, which one was the <u>most</u> important when choosing between the options? *(Please tick only one answer)*

○ The impact of additional daily time for treatment

○ The rate and severity of side effects

○ Whether treatment was more accurate

○ Whether there would be pain, and its duration

○ Being able to meet the costs of care

○ The impact of additional appointments

20)

21) Are there any factors you would consider that we are missing? _____ _____ _____ _____

22)

- Thinking about the factors which varied in each of the questions, which one was the least important when choosing between the options? *(Please tick only one answer)*

○ The impact of additional daily time for treatment

○ Whether treatment was more accurate

○ Whether there would be pain, and its duration

○ Being able to meet the costs of care

○ The impact of additional appointments

○ The rate and severity of side effects

- Did you have a strategy, or decision rule, for how you made your choices? *(Please tick)*

○ I did not have a strategy

○ I focused only on the factors I thought were important

○ I considered most of the factors all the time.

○ I considered all the factors each time.

○ Other (please specify): _____

Please only answer this next question if you focused only on factors you thought were important:

b. In what order did you think about the factors when making your decision? Please number only those that you focused on, and in the order of importance to your decision making from most (starting with the number 1) to least important.

☐ The impact of additional daily time for treatment

☐ The rate and severity of side effects

☐ Whether there would be pain, and its duration

☐ Being able to meet the costs of care

☐ The impact of additional appointments

☐ Whether treatment was more accurate

- Did the number of factors (rows) affect your ability to answer each question? (*Please tick only one*)

○ The number of factors did not affect how I answered

○ There were too many factors and it made it difficult to answer the questions

○ There were too many factors so I only focused on the ones I thought were important

○ Other_____
_____
_____

Section 3: General Demographics

The following questions ask some general questions about you.

- Have you ever had a prostate cancer diagnosis?

○ Yes ○ No

- What is your year of birth? _____

23)

- What is your current postcode? _____

- What is your current relationship status: (*select only one answer*)

○ Single, never married ○ Widowed

○ Married or domestic partnership ○ Divorced or separated

24)

- What best describes your current employment status:

○ Full-time employment

○ Part-time employment

○ Casual

○ Retired

○ Unemployed

○ Prefer not to say

25)

- What best describes your highest level of education: (*select only one answer*)

  ○ Less than high school

  ○ High school (or equivalent)

  ○ Apprenticeship, TAFE or technical school

  ○ Undergraduate degree (e.g. Bachelor)

  ○ Postgraduate degree (e.g. Masters or PhD)

  ○ Prefer not to say

  26)

- What is your approximate total household income before taxes (include income from wages/salaries, government benefits, pensions, investments and other incomes that might have been received)?

○ Negative or zero Income

○ $1 - $9,999 per year ($1 - $189 per week)

○ $10,000 - $19,999 per year ($190 - $379 per week)

○ $20,000 - $29,999 per year ($380 - $579 per week)

○ $30,000 - $39,999 per year ($580 - $769 per week)

○ $40,000 - $49,999 per year ($770 - $959 per week)

○ $50,000 - $59,999 per year ($960 - $1,149 per week)

○ $60,000 - $79,999 per year ($1,150 - $1,529 per week)

○ $80,000 - $99,999 per year ($1,530 - $1,919 per week)

○ $100,000 - $124,999 per year ($1,920 - $2,399 per week)

○ $125,000 - $149,999 per year ($2,400 - $2,879 per week)

○ $150,000 - $199,999 per year ($2,880 - $3,839 per week)

○ $200,000 or more per year ($3,840 or more per week)

○ Prefer not to say ○ Don't know

- Are you of Aboriginal and/or Torres Strait Islander origin?

○ Aboriginal and Torres Strait Islander ○ Neither Aboriginal and/or Torres Strait Islander

○ Aboriginal

○ Torres Strait Islander

- Where were you born?

○ Australia ○ Other *(please state)* _____

- Which language do you mainly speak at home?

○ English ○ Other *(please state)* _____

27)

- In general, would you say your health is: (*please circle one*)

Excellent Very good Good Fair Poor

Section 4: Prostate Treatment Questions

The following questions are to be answered if you identified that you have been diagnosed with prostate cancer in the past.

- What types of tests did you have before your doctor told you had prostate cancer? (*please tick all that apply*)

○ Blood test

○ Biopsy

○ Imaging e.g. an Ultrasound, Magnetic Resonance Imaging (MRI) or *Positron Emission Tomography* (*PET*)

○ Other _____

○ Not sure

- *Did you receive treatment for your prostate cancer?*

○ Yes

○ No

- What treatment did you have for your prostate cancer? (*please tick all that apply*)

○ Hormones (injections)

○ Surgery

○ Radiation therapy (external radiation)

○ Brachytherapy (internal radiation)

○ Chemotherapy

○ Other _____

○ Not sure

If you had Radiation therapy:

- As part of your radiation therapy preparation or treatment, did you have any of the following procedures. If unsure of the procedures, hover over to see a short description: (*tick all that apply*)

  ○ Gold seed markers

  ○ Clarity ultrasound monitoring

  ○ Calypso tracking

  ○ SpaceOAR

  ○ Other _____

  ○ Not sure

Descriptions:

- *Gold seed markers – small gold beads (usually 3) are inserted into your prostate using ultrasound guidance, usually with the probe in your back passage. This may be while you were awake or asleep and occurs before your treatment course commences. These are used to locate your prostate every day for radiation therapy treatment.*

- *Clarity ultrasound monitoring – an external ultrasound probe sits against your skin during the radiation simulation/planning CT and every day for treatment, alerting treatment staff if your prostate moves*
- *Calypso tracking – 3 small beacons are inserted into your prostate using ultrasound guidance, usually with the probe in your back passage. This may be while you were awake or asleep and occurs before your treatment course commences. A detector plate sits over your pelvis during radiation therapy treatment, alerting treatment staff if your prostate moves*
- *SpaceOAR – prior to your radiation therapy treatment course, a gel-like substance is injected between your prostate and your bowel to separate them*

- Please add your initials and date of birth if you agree to allow the researchers to look up your clinical history in your medical chart for further details about your prostate cancer and treatment. This will be added to and compared against your survey answers, looking for patterns and differences. Once the researchers have gathered the further information, your initials and date of birth will be removed from the research database, so your responses are kept de-identified.

  28) **Please note, this is optional.** You can choose not to complete this section. Your answers to the rest of the survey will still be included in our research.

  29) Initials: _____

  30) Date of birth: _____

- Do you have anything else you would like to tell the researchers about the survey, or the imaging options presented? *(Please note, these responses will not be actively monitored. If you have any questions or concerns about prostate cancer or its treatment, please seek the advice of your health care provider. Cancer Council Australia also provides general help and support about cancer: http://www.cancer.org.au or 13 11 20.)*

31) _____
_____
_____
_____

End of survey information:

Thank you for your time in completing this survey.
If you have any questions or concerns about prostate cancer or its treatment, please seek the advice of your health care provider. Cancer Council Australia also provides general help and support about cancer: http://www.cancer.org.au or 13 11 20.
If this has raised any distressing emotions or concerns, please contact the Cancer Council on **13 11 20** or https://www.cancer.org.au/about-cancer/patient-support/ or Beyond Blue on **1300 22 4636 or** https://www.beyondblue.org.au.
To find out the overall findings of this project, a social media post will be published on the Australian Institute of Tropical Health and Medicine (https://www.facebook.com/AITropHealthMed/), expected in the final quarter of 2020.

Reward:
As a small token of gratitude for completing this survey, you have the following option (*Please tick*):

○ Email me a Woolworths gift e-card to the value of $4.00

- Please print your email address: _____
- *Please note: the email address provided will not be linked to any of your previous answers, maintaining your confidentiality*

○ Donate the $4.00 to the Prostate Cancer Foundation of Australia

Appendix F: DCE Piloting Results

A note of explanation: This appendix contains the report from the DCE pilot, including reflection comments and recommendations for changes. This was presented at a research team meeting for ratification prior to changes and main rollout.

Piloting the DCE

A "think aloud" exercise was firstly undertaken, with the health consumer investigator completing the DCE alongside the PI, and discussing thoughts and interpretations throughout. This led to some minor wording updates prior to formal piloting to ensure clarity of meaning.

A general population cohort was sought using an online recruitment panel, with a total of 57 men completing the pilot survey. Similarly, 150 men who had attended the department regarding prostate cancer were mailed a letter of invite, with 27 completing the survey (21 online and 6 requesting a paper copy). The average time to complete was 12 minutes for the general population and 31 minutes for the cancer population. Demographics of the pilot participants are summarised below.

The overall responses of the pilot indicated a satisfactory level of understanding, with only minor editing of wording and question placement implemented prior to the main survey rollout. No changes were made to the attributes or levels (As per Chapter 4, Table 4.1).

Recruitment

Pilot Population One (P1: TCC) was from the Townsville Cancer Centre Database, with a letter of invite sent to 150 men who have presented to TCC in regards to prostate cancer between 2009 to 2019. Fifty of these were patients recruited to the previous study, the remaining 100 were chosen at random from the database. The invite letter was posted on 21/02/2020. 10 requested a paper copy of the survey. To date, there has been a 16.7% response rate with completes, 22.6% when considering incomplete surveys.

Total Completes	27
Online	21
Paper	6
Partial Completes	
DCE + some demographics	4
DCE only	3
Partial DCE + all demographics	2 (both paper)

Pilot Population Two (P2: GenPop) was recruited through the online panel of Pureprofile. Recruitment of n=58 (for a target of n=50) was completed within one day, on 22/02/2020.

The following report only includes the completed survey data (all questions).

	P1: TCC	**P2: GenPop**
Sample	25	58
Age		
18-29	0	11 (18.9%)
30-39	0	12 (20.7%)
40-49	0	8 (13.8%)
50-59	0	8 (13.8%)
60-69	1 (4%)	10 (17.2%)
70-79	15 (60%)	7 (12.1%)
80+	9 (36%)	2 (3.4%)
Missing	0	0
Location		
QLD	25 (100%)	11 (19.0%)
NSW	0	18 (31.0%)
VIC	0	14 (24.1%)
TAS	0	0
SA	0	3 (5.2%)
NT	0	1 (1.7%)
ACT	0	1 (1.7%)
WA	0	10 (17.2%)
Relationship status		
Single, never married	1 (4%)	17 (29.3%)
Married or domestic partnership	19 (76%)	30 (51.7%)
Widowed	3 (12%)	1 (1.7%)
Divorced or separated	2 (8%)	7 (12.1%)
Did not answer	0	3 (5.2%)
Employment status		
Full-time employment	1 (4%)	28 (48.3%)
Part-time employment	0	5 (8.6%)
Casual	1 (4%)	4 (6.9%)

	P1: TCC	P2: GenPop
Retired	22 (88%)	14 (2.4%)
Unemployed	1 (4%)	7 (12.1%)
Prefer not to say	0	0
Level of education		
Less than high school	4 (16%)	0
High school (or equivalent)	6 (24%)	18 (31.0%)
Apprenticeship, TAFE or tech school	8 (32%)	16 (27.6%)
Undergraduate degree	5 (20%)	18 (31.0%)
Postgraduate degree	1 (4%)	4 (6.9%)
Prefer not to say	1 (4%)	2 (3.4%)
Annual household income		
Negative or zero Income	0	1 (1.7%)
$1 - $9,999	0	3 (5.2%)
$10,000 - $19,999	5 (20%)	4 (6.9%)
$20,000 - $29,999	3 (12%)	5 (8.6%)
$30,000 - $39,999	2 (8%)	6 (10.3%)
$40,000 - $49,999	4 (16%)	6 (10.3%)
$50,000 - $59,999	1 (4%)	5 (8.6%)
$60,000 - $79,999	4 (16%)	7 (12.1%)
$80,000 - $99,999	3 (12%)	4 (6.9%)
$100,000 - $124,999	0	8 (13.8%)
$125,000 - $149,999	0	3 (5.2%)
$150,000 - $199,999	1 (4%)	1 (1.7%)
$200,000 or more	1 (4%)	1 (1.7%)
Prefer not to say	1 (4%)	4 (6.9%)
Ethnicity		
Aboriginal and Torres Strait Islander	0	1 (1.7%)
Aboriginal	0	3 (5.1%)
Torres Strait Islander	0	1 (1.7%)
Neither	25 (100%)	52 (89.7%)
Born		
Australia	20 (80%)	43 (74.1%)
Other	5 (20%)	15 (25.8%)
Language		
English	23 (92%)	54 (93.1%)
Other	2 (8%)	4 (6.9%)
Health State		
Excellent	0	4 (6.9%)
Very Good	7 (28%)	23 (39.7%)
Good	10 (40%)	17 (29.3%)
Fair	6 (24%)	10 (17.2%)
Poor	1 (4%)	4 (6.9%)

Choice Sets

P1: TCC

Coefficients :					
	Estimate	**Std. Error**	**z-value**	**Pr(>|z|)**	**Signif**
Pain	-0.3115686	0.0547855	-5.6871	1.292e-08	***
Cost	-0.1372948	0.0705865	-1.9451	0.05177	.
SideEffect	-0.0322816	0.1294316	-0.2494	0.80304	
Accuracy	0.6129422	0.1315571	4.6591	3.175e-06	***
AddTime	0.0679528	0.1002295	0.6780	0.49779	
AddAppt	0.0045945	0.0815729	0.0563	0.95508	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Log-Likelihood: -174.63

P2: GenPop

Coefficients :					
	Estimate	**Std. Error**	**z-value**	**Pr(>|z|)**	**Signif**
Pain	-0.455420	0.049992	-9.1098	< 2e-16	***
Cost	-0.586031	0.063654	-9.2064	< 2e-16	***
SideEffect	-0.126445	0.113501	-1.1140	0.26526	
Accuracy	0.315406	0.114670	2.7505	0.00595	**
AddTime	-0.147987	0.085711	-1.7266	0.08424	.
AddAppt	-0.121158	0.071770	-1.6881	0.09138	.

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Log-Likelihood: -239.94

P1: TCC

	Coefficients :	**Estimate**	**Std. Error**	**z-value**	**Pr(>|z|)**	**Signif**	**Wald**
Pain	Low levels (1 - 3) : No pain	-0.704478	0.320616	-2.1973	0.0280016	*	X2 = 36.4, df = 4, P(> X2) = 2.4e-07
	Medium levels (4 - 6) : No pain	-0.626068	0.244800	-2.5575	0.0105437	*	
	High levels (7 - 9) : No pain	-1.028100	0.272359	-3.7748	0.0001601	***	
	Worst level of pain (10) : No	-1.594869	0.317866	-5.0174	5.237e-07	***	
Cost	$50 : Zero	0.086980	0.221345	0.3930	0.6943467		X2 = 9.2, df = 3, P(> X2) = 0.027
	$150 : Zero	-0.140773	0.222637	-0.6323	0.5271921		
	$2500 : Zero	-0.531484	0.223401	-2.3791	0.0173568	*	
Side Effects	Decreased : Same	-0.008096	0.129309	-0.0626	0.9500769		X2 = 0.0039, df = 1, P(> X2) = 0.95

Accuracy	Increased : Same	0.636841	0.132011	4.8242	1.406e-06	***	X2 = 23.3, df = 1, P(> X2) = 1.4e-06
Add Time	15 mins : 5 mins	-0.132973	0.191183	-0.6955	0.4867232		X2 = 1.1, df = 2, P(> X2) = 0.58
	30 mins : 5 mins	0.034293	0.200323	0.1712	0.8640738		
Addl Appts	One appt : No appt	0.120364	0.207023	0.5814	0.5609667		X2 = 0.36, df = 2, P(> X2) = 0.83
	Two appts : No appt	0.012930	0.159924	0.0808	0.9355617		

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Log-Likelihood: -180.39

Wald: X2 = 128.5, df = 13, P(> X2) = 0.0

P2: GenPop

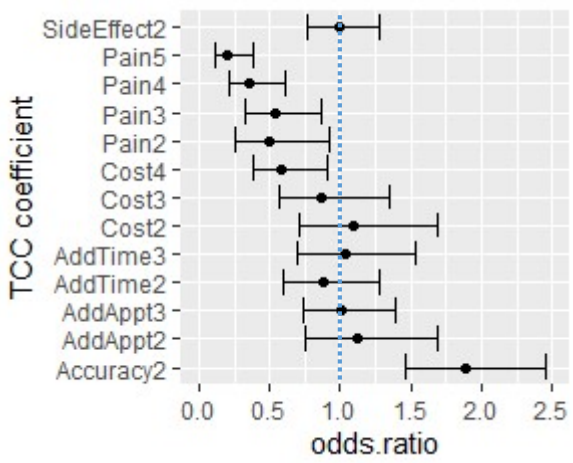
	Coefficients :	**Estimate**	**Std. Error**	**z-value**	**Pr(>|z|)**	**Signif**	**Wald**
Pain	Low levels (1 - 3) : No pain	-0.155904	0.276200	-0.5645	0.572441		X2 = 83.2, df = 4, P(> X2) = 0.0
	Medium levels (4 - 6) : No pain	-1.058536	0.236959	-4.4672	7.926e-06	***	
	High levels (7 - 9) : No pain	-1.055114	0.226547	-4.6574	3.203e-06	***	
	Worst level of pain (10) : No	-1.877324	0.291814	-6.4333	1.249e-10	***	
Cost	$50 : Zero	-0.431174	0.197709	-2.1809	0.029194	*	X2 = 86.0, df = 3, P(> X2) = 0.0
	$150 : Zero	-1.024359	0.197238	-5.1935	2.064e-07	***	
	$2500 : Zero	-1.780226	0.201996	-8.8132	< 2.2e-16	***	
Side Effects	Decreased : Same	-0.132465	0.115071	-1.1512	0.249669		X2 = 1.3, df = 1, P(> X2) = 0.25
Accuracy	Increased : Same	0.324602	0.116645	2.7828	0.005389	**	X2 = 7.7, df = 1, P(> X2) = 0.0054
Additional Time	15 mins : 5 mins	-0.035084	0.174088	-0.2015	0.840284		X2 = 3.3, df = 2, P(> X2) = 0.19
	30 mins : 5 mins	-0.264810	0.175968	-1.5049	0.132355		
Additional Appts	One appt : No appt	-0.134682	0.181635	-0.7415	0.458390		X2 = 2.8, df = 2, P(> X2) = 0.24
	Two appts : No appt	-0.244340	0.145037	-1.6847	0.092051	.	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Log-Likelihood: -237.06

Wald: X2 = 17.6, df = 10, P(> X2) = 0.063

Odds Ratios


SideEffect2
Pain5
Pain4
Pain3
Pain2
Cost4
Cost3
Cost2
AddTime3
AddTime2
AddAppt3
AddAppt2
Accuracy2
TCC coefficient
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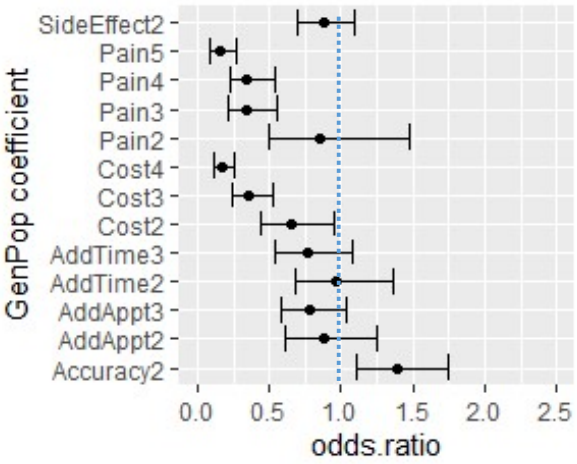
0.5
1.0
1.5
2.0
2.5
odds.ratio


SideEffect2
Pain5
Pain4
Pain3
Pain2
Cost4
Cost3
Cost2
AddTime3
AddTime2
AddAppt3
AddAppt2
Accuracy2
GenPop coefficient
0.0
0.5
1.0
1.5
2.0
2.5
odds.ratio

Embarrassment follow-up questions

Where 0 is no embarrassment and 10 is extremely embarrassing:

	P1: TCC	P2: GenPop
Potential Embarrassment		
Median	0	3
Mean	0.6	3.41
1st Q	0	0
3rd Q	1	5
Min	0	0
Max	6	10
Digital Rectal Exam		
Median	1	5.5
Mean	2.4	5.12
1st Q	0	2
3rd Q	4	7
Min	0	0
Max	9	10
Internal US		
Median	0	5.5
Mean	1.84	5.10
1st Q	0	2
3rd Q	2	7
Min	0	0
Max	10	10
External US		
Median	0	3
Mean	1.12	4.03
1st Q	0	1
3rd Q	1	7
Min	0	0
Max	7	10

Do you have anything else you would like to tell the researchers about the survey, or the imaging options presented?

	P1:TCC	P2: GenPop
Positive	Survey was quick and concise.	This is good and way to provide information I think they have captured the true sense of the understanding and provide us enough information to get the details for the systems
Negative	**Not understood at all. Just pressed right hand button to progress to next question** *Comment: This respondent selected "2" for all choice set. This data has been kept in the model, however an example of a check required for final analysis.*	
Reflection &/or Criticism on Survey	Obviously cost is a factor but ideally I would select one in which the 1 mm accuracy and the lowest probability of side effects prevailed. While I might be slightly embarrassed at having the Clarity utrasound technique applied the most important aspect was the accuracy of the radiation beam in relation to the invading cancer. Severe claustrophobia and the mitigation of it's effects during the procedure would be a primary factor in my choice of treatment. **Pain: no real idea what is intended - only once, when occurs every day, entire session? (My treatment did not involve pain so no idea). Digital rectal exam - never had one - only what others tell me. Dignity rather than embarrassing. Additional time - painful or not??** *Comment: This was specified in the attribute description*	**Cost is a significant factor in the treatment options offered. One looks for the lowest cost, lowest pain, least time combos. To get accurate info, you should ascertain the incomes of patients surely? The use of options assumes the ability to make a choice. If a person is in a low income bracket-there is NO choice.** *Comment: This is an example where having this free text after the demographics questions would have helped this respondent – but a very insightful comment nonetheless.* the pain levels and experiencing them daily is a big consideration after seeing how daily painful treatment can affect people long term. My basic premise for selecting which treatment option for preference was based on three aspects 1) accuracy of treatment 2) cost and 3) pain. I do not feel any embarrassment in any of the procedures sure the probe or finger up the anus is uncomfortable but necessary.
	A little more explanation at start would be great.	My thinking is minimal pain to have to go through It's all about the money I was looking for the option with the lowest amount of pain and side effects.

	P1:TCC	P2: GenPop
		My first preference would be the one that is more effective in treating prostate cancer not the procedure. I would be asking how long the pain levels last.....I could tolerate extreme pain for a short while, or very low level for a longer time
Personal Experience &/or Reflection	My embarrassment level would be low because I would know whatever is being done is helping me. The medical person do their job and therefore helping me in the long-term. I have had external radiation and brachytherapy for prostate cancer. I can only comment on the professional treatment at The General Hospital, first class! was lot easer after the tour of the versatility and explanation of the radiation machine by the nurses and my operation in the procedure. I was able to prepare my self and was able relax co-operate with the nursers easier. I am participating in this survey in the hope that it will assist future treatment. I finished my eight weeks of radiation treatment for prostate cancer on the fifth of September 2019,had my psa done on the fifth of February 2020 and it came back as normal at 2.5 and all side effects have subsided. I am one very happy patient and can not thank all the wonderful people at the Townsville cancer clinic enough.	such procedure would not cause me any embarrassment, Can put up with some pain and repeated visits, as long as it achieves a long term affect Sounds painful **Option 2 overall better as no insertion** *Comment: I propose that this is regards to the overall description and not the unlabelled choice sets?*
Personal Experience &/or Reflection	**I did not experience any pain or side effects for radiation except when a computer glitch radiated my prostrate which was notified by staff and immediately rectified** *Comment: I couldn't read a remark like this and not be curious. As this was a respondent who gave permission to look at clinical details, I looked into this described scenario – as far as I could determine it was a prostate motion*	

	P1:TCC	P2: GenPop
	correction, so it is interesting that this is what he took away from it…	

Clarity of Questions

	P1: TCC	P2: GenPop
The language used in the questions was clear.		
Strongly agree	4 (16%)	27 (46.6%)
Agree	16 (64%)	25 (43.1%)
Neither	3 (12%)	6 (10.3%)
Disagree	1 (4%)	0
Strongly disagree	1 (4%)	0
Missing	0	0
The questions were difficult to understand.		
Strongly agree	1 (4%)	2 (3.4%)
Agree	1 (4%)	7 (12.1%)
Neither	4 (16%)	14 (24.1%)
Disagree	12 (48%)	21 (36.2%)
Strongly disagree	6 (24%)	14 (24.1%)
Missing	1 (4%)	0
The task was difficult to complete.		
Strongly agree	1 (4%)	5 (8.6%)
Agree	2 (8%)	5 (8.6%)
Neither	6 (24%)	12 (20.7%)
Disagree	7 (28%)	20 (34.4%)
Strongly disagree	7 (28%)	16 (27.6%)
Missing	2 (8%)	0
The instructions for the survey were clear.		
Strongly agree	6 (24%)	19 (32.8%)
Agree	15 (60%)	28 (48.3%)
Neither	1 (4%)	10 (17.2%)
Disagree	2 (8%)	1 (1.7%)
Strongly disagree	1 (4%)	0
Missing	0	0
The description of prostate cancer and the procedure was clear.		
Strongly agree	4 (16%)	18 (31.0%)
Agree	13 (52%)	26 (44.8%)
Neither	6 (24%)	13 (22.4%)
Disagree	0	1 (1.7%)
Strongly disagree	1 (4%)	0
Missing	1 (4%)	0
The description was relevant to the task.		
Strongly agree	6 (24%)	16 (27.6%)
Agree	14 (56%)	32 (55.2%)
Neither	1 (4%)	9 (15.5%)
Disagree	2 (8%)	1 (1.7%)
Strongly disagree	1 (4%)	0
Missing	1 (4%)	0

	P1:TCC	P2: GenPop
Positive	Survey was straight forward	very easy it is not difficult for me but nice question.
Negative	**Whole survey so far requires a revamp** *Comment: This was the same individual who did not understand the survey in above comment table.*	Maybe work on explaining it a little easier
Reflection &/or Criticism on Survey	An explanation of the reason/s for the differing levels of pain ascribed to the different treatment options would be helpful. **Which questions? Options 8-10? Why Q8 when no info given on imaging or what is doing the imaging?** *Comment: The DCE is purposively unlabelled, and I suggest it remains that way, given that already TCC respondents tried to relate it back to their experiences.* This is a very simple survey. Without knowing the underlining reasons for cost vs no cost and pain vs no pain and other factors the options I chose were very subjective. The description or knowledge of or a description? I have no idea which procedure. I really do not know what radiation therapy treatment without imaging actually is - relevant or necessary?	Was a little confusing but I got the hang of it
Personal Experience &/or Reflection	Glad to participate I have completed the radiation procedure and are now almost regained control blades and bowl but still have pain in back and legs **Because I have had 8 weeks of radiation I found questions difficult to answer truthfully** *Comment: This was a respondent who could not separate hypothetical from actual experience* As a matter of interest: The treatment was excellent and saved my life. One point - for over a year sudden toilet movements required male nappies	**Just what happen when comes down to it** *Comment: Interesting that this came from one of the general population!* **I don't like to think about it** *Comment: Not sure if this is PCa in general, treatment or the survey* do not know much about

	P1:TCC	P2: GenPop
	Because I have had my prostate removed I am unfamiliar with the procedures in 12-2 and 12-3	

Factor importance

How much did each of the below factors influence your decision? (please rate all the factors)	P1: TCC	P2: GenPop
Being able to meet the costs of care	32)	33)
Not at all	34) 10 (40%)	35) 5 (8.6%)
Slightly	36) 4 (16%)	37) 9 (15.5%)
Moderately	38) 5 (20%)	39) 14 (24.1%)
Very much	40) 5 (20%)	41) 13 (22.4%)
Extremely	42) 0	43) 17 (29.3%)
Missing	44) 1 (4%)	45) 0
The rate and severity of side effects	46)	47)
Not at all	48) 2 (8%)	49) 3 (5.2%)
Slightly	50) 14 (56%)	51) 11 (19.0%)
Moderately	52) 5 (20%)	53) 25 (43.1%)
Very much	54) 4 (16%)	55) 14 (24.1%)
Extremely	56) 0	57) 5 (8.6%)
Missing	58) 0	59) 0
The impact of additional appointments	60)	61)
Not at all	62) 16 (64%)	63) 22 (37.9%)
Slightly	64) 7 (28%)	65) 13 (22.4%)
Moderately	66) 1 (4%)	67) 15 (25.9%)
Very much	68) 0	69) 6 (10.3%)
Extremely	70) 0	71) 2 (3.4%)
Missing	72) 1 (4%)	73) 0

Whether there would be pain, and its duration	74)	75)
Not at all	76) 5 (20%)	77) 4 (6.9%)
Slightly	78) 8 (32%)	79) 8 (13.8%)
Moderately	80) 5 (20%)	81) 11 (19.0%)
Very much	82) 3 (12%)	83) 16 (27.6%)
Extremely	84) 3 (12%)	85) 19 (32.8%)
Missing	86) 1 (4%)	87) 0
The impact of additional daily time	88)	89)
Not at all	90) 14 (56%)	91) 15 (25.9%)
Slightly	92) 6 (24%)	93) 13 (22.4%)
Moderately	94) 4 (16%)	95) 20 (34.5%)
Very much	96) 0	97) 4 (6.9%)
Extremely	98) 0	99) 6 (10.3%)
Missing	100) 1 (4%)	101) 0

Comment: It was noted at the time of report that the above did not ask about accuracy – this is to be added for the full survey, should this question set be retained.

The **most** important factor	**P1: TCC**	**P2: GenPop**
The impact of additional daily time for treatment	0	1 (1.7%)
The rate and severity of side effects	7 (28%)	7 (12.1%)
Whether there would be pain, and its duration	7 (28%)	18 (31.0%)
Being able to meet the costs of care	1 (4%)	24 (41.4%)
The impact of additional appointments	0	1 (1.7%)
Whether treatment was more accurate	9 (36%)	7 (12.1%)

	Were there any factors missing?	
	P1:TCC	**P2: GenPop**
Positive	No! You have covered the key items	
Reflection &/or Criticism on Survey	**Whether the treatment was more effective in the long term** *Comment: This is covered in accuracy – as described in introduction.* **Are all of the options day visits or do they require hospitalisation. Is there a need to provide transport other than by private vehicle.** *Comment: Again, an interesting reflection. I could consider adding that they are both out-patient options to the initial description. Regardless of IGRT option, transport would not change, and therefore do not consider this an important factor to add to the design.* **Factors? Duration not mentioned, how often, when it occurred in the treatment - whether every day or once. My main concern before my treatment was side effects (permanent) but both options in every case are the same side effects or accuracy so irrelevant here.** *Comment: Duration is covered in both the introduction and the attribute descriptions (particularly pain). I had a look at the choice sets and side effects/accuracy attributes were the same for his survey – to double check randomisation/design for the paper survey.*	**pre-existing disability (chronic pain)** *Comment: This is an interesting reflection which would be most captured in the DCE as time of treatment. This will also be somewhat captured in the health status demographics.*
Personal Experience	none really what ever had to done was the important issue	the cost

	Were there any factors missing?	
	P1:TCC	P2: GenPop
&/or Reflection		It all about the m

The **least** important factor	P1: TCC	P2: GenPop
The impact of additional daily time for treatment	7 (28%)	16 (27.6%)
The rate and severity of side effects	4 (16%)	6 (10.3%)
Whether there would be pain, and its duration	1 (4%)	9 (15.5%)
Being able to meet the costs of care	5 (20%)	8 (13.8%)
The impact of additional appointments	6 (24%)	17 (29.3%)
Whether treatment was more accurate	1 (4%)	2 (3.4%)

	P1: TCC	P2: GenPop
I did not have a strategy	3 (12%)	11 (18.9%)
I focused only on the factors I thought were important	9 (36%)	21 (36.2%)
I considered most of the factors all the time.	2 (8%)	9 (15.5%)
I considered all the factors each time.	9 (36%)	16 (27.6%)
Other	2 (8%)	1 (1.7%)

	Did you have a strategy, or decision rule, for how you made your choices? "Other" responses:	
	P1:TCC	P2: GenPop
Response	I Have the procedure be for having to start the Survey this is 2 months later	Cost

	P1: TCC	P2: GenPop
The number of factors did not affect how I answered	18 (72%)	40 (69%)
There were too many factors and it made it difficult to answer the questions	2 (8%)	10 (17.2%)
There were too many factors so I only focused on the ones I thought were important	3 (12%)	8 (13.8%)
Other	2 (8%)	0

	Other responses to Q14 "Did the number of factors (rows) affect your ability to answer each question?"
P1:TCC	Insufficient factors offered
	Factors too broad
	Factors destroyed necessary information
	Insufficient information rather than factor - the devil is in the detail
	none were relevant

Comment: Only the TCC population selected "other" to the above questions. When looking at the other responses for the above respondents around clarity, instructions and factors, there were varied and somewhat inconsistent. Additionally, I took three phone calls from respondents who struggled to understand that the DCE was hypothetical and were inclined to relate it back to what their experience of prostate cancer had been, reflected in the response "none were relevant". For this reason, I think there is value in keeping these follow up DCE questions to help interpret final results.

Prostate Treatment Questions

Previous PCa Diagnosis?	P1: TCC	P2: GenPop
Yes	18 (72%)	10 (17.2%)
No	7 (28%)	48 (82.7%)

Comment: The expectation was for the 100% of the TCC population to indicate yes to this question.

Upon discussion, the current wording of the question "*Have you had a previous prostate cancer diagnosis?"* may have be interpreted as a previous diagnosis to the current diagnosis. Therefore, a rewording to *"Have you ever had a prostate cancer diagnosis?"* is recommended.

Test for Diagnosis	P1: TCC (out of 20 who answered)
Blood Test	19 (95%)
Biopsy	16 (80%)
Imaging	14 (70%)
Other	1 (5%)
Not Sure	0

PCa Treatment?	P1: TCC
Yes	19 (95%)
No	1 (5%)

Treatment	P1: TCC
Hormones (injections)	12 (60%)
Surgery	2 (10%)
Radiation therapy	20 (100%)
Brachytherapy	2 (10%)
Chemotherapy	0
Other	0
Not Sure	1 (5%)

Other

Timing

While extensive analysis was not performed, the average time to complete the survey online was 31 minutes for P1 and 12 minutes for P2. While P1 has additional questions around their PCa diagnosis and treatment, it is not expected that this should add such a length of time, suggesting that the PCa population may be giving more thought to each choice set. The information sheet currently reports 20 to 30 minutes to complete, therefore this could be updated to 15 to 20 minutes for the P2 main survey.

Reward for TCC population

Following the logistical challenges which presented at pilot roll out to offer a reward to the TCC respondents, it is of note that only one respondent has chosen the Woolworths ecard, with the remainder either electing for the Prostate Cancer Foundation of Australia donation or not completing this question. As per the PICF and the information on the question itself, I will continue to offer this for up to 250 respondents in the main rollout.

Respondent state

A respondent state cookie was implemented for both survey versions at the recommendation of Survey Engine – this was to prevent a respondent completing the survey multiple times, particularly to prevent "gaming" of the rewards. However, it appears that for some of the TCC population, if they had the online survey open and have not completed it before the automatic time out, then they are unable to complete it when returning. This has happened on four occasions according the pseudo IP recorded. I would therefore suggest that this cookie is deactivated for the main roll out, with the small risk that a respondent could complete the survey multiple times with multiple email addresses. However this is outweighed by the benefit of potentially increasing response rate.

Recommendations for changes to survey for main roll out

1. **Move free text box to very end of survey**

   102) To ensure there isn't added frustration of respondents providing information there that is then asked later, particularly in demographics

   103)

2. **Change wording to "Have you ever had a prostate cancer diagnosis"**

   104) As discussed above, as it would seem some of the TCC population were interpreting the original wording of "Have you had a previous prostate cancer diagnosis?" as previous to their current diagnosis.

   105)

3. **Keep follow up questions**

   106) Particularly as some of the TCC population seem to struggle in separating the hypothetical nature of these questions with their own personal experience, there is value in collecting data around the clarity of the questions, their decision processes and their opinions on the factors presented. I do not think many respondents would provide this information unprompted in the free-text box.

   107)

4. **Accuracy in Factor importance questions**

   108) As previously described, accuracy was not listed in the factor importance questions – this oversight is to be addressed in the main roll out surveys.

   109)

Appendix G: Image Guidance and Treatment Margins in Prostate Cancer Radiation Therapy: A Systematic Literature Review

A note of explanation: This systematic review was undertaken to develop the initial PhD program plan, particularly the RCT. It was submitted for publication, and the peer reviewers came back suggesting it needed reworking into 2 separate reviews, one on IGRT and one on margin reduction. At this time, however, the focus of the PhD was moving towards greater emphasis on the patient preferences line of enquiry, and so the decision was made to focus on that rather than rework this literature review. The following is the original submitted manuscript. With thanks to Hana Grigg and Thanh Vu for their assistance in screening and cross-checking data synthesis.

Abstract

Introduction

Technological advances in the planning and treatment of prostate cancer with external beam radiation therapy (EBRT) have led to image-guided radiation therapy (IGRT) and the consideration of treatment margin reduction. This systematic review summarises the current literature on IGRT and treatment margins in the context of prostate EBRT.

Methods

Key search terms were used to interrogate databases. Three investigators independently searched, evaluated and determined inclusion of the literature. All articles meeting inclusion criteria were synthesised by one investigator and cross checked.

Results

A total of 20 articles were included for final synthesis.

Conclusions

High-quality studies evaluating clinical outcomes with IGRT or reduced treatment margins are limited. Inconsistencies in factors such as toxicity scoring and QOL tool utilised, prescriptions and treatment delivery modalities, and various methods and frequencies of IGRT made comparisons difficult. However, an overall tendency to improved clinical outcomes was noted with IGRT. Few studies robustly evaluated the reduction of PTV margins, with many including

a historical comparison. These findings highlight the importance of rigorous research and clinical trials within the radiation oncology community to evaluate advances.

Keywords

Prostate cancer, radiation therapy, Image-guided radiation therapy, treatment margins

Background

Accuracy is paramount in radiation therapy delivery. However, the high mobility of the prostate means accurate dose delivery to the prostate while minimising dose to surrounding tissue is a challenge.[1–4] Factors such as the degree of bladder and rectal filling influence both the daily position and magnitude of motion of the prostate during treatment.[5–8] Current IGRT techniques allow for accurate interfraction correction,[9–11] however intrafraction monitoring and correction is not yet standard practice.[12–14]

The current recommended planning target volume (PTV) margin without intrafraction correction is 10mm, except posteriorly where 5-7mm is added. [15] It is widely accepted that reduced margins should only be considered with a rigorous IGRT protocol. [15–17] This literature review aims to evaluate the existing literature regarding margin reduction and IGRT protocols, with a focus on clinical outcomes.

Method

A question was developed using the Population, Intervention, Control, Outcomes (PICO) framework and inclusion/exclusion criteria were developed as per Table 1 & 2 (Appendix G).[18] The literature search occurred in October 2016 to March 2017. Key search terms included: “prostate cancer”; “external beam radiation therapy”; “image-guided radiation therapy”; “margin”; “toxicity”; and “survival” and all synonyms of these. Databases searched were Medline OVID, Scopus, Cinahl, Informit and Google Scholar. Articles were limited to those available in English and published from 2000 to January 2017. A total of 3 investigators (AB, HG & TV) independently searched and evaluated the literature, and agreed on the included articles. Agreement for inclusion was reached by performing individual assessments, and confirming at least one other reviewer agreed to the inclusion. Ambiguous studies were discussed amongst the 3 reviewers until consensus was reached. Each article was assessed on

the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and critical appraisals performed.[19] The synthesis of the included papers was completed by one investigator (AB) and independently cross-checked by one of the other two investigators (HG & TV).

Table 1 (Appendix G): Question developed using population, intervention, control, outcomes (PICO)

	IGRT	**Reduced Margins**
Population	Prostate Cancer patients treated with EBRT	
Intervention	IGRT inter and/or intrafraction correction	Reduced margins (<7mm)
Control	No IGRT	Standard margins (7-10mm)
Outcomes	Survival Toxicities/Side Effects (Acute and Late)	

Table 2 (Appendix G): Inclusion/exclusion criteria

Inclusion	**Exclusion**
Humans Margins OR IGRT specified Outcomes reported (at least one): • Toxicities • Survival English translation available	Brachytherapy regimes Post-prostatectomy Pelvic nodes Dosimetric only studies Studies prior to 2000

Results

Initial searches yielded 522 articles after duplicate removal with the majority discarded following title and abstract perusal. A full text review was performed on 66 articles, excluding a further 46. Reasons for exclusion are summarised in Figure 1 (Appendix G). Table 3 (Appendix G) synthesises the study and technical information of the evaluated studies.

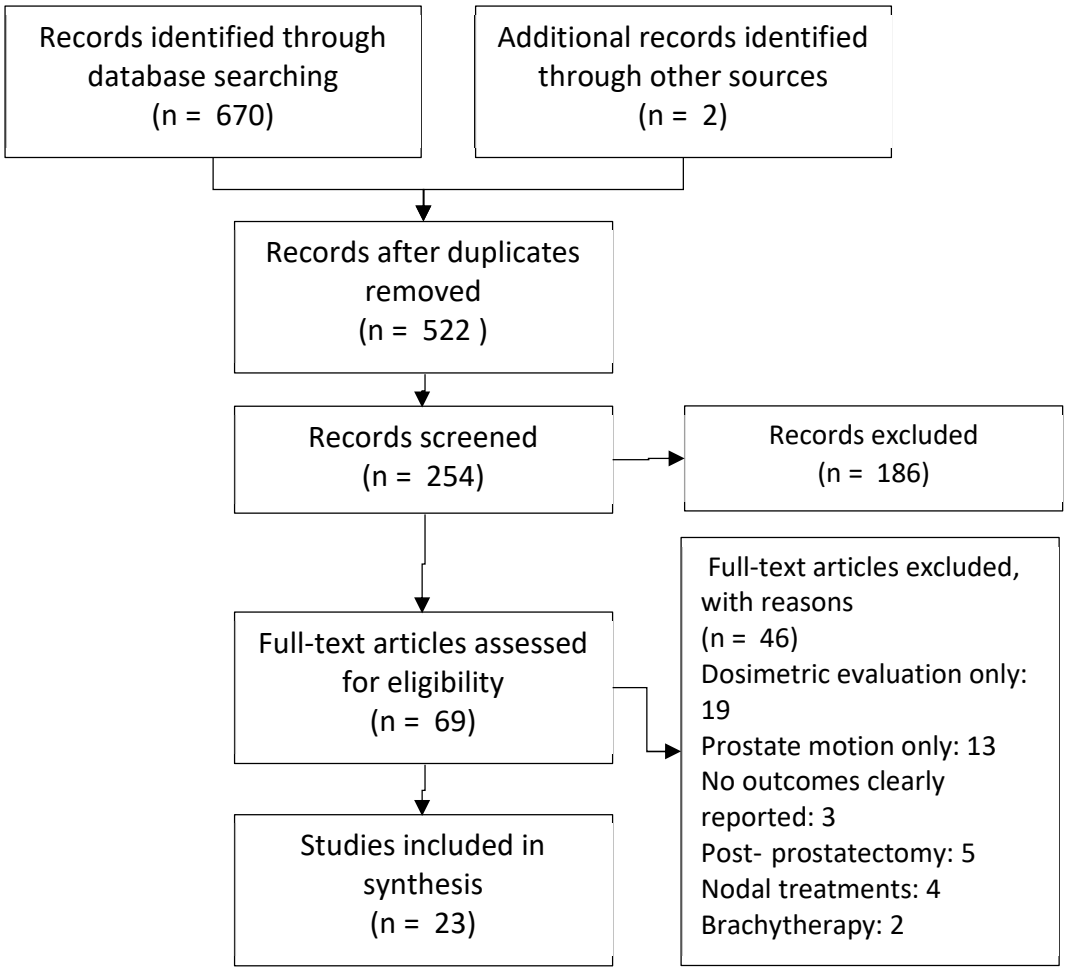


Figure 1 (Appendix G): PRISMA flowchart of literature search and screening

Radiation Treatments

A range of prescriptions and modalities were used in previous studies. The most common prescription was 78Gy in 39 fractions, ranging from 74 to 86.4Gy in 1.8 to 3.7Gy per fraction,[20–22] with one hypofractionation regimen of 36.25Gy in 5 fractions (7.25Gy per fraction).[23] Intensity-Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) were the most common modalities.

IGRT Regimens

All studies, except one, included IGRT details. However, frequency of imaging or matching parameters (such as fiducial markers (FMs), bony, soft tissue or other) were not always specified, particularly in historical cohorts.[21,24–31] The most common interfractional methods were FMs with kilovoltage (kV) imaging,[22,29,32–35] megavoltage (MV) electronic portal imaging

(EPI),[20,36,37] or cone-beam computed tomography (CBCT).[23,38,39] Three methods of intrafractional monitoring and correction were reported: electromagnetic beacons,[21] near-continuous fluoroscopy or kV monitoring of fiducials throughout treatment delivery.[23,32]

PTV Margins

PTV margins were reported in all studies with some reporting margins as a range. Median margins were 8mm, and 6mm in the posterior direction (range: 0-20mm). Importantly, two studies included a prostate-only boost phase with a zero posterior margin, but neither reported intrafraction motion correction.[38–40] Individualised margins were generated in 2 studies, from inter- and intrafraction data of the first 5-9 treatment fractions.[20,37] For this review, reduced margins were defined as ≤7mm in all directions.

Discussion

Reduced Margins with IGRT

Reduced margins were examined in 13 studies (65%) using daily interfraction IGRT protocol.[21–23,27,32,33,36,40–43] Three studies incorporated intrafraction monitoring and correction[21,23,32] and these three reported the smallest margins (3-5mm). One study without intrafraction monitoring also reduced posterior margins to 3mm. [42]

Jesper and Lotte [41] used 5mm isotropic margins with daily matching to prostatic stent and Guckenberger et al. [38,39] also reduced margins to 5mm for phase 2 (prostate only). Similarly, Wortel et al. [40] reduced margins for the boost phase to 3-5mm, but with a 0mm posterior margin. Two studies generated individualised margins after commencing with PTV margins of 10mm.[20,37] Cheung et al. [37] used FMs and EPIs to collect pre- and post- treatment motion data from the first nine treatments to individualise margins for the IMRT boost of 30Gy in 10 fractions with daily interfraction correction. The average margins of 3-4mm generated were in keeping with published data. [6,44] Cheung et al. [37] recognised that transient motion of the prostate may have occurred, but not been captured using the pre- and post-imaging method. In comparison, Vargas et al.[20] constructed patient-specific margins using a total of 5 computed tomography (CT) scans and 4 sets of EPIDs acquired in the first week of treatment, however the individualised margins were not reported.

Survival Outcomes

This review synthesised freedom from biochemical failure (FFBF) as it was the most commonly reported survival outcome. Reporting timeframes varied from two to five years. All studies, except one, specified the Phoenix definition of biochemical failure (PSA nadir +2 ng/ml) and the exception defined biochemical failure as three consecutive PSA increases (the ASTRO definition).[26]

Three-year survival increased significantly (p=0.05) between daily (97%) and weekly interfraction correction (77%) within high-risk (HR) patients with 10mm margins (6mm posterior).[29] This improvement in survival observed by Zelefsky et al. [29] is consistent with Sviestrup et al. [33], where 3 year FFBF in a cohort of weekly bony EPID IGRT was 86% compared to 90.3% in daily FM interfractional correction. However, different prescriptions of 76Gy versus 78Gy were used by Sviestrup et al. [33] which may have contributed to the improved survival.

Comparison of IGRT to non-IGRT cohorts by Zhong et al. [30] show no significant difference in 5-year survival (p=0.427). However, IGRT was not performed daily, instead CBCTs on first 3 fractions then weekly thereafter.[30] Likewise, in a historical comparison Kok et al. [34] found no significant difference in FFBF (p=0.143) comparing weekly EPID bony matching to daily FM interfraction correction. However, different prescriptions were used for the weekly group (78Gy), compared to the daily group (74Gy)), a dose difference which could have tempered any possible survival advantage gained from IGRT.[34]

Reduced margins (3-5mm) coupled with rectal distension at planning CT dramatically reduced 5-year FFBF from 89% to 75%.[22] This reduction was possibly due to intrafraction motion and margins were increased to 6mm to account for this. Takeda et al. [42] reported a 5-year FFBF of 100% for intermediate-risk (IR) and 82.2% for HR with similar margins (5mm/3mm posterior) and daily interfraction correction. These results are comparable to Ricardi et al. [35] of 3-year IR FFBF of 98% with standard margins and daily ultrasound interfraction correction. In contrast, Jesper and Lotte [41] reports lower IR (85%) and HR survival (77%) with daily imaging. Similarly, 82% 5-year survival was seen in patients with a reduced margin of 5mm and 0mm posteriorly for phase 2 prostate-only treatment and only interfractional correction with daily

CBCT. Correlation of potential geographic miss and location of the recurrence would be of interest, but at the expense of further diagnostic imaging.

Shimizu et al. [32] reported FFBF with IMRT, after interfractional correction and reduced 3mm margins at 3 years at 100%, 93.8% and 89.5% for low (LR), IR and HR respectively, and at 5 years 100%, 84% and 79.6%. It was concluded that the reduction of margins did not increase biochemical failure, with a corresponding low toxicity rate as detailed.

Toxicity Outcomes

Acute toxicity was reported in 61% of studies (6 using RTOG scoring and 8 using CTCAE scoring). Late toxicity was reported in 74% of studies (9 using RTOG and 8 using CTCAE). 11 studies reported both acute and late toxicities.

No significant differences in acute genitourinary (GU) toxicities were found by Pollack et al. [24] when comparing hypofractionated treatment (70.2Gy/26#) with reduced margins (7mm/3mm posterior) to standard treatment (8mm/5mm posterior). However, a slight increase in GI toxicities in the hypofractionated cohort was noted during weeks 2-4 of treatment [24]. Neither study included an IGRT protocol, and differences in IGRT may influence results.

Comparing daily US to weekly bony EPID correction, Bohrer et al. [28] found daily US correction reduced gastrointestinal (GI) toxicity, particularly proctitis ($p = 0.018$). However, there was no significant difference in GU toxicity and the sample size of 42 was recognised as a limitation. Notably, the large PTV margin of 15mm in all directions was one of the largest in this review. However, late GI toxicity >Grade 3 (G3) of 10% for the EPID cohort only is reported - comparable to other studies with smaller margins. This may be due to the lower dose of 70Gy in 35 fractions.

Liauw et al. [25] reported low rates (≤6%) of acute and late G3 GI and GU toxicity using IMRT with 10mm isotropic margins. Cheung et al. [37] reported similar G3GU and G3GI (9% and 0% respectively) comparing 3DCRT with standard margins and IMRT boost with individualised margins. Further long-term follow up requirements were recognised. Late G3 GI and GU toxicity was 2%, treated with both reduced margins and daily interfraction correction.[22] With

margins of 5-7mm, few toxicities were reported by Langenhuijsen et al. [36], with late G3 <10% for both GI and GU, however the reporting of toxicities seemed convoluted with dosimetric assessment reporting.

The necessity of IGRT protocols when treating IMRT was recognised by Cheung et al. [37], demonstrating increased acute rectal toxicity when compared to the cohort not using IGRT (80% G2GI for non-IGRT versus 13% for IGRT). However, sample sizes were small, and the IGRT group had significantly smaller margins of 2-3mm compared to 10mm/7mm in the non-IGRT group potentially contributing to the decreased toxicity. Interpretation is difficult as nodes were sometimes treated but details of the number of patients with nodes treated was not reported. These results are supported by Kok et al. [34], showing significant reduction in the likelihood of >G2 GI toxicity (Hazard ratio 3.66, p=0.003) and a reduction in the duration of >G2 GU toxicity (Hazard ratio 0.24) with daily IGRT versus weekly bony correction.

Similarly, Bohrer et al. [28] compared patients treated with daily interfractional US correction to weekly bony EPID correction showing a significant difference in acute rectal toxicity (10% >G3GI in the weekly cohort compared to none in the daily cohort). While this study demonstrates an improvement, the 15mm margins in both cohorts were amongst the largest in all studies.

Daily interfractional corrections with a margin of 7mm with 5mm posterior yielded acute RTOG ≤G2 toxicities of 27% and 29% for GI and GU respectively, including both 3DCRT and IMRT to 78Gy [36]. Late toxicities ≤G2 in this study were 33% and 32% respectively, with total G3 toxicities <10% [36]. These toxicities seem high compared to Ricardi et al. [35], with acute RTOG ≤G2 of 12% and 26% for GI and GU respectively, using a hypofractionated IMRT prescription of 70.2Gy in 26 fractions, with daily US correction, with larger margins (10mm isotropic, 7mm posterior). Ricardi et al.[35] also reported lower G2 late toxicities of 9% (GI) and 6% (GU).

Guckenberger et al. [38] reports acute CTCAE ≥G2GI 12% and ≥G2GU 42%, with late ≥G2GI 2% and ≥G2GU 8%, treated with a margin reduction in phase 2, but with intermittent imaging. Takeda et al. [42] reports even lower toxicity, with acute CTCAE ≥G2GI 2% and ≥G2GU 9%, and late ≥G2GI and ≥G2GU of 6% each, treated with reduced margins (3-5mm) and daily FM interfraction correction. Both of these studies report lower toxicities than Vargas et al. [20] with

acute CTCAE ≥G2GI 34% and late ≥G2GI 10%. Potentially, the individualised margins created by Vargas et al. [20] encompassed more surrounding tissue in some of the cohort, thus increasing toxicities – unfortunately the margins are not reported.

Late toxicities in a cohort of 3DCRT with offline bony anatomy imaging compared to IMRT with daily FM interfraction correction reduced G2 GI toxicities in the IGRT cohort (24.9%) compared to the non-IGRT cohort (37.6%, p=0.005). GU toxicities however were comparable (46.2% and 36.4%, IGRT and non-IGRT respectively, p=0.33).[40] Comparison of the same modality with and without IGRT is preferable, as the reduction in rectal toxicities may have been a result of both a superior IMRT plan and daily IGRT. Promisingly, with 3mm margins and daily inter and intrafraction correction, Shimizu et al. [32] reported low acute and late toxicity rates, with no acute or late GI toxicity >G2 and only 1% acute G2GU and 3% late G2GI toxicity.

Limitations

Confounding factors other than IGRT or margins contribute to patient outcomes including co-morbidities and medications, hormonal therapy and prostate size. Patient characteristics and cofounders were not synthesised in this review, however the importance of reporting such in future prospective IGRT/reduced margin studies are essential in interpreting the results.

Conclusion

Inconsistent reporting of results made systematic analysis difficult. Inconsistencies include: variations in toxicity scoring and QOL tool utilised; different radiation prescriptions; and treatment delivery modalities. Clinical outcomes improved overall despite variations in method and frequency of IGRT. Evaluations of PTV margin reduction were not robust as many studies used historical comparisons. Historical data complicates interpretation of results because of changes in IGRT methods, radiation prescriptions and treatment modalities over time.

Intrafraction monitoring solutions have been on the market for the last decade. However, most publications to date report only on the implementation and pilot studies of the system itself. While image-guidance and margins are of paramount importance in the EBRT treatment

of prostate cancer, there are few high-quality studies evaluating the clinical outcomes when image-guidance and/or margins are altered. This highlights the importance of rigorous research and clinical trials within the radiation oncology community to evaluate advances.

Table 3 (Appendix G): *Synthesis of study details and technical data*

Reference & Study Design (Morbidity Measure)	Sample Size	Margins (mm)‡	IGRT			Prescription & Modality (Gy/fractions)	Survival (Phoenix definition)	Toxicity Grading			
			Details	Inter Correction	Intra Correction			Acute GI	Acute GU	Late GI	Late GU
Pollack *et al*. [24] RCT (RTOG)	50	8 (5P)	NR	NR	NR	76/38 IMRT	NR	G1: 40% G2:8% G3: 0%	G1: 28% G2: 54% G3: 2%	G1: 12% G2:2% G3: 0%	G1: 31% G2: 8% G3: 0%
	50	7 (3P)				70.2/26 IMRT		G1: 40% G2:18% G3: 0%	G1: 44% G2: 40% G3:8%	G1: 16% G2: 0% G3: 0%	G1: 30% G2: 6% G3: 0%
Liauw *et al*. [25] Prospective (RTOG)	130	10 With US: 6P	Bony EPID – frequency NR Daily US from 2003 (*n* NR)	Y (for Daily US from 2003, *n* NR)	N	74-76Gy IMRT	4-year LR: 97% IR: 94% HR: 87%	G2: 38% G3: 0%	G2: 45% G3: 2%	G2: 9% G3: 5%	G2: 31% G3: 6%
Langenhuijsen *et al.* [36] Prospective (RTOG)	93	7 (5P)	FMs + EPID	Y	N	78/39 3DCRT and IMRT *n*=NR	NR	≤G2: 27%	≤G2: 29%	≤G2: 33% ≥G3: <10%	≤G2: 32%
Engels *et al.* [22] Prospective (RTOG)	50	25pts: 3 LR, 5 AP, 4 SI 25pts: 6	FMs + kVs (with 6DOF couch)	Y	N	78/39 *n*=38 70/35 *n*=5 56/16 *n*=7	5-year All =83% HR :75% IR-LR:90%	NR		≥G3: 2%	≥G3: 2%
De Meerleer *et al.* [27] Prospective (RTOG)	114	7 AP/LR, 10 SI	EPID (details NR)	NR	N	74-76/36-37 IMRT	NR	G1: 39% G2:27% G3: 0%	G1: 47% G2: 36% G3:7%	NR	

De Meerleer *et al.* [26] Retrospective (RTOG)	133	7 AP/LR, 10 SI 4 with US *n*=15	EPID (details NR) US (n=15) (details NR)	NR	N	74-76/36-37 IMRT	5-year LR = 100% IR = 94% HR = 74%	NR		G1: 47% G2:17% G3: 1%	G1: 43% G2: 19% G3:3%
Cheung *et al.* [37] Prospective (CTCAE)	33	Ph1: 10 Ph2: Individualised margins from intrafraction motion data gathered in first 9#s: Average (range):3 LR (2-5);3 SI (2-7);4 AP (2-8)	Ph1: EPIDs (with FMs) before and after treatment No online correction Ph2: Daily FM-EPID correction	Y (Ph 2 only)	N	Ph1: 42/21 3DCRT Ph2: 30/10 MRT boost	NR	G1: 76% G2:12% G3:0%	G3: 9%	NR	
Bohrer *et al.* [28] Prospective (RTOG)†	22	15 (1/3 rectum circumference included in P)	US (transabdo) daily	Y	N	70/35 3DCRT	NR	NR	G2: 5%	≥G3:0%	≥G3:14%
	20		EPID (bony) *weekly correction*	N	N				NR	≥G3: 10%	≥G3:10%
Vargas *et al.* [20] Prospective (CTCAE)	331	Individualised from 5CTs & 4 sets of EPIDS taken in 1st week (10 for 1st week)	Daily EPID + weekly CTs	Y (matching NR)	N	63-79.2/35-44 3DCRT	NR	≥G2:34% G3: 1%		G2:10% G3: 3%	
Shimizu *et al.* [32] Prospective	110	3	Daily fluoroscopy to FMs	Y	Y	70/35 IMRT	FFBF 3 years LR = 100%	G1: 6% ≥G2:0%	G1:40% G2:1%	G1: 7% ≥G2: 0%	G1:16% G2:3%

(CTCAE)							IR = 93.8% HR = 89.5% 5 years LR = 100% IR = 84% HR = 79.6%				
Zelefsky *et al.* [29] Retrospective - Historical Comparison (CTCAE)	186	10 (6P)	Daily kVs matching to FMs	Y	N	86.4Gy (fractionation NR) IMRT	3 years HR = 97%	G1: 23% G2:1% G3: 0%	G1: 62% G2: 18% G3:0%	NR	NR
	190		Weekly imaging (matching NR)	N	N		3 years HR = 77.7%	G1: 17% G2:1% G3: 1%	G1: 35% G2: 27% G3:0%		
Wortel *et al.* [40] Comparison of 2 RCTs (RTOG)	189	10 Boost: 5	Offline - bony anatomy	N	N	78/39 3DCRT	NR	NR	NR	*3-year* ≥G2:31% ≥G3: 3% *5-year* ≥G2:38% ≥G3: 3%	*3-year* ≥G2:32% ≥G3: 9% *5-year* ≥G2:36% ≥G3:16%
	242	5-8 Boost: 3-5 (0P)	FMs (except CBCT in 4%)	Y	N	78/39 IMRT	NR			*3-year* ≥G2:19% ≥G3: 2% *5-year* ≥G2:25% ≥G3: 2%	*3-year* ≥G2:36% ≥G3:10% *5-year* ≥G2:46% ≥G3:12%
Zhong *et al.* [30] Retrospective -Historical Comparison (CTCAE)	65	8-10 (6P) Last 5#s: 3-4	CBCT – first 3#s then weekly thereafter (Total of 10-15)	N	N	76-80/38-40 IMRT Nodes included if required, *n* NR	No significant improvement between groups at 5 years (p=0.427)	G1: 25% G2: 3% G3: 0%	G1: 35% G2: 15% G3: 0%	G1: 6% G2: 2% G3: 0%	G1: 6% G2: 2% G3: 0%

	62	8-10 (6P)	NR	NR	NR			G1: 23% G2: 5% G3: 0%	G1: 39% G2: 19% G3: 0%	G1: 5% G2: 2% G3: 2%	G1: 10% G2: 3% G3: 0%
Sveistrup *et al.* [33] Retrospective -Historical Comparison (CTCAE)	115	10-20	Weekly EPID – bony matching	N	N	76/38 3DCRT	3-year actuarial BBFS =86%	NR	NR	2-year actuarial likelihood ≥G2: 57.3%	2-year actuarial likelihood ≥G2: 41.8%
	388	5 LR/AP & 7 SI	FMs + kVs daily	Y	N	78/39 IMRT *n*=236 VMAT *n*=152	3-year actuarial BBFS =90.3% (p=0.386)			2-year actuarial likelihood ≥G2: 5.8%	2-year actuarial likelihood ≥G2: 29.7%
Jesper and Lotte [41] Prospective (RTOG)	90	5	Daily imaging matching to prostatic stent	Y	N	78/39 3DCRT	BFFF 5-year: LR: 100% IR: 85% HR: 77%	NR	NR	G2: 0%	G2: 5%
Guckenberger *et al.* [38] Prospective (CTCAE)	100 (25 with nodes treated)	Prostate + SV: 10 (7P) Prostate: 5 with no rectal overlap	Daily CBCT for first 5#s then 2-3 weekly Prostate soft tissue match.	N	N	73.91/32 LR IMRT *n*=26 76.23/33 (60/33 SVs) for IR & HR IMRT *n*=74	NR	≥G2: 12%	≥G2: 42%	≥G2: 2%	≥G2: 8%
Guckenberger *et al.* [39] Prospective (CTCAE)	150	Prostate + SV: 10 (7P) Prostate: 5 with no rectal overlap	Daily CBCT+FMs	Y	N	73.9-76.2/32-33 IMRT	5-year FFBF All: 82% LR: 88% IR: 80% HR:78%	G1: 19% G2: 5% G3: 0%	G1: 48% G2: 32% G3: 3%	G1: 6% G2: 1% G3: 1%	G1: 20% G2: 11% G3: 5%

Kok *et al.* [34] Retrospective -Historical Comparison (CTCAE)	311	10 (7P)	EPID bony match – first 3#s then weekly	N	N	78/39 3DCRT	No statistical significant difference in FFBF (p = 0.143)	NR	NR	Significantly reduced likelihood (Hazard ratio 3.66, p=0.003) of ≥G2GI toxicity and reduced duration of ≥G2GU toxicity (Hazard ratio 0.24) when treated with IGRT.	
	243	10 (7P)	FMs with daily kVs	Y	N	74/37 3DCRT					
Ricardi *et al.* [35] Prospective (RTOG)	74	10 (7P)	Daily 3D US	Y	N	70.2/ 26 IMRT	3-year FFBF IR: 98%	G1: 30% G2: 12% G3: 1%	G1: 23% G2: 26% G3: 4%	≥G2: 9%	≥G2: 6%
Takeda *et al.* [42] Prospective (CTCAE)	141	5 (3P)	FMs with daily kVs	Y	N	76/38 *n*=13 80/40 *n*=128 IMRT	5-year FFBF IR: 100% HR: 82.2%	G1: 20% G2: 1% G3: 0%	G1: 60% G2: 9% G3: 0%	≥G2: 6%	≥G2: 6%

‡ Isotropic unless specified, P=posterior, † = percentages extrapolated, NR=not reported, Y=yes, N=no, *n*=number of patients

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