Spatial dose-response models of rectal toxicities for patients undergoing prostate radiotherapy

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Abstract

Treatment options for prostate cancer include external beam radiotherapy (EBRT) with or without a boost dose from high-dose-rate brachytherapy (HDR-BT). The curative intent of such treatments is constrained by gastrointestinal complications following undesirable irradiation of the rectum. Consequently, the aim of this study was to model how the distribution of dose to the rectum from combined prostate EBRT/HDR-BT relates to observed late gastrointestinal complications. The data in this study comes from a large multi-centre trial undertaken across Australia and New Zealand. The analysis included dosimetric data for up to 167 patients who received combined EBRT/HDR-BT. The data for 724 patients who received EBRT were also used for some analyses. An understanding of how the dose to rectum in the treatment plan influences complications can be used to improve future treatments. Relating the dose from treatment to observed complications involved three stages.

Stage 1: Advanced methods to accumulate the planned dose for EBRT followed by HDR-BT

The anatomy in a EBRT planning CT is different to the anatomy in a HDR-BT planning CT acquired at a later date. Consequently, advanced methods involving deformable image registration are required to adjust for anatomical differences before accumulating the rectal dose. This study is the first to comparatively evaluate deformable registration methods used to register the rectums in the EBRT and HDR-BT CTs of prostate cancer patients (Chapter 2). The evaluation identified the rigid plus deformable multi-pass registration method within Velocity Advanced Imaging as the most appropriate for the rectum. This is also the first study for combined prostate EBRT/HDR-BT to quantify the difference in rectal dose between the registration-based dose accumulation method and an alternative simple parameter-adding method which requires assumptions (Chapter 3). It was determined that the simple parameter-adding method does not provide conservative estimates when registration and contouring uncertainties are present near the
anterior rectal wall.

**Stage 2: Associating dose-volume metrics from planned dose with symptoms**

Treatment plans are clinically assessed in terms of dose-volume metrics. One method for associating dose-volume metrics with observed complications is to determine those metrics which are different for groups of patients with and without complications or to determine the odds ratio for a unit increase in the value of a metric. This is the first study for combined prostate EBRT/HDR-BT to determine which metrics obtained by the registration-based method were associated with gastrointestinal toxicities and to compare those findings with the analysis repeated for metrics obtained by the simple parameter-adding method (Chapter 4). The findings from registration-based accumulation were in most cases consistent with parameter-adding results. The mid-high dose range and near-maximum doses were important for rectal bleeding with mid-high dose ranges also important for stool frequency and urgency/tenesmus.

An alternative dose-response method is to fit a Normal Tissue Complication Probability (NTCP) model to the observed complications. NTCP models include fitting parameters where parameter values summarise the influence of doses on complications. This is the first study for combined prostate EBRT/HDR-BT to obtain estimates of the fitting parameters for various types of gastrointestinal complications and to compare the estimates with the values determined for complications observed after EBRT only (Chapter 5). This study also included a correction for the different dose fractions of EBRT and HDR-BT by including the linear-quadratic model and obtaining the best estimate of the alpha-beta ratio. The results indicated that late rectal bleeding is influenced by high doses and that the most appropriate alpha-beta ratio is 3.1 Gy.

**Stage 3: Using novel methods to relate spatial features of dose distributions to symptoms**

Methods that correlate dose-volume metrics with complications or fit NTCP models to complications are neglecting spatial information for dose distributions. Studies
have demonstrated that the spatial arrangement of dose influences complications. One method for including spatial information is to obtain 2D dose-surface maps for the 3D rectal surface dose by virtually unfolding the rectum. This is the first study for combined prostate EBRT/HDR-BT to relate voxel-wise features of dose-surface maps and parameterised spatial patterns to complications (Chapter 6). This study also explored a number of novel ways of characterising shapes of clusters formed by thresholding dose-surface maps. Spatial features for mid-high dose clusters were strongly associated with toxicities (e.g. cluster area, perimeter, compactness, circularity, eccentricity of ellipse fits of clusters and confinement of clusters to the ellipse fits).
Thesis declaration

I, Calyn R. Moulton, as the PhD candidate certify that:

I was solely responsible for coding and preparing this thesis in \LaTeX. This thesis has been substantially accomplished during enrolment in the degree. This thesis does not contain material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution. No part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of The University of Western Australia and where applicable, any partner institution responsible for the joint-award of this degree. This thesis does not contain any material previously published or written by another person, except where due reference has been made in the text. The work is not in any way a violation or infringement of any copyright, trademark, patent or other rights whatsoever of any person. The research involving human data reported in this thesis was assessed and approved by The University of Western Australia Human Research Ethics Committee, Approval #: RA/4/1/5601. Written patient consent has been received and archived for the research involving patient data reported in this thesis. The work described in this thesis was funded by the National Health and Medical Research Council (300705, 455521, 1006447), the University of Western Australia, an Australian Postgraduate Award, an Ana Africh Scholarship, the Hunter Medical Research Institute, the Health Research Council (New Zealand), Abbott Laboratories and Novartis Pharmaceuticals. This thesis contains published work and/or work prepared for publication, some of which has been co-authored.

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Date:
Thesis structure

This thesis is presented as a series of stand-alone papers where each chapter of results has been published or submitted to a journal. Consequently, each chapter has its own bibliography and supplementary material. The thesis has been structured to present a complete and coherent coverage of the research undertaken whilst containing stand-alone papers. As such, the thesis contains a general introduction and general discussion of the research. Additionally, the chapter for each paper contains a foreword which introduces the topic covered by the chapter and establishes how the chapter links to other chapters in the overall scheme of the research undertaken. This thesis is in agreement with The University of Western Australia Doctor of Philosophy Rules for the content and format of a thesis (rules 39-45), which allow a thesis to be a series of papers.

The thesis contains eight chapters:

Chapter 1 is a general introduction to the thesis as it includes a description of the research topic, an overview of existing literature and an explanation of how subsequent chapters of this thesis are novel.

Chapters 2-6 are published original articles and submitted original manuscripts which detail the results of various investigations undertaken during the three stages of completing the research topic. Chapters 2-6 are stand-alone chapters as this is a thesis as a series of papers.

Chapter 7 provides a general discussion of all results and findings by interpreting, linking and comparing the results and findings of each chapter.

Chapter 8 provides a general conclusion for all major findings in the thesis chapters.
Authorship declaration: Co-authored publications

This thesis contains work that has been published and prepared for publication. All co-authors of the various work have consented to the use of material within this thesis. My contributions to the publications and manuscripts are outlined below.


Location in thesis: Chapter 2

Contributions: The candidate was solely responsible for retrieving missing data from back-up tapes, importing treatment data, managing imported data, creating relevant code, conducting data analysis, interpreting data, drafting the manuscript and revising the manuscript.


Location in thesis: Chapter 3

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Location in thesis: **Chapter 4**

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Location in thesis: **Chapter 5**

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Location in thesis: **Chapter 6**

Contributions: The candidate was solely responsible for retrieving missing data from back-up tapes, importing treatment data, managing imported data, creating relevant code, conducting data analysis, interpreting data, drafting the manuscript and revising the manuscript.
The co-authors were responsible for implementing and managing the trial from which the data came, proposing the general topic for the candidate’s thesis, providing feedback on analysis presented by the candidate, providing feedback on draft manuscripts, and assessing the validity of scientific and clinical recommendations proposed by the candidate in manuscripts.

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Presentations

Oral


3. **C. R. Moulton**, M. A. Ebert, M. J. House, V. Lye, C. I. Tang, M. Krawiec, and J. W. Denham, “Evaluation results for the use of deformable image registration (DIR) on CT datasets sourced from patients receiving a combination of high-dose rate brachytherapy (HDR-BT) and external beam radiotherapy (EBRT),” *Combined Scientific Meeting: Imaging and Radiation in Personalised Medicine*, Melbourne, Australia, 4-7 September 2014.


**Poster**

1. C. R. Moulton, M. A. Ebert, M. J. House, V. Lye, C. I. Tang, M. Krawiec, and J. W. Denham, “Evaluation results for the use of deformable image registration (DIR) on CT datasets sourced from patients receiving a combination
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Lastly, I would like to dedicate this thesis to my recently-born son. I hope I can provide you with the same quality of support my family has shown me. May this thesis be a reminder to me to support your education.
Chapter 1: General introduction

1.1 Background and literature review
  1.1.1 Prostate cancer
  1.1.2 Radiation therapy treatments for prostate cancer
  1.1.3 Side effects of prostate radiotherapy
  1.1.4 Using a dose-volume histogram to assess a dose distribution
  1.1.5 Modifications of dose-volume histograms to include spatial information
  1.1.6 Alternatives to the DVH that include spatial information
  1.1.7 Adjusting for different dose fractionation
  1.1.8 Accumulating dose

1.2 Information on the RADAR trial
  1.2.1 External beam radiotherapy followed by high-dose-rate brachytherapy
  1.2.2 External beam radiotherapy
  1.2.3 Toxicity assessments

1.3 Novel aims of the study

XVIII
1.3.1 Stage I: Advanced methods to accumulate the planned dose for EBRT followed by HDR-BT ........................................... 14
1.3.2 Stage II: Associating dose-volume metrics from planned dose with symptoms ............................................................ 15
1.3.3 Stage III: Using novel methods to relate spatial features of dose distributions to symptoms ........................................ 16
1.4 References ........................................................................ 17

Stage I: Advanced methods to accumulate the planned dose for EBRT followed by HDR-BT 37

Chapter 2: Image registration 39
2.1 Foreword for manuscript ......................................................... 40
2.2 Manuscript details ................................................................. 41
2.3 Abstract ............................................................................. 42
2.3.1 Background .................................................................... 42
2.3.2 Methods ......................................................................... 42
2.3.3 Results ........................................................................... 42
2.3.4 Conclusions .................................................................... 43
2.4 Introduction ........................................................................ 44
2.5 Patient data ......................................................................... 45
2.6 Methods ............................................................................. 47
2.6.1 Rigid registration .............................................................. 47
2.6.2 Image preprocessing ......................................................... 48
2.6.3 Non-rigid registration (deformable image registration) ...... 48
2.6.4 Visual assessments ............................................................ 49
2.6.5 Structure-correspondence metrics .................................... 49
2.6.6 Image-similarity metrics ................................................... 50
2.6.7 Displacement-vector-field metric ..................................... 50
2.6.8 Statistical analysis ........................................................... 50
2.7 Results .............................................................................. 50
2.7.1 Visual assessments .......................................................... 50

XIX
4.5.2 Toxicity outcomes .................................................. 113
4.5.3 Registration process .......................................... 115
4.5.4 Obtaining dose-volume histograms ....................... 115
4.5.5 Response modelling ............................................. 116
4.6 Results ................................................................. 117
4.7 Discussion ............................................................... 122
  4.7.1 It is important to explore dose-toxicity modelling in a variety
      of registration contexts ........................................... 122
  4.7.2 Studies had identified important dose-volume metrics for a
      variety of prostate radiotherapy techniques .................... 123
  4.7.3 The findings indicate a serial response for rectal bleeding ... 126
  4.7.4 The mid-dose region is important for bleeding/non-bleeding
      toxicities ............................................................... 126
  4.7.5 Toxicity is also influenced by low doses and the lower end of
      the mid-dose range .................................................... 127
  4.7.6 Software developments to improve contour consistency and
      registration accuracy for the prostate/rectum interface would
      be of great benefit .................................................... 127
  4.7.7 Inter-fraction motion should be considered ................. 129
  4.7.8 Avenues and recommendations for further analysis .......... 130
4.8 Conclusions ............................................................ 131
4.9 Declarations .......................................................... 131
  4.9.1 Ethics approval and consent to participate ................... 131
  4.9.2 Consent for publication .......................................... 131
  4.9.3 Availability of data and material ............................. 132
  4.9.4 Competing interests ............................................ 132
  4.9.5 Funding ............................................................ 132
  4.9.6 Authors’ contributions .......................................... 132
  4.9.7 Acknowledgements .............................................. 132
4.10 Supplements 4A-4H ............................................... 133
  4.10.1 Supplement 4A .................................................. 133
  4.10.2 Supplement 4B .................................................. 136

XXII
Chapter 5: Complication probability

5.1 Foreword for manuscript ........................................... 158
5.2 Manuscript details .................................................. 159
5.3 Abstract ............................................................... 160
  5.3.1 Purpose ............................................................. 160
  5.3.2 Methods ........................................................... 160
  5.3.3 Results ............................................................. 160
  5.3.4 Conclusions ...................................................... 160
5.4 Introduction .......................................................... 162
5.5 Methods ............................................................... 163
  5.5.1 Trial details ....................................................... 163
  5.5.2 External beam radiotherapy followed by high-dose-rate
       brachytherapy ....................................................... 163
  5.5.3 External beam radiotherapy .................................... 164
  5.5.4 Toxicity scoring ................................................. 164
  5.5.5 Registration process for patients receiving combined
       EBRT/HDR-BT ...................................................... 165
  5.5.6 Dose-volume histogram data .................................. 165
  5.5.7 Normal tissue complication probability ....................... 167
  5.5.8 Impact of the dose fraction correction ....................... 168
5.6 Results ............................................................... 169
  5.6.1 Rectal bleeding .................................................. 172
  5.6.2 Non-bleeding toxicities ....................................... 172
5.7 Discussion ............................................................. 173

XXIII
Stage III: Using novel methods to relate spatial features of dose distributions to symptoms 199

Chapter 6: Spatial analysis 201

6.1 Foreword for manuscript 202
6.2 Manuscript details 203
6.3 Abstract 204
  6.3.1 Background 204
  6.3.2 Methods 204
  6.3.3 Results 204
  6.3.4 Conclusions 205
6.4 Introduction 206
6.5 Methods 207
  6.5.1 Patient data 207
  6.5.2 Toxicity outcomes 208
6.5.3 Registration process .......................... 209
6.5.4 Obtaining dose-surface maps .................. 211
6.5.5 Features of the spatial distribution ............ 211
6.5.6 Response modelling .......................... 212

6.6 Results ........................................ 214
6.6.1 Rectal bleeding .............................. 214
6.6.2 Stool frequency .............................. 215
6.6.3 Completeness of evacuation ................... 215
6.6.4 Anorectal pain .............................. 216
6.6.5 Diarrhoea .................................. 216
6.6.6 Urgency and tenesmus ......................... 216
6.6.7 Proctitis .................................. 221

6.7 Discussion ..................................... 221

6.8 Conclusions .................................... 224

6.9 Declarations ................................... 225
6.9.1 Conflict of interest disclosure ................. 225
6.9.2 Acknowledgements ............................ 225

6.10 Supplements 6A-6G ............................ 226
6.10.1 Supplement 6A .............................. 226
6.10.2 Supplement 6B .............................. 229
6.10.3 Supplement 6C .............................. 230
6.10.4 Supplement 6D .............................. 232
6.10.5 Supplement 6E .............................. 233
6.10.6 Supplement 6F .............................. 235
6.10.7 Supplement 6G .............................. 236

6.11 References .................................... 238

Chapter 7: General discussion ......................... 247
7.1 Foreword for discussion .......................... 248
7.2 Quality control of registrations .................. 249
7.3 Options for accumulating rectal dose .......... 250
7.4 Dose-volume analysis ........................... 250
7.5 Spatial information from the dose distribution 252
Chapter 8: General conclusion

8.1 Foreword for conclusion ................................. 272

8.2 Important findings ........................................ 273

8.2.1 Stage 1: Advanced methods to accumulate the planned dose for EBRT followed by HDR-BT ................. 273

8.2.2 Stage 2: Associating dose-volume metrics from planned dose with symptoms ................................. 274

8.2.3 Stage 3: Using novel methods to relate spatial features of dose distributions to symptoms ....................... 275
List of abbreviations

3D-CRT 3D conformal radiation therapy
%Diff Median pairwise percentage difference
α/β Alpha-beta ratio
AAPM American Association of Physicists in Medicine
ACE Angiotensin-converting enzyme
ASD Average surface distance
cc Cubic centimetres
CERR Computational environment for radiotherapy research
CI Confidence interval
CT Computed tomography
CTCAE Common toxicity criteria for adverse events
CTV Clinical target volume
D Rigid plus image processing plus Demons-DIR in DIRART
D_{eff} Effective homogeneous dose
DIR Deformable image registration
DIRART Deformable image registration and adaptive radiotherapy research
DSC Dice similarity coefficient
DSH Dose-surface histogram
DSM Dose-surface map
DVF Displacement vector field
DVH Dose-volume histogram
DVSH Dose-volume scoring-function histogram
D_{X\%} Minimum dose to the most irradiated X percent of the rectal volume after applying an α/β
D_{Xcc} Minimum dose to the most irradiated X cubic centimetres of the rectal volume after applying an α/β
EQD$_{2\alpha/\beta}$ Gy  
Equieffective dose given in a reference 2 Gy per fraction using $\alpha/\beta$

EQD$_{X\alpha/\beta}$ Gy  
Equieffective dose given in a reference $X$ Gy per fraction using $\alpha/\beta$

EBRT  
External beam radiotherapy

ESTRO  
European Society for Radiotherapy and Oncology

GEC  
Groupe Européen de Curiethérapie

gEUD  
Generalised equivalent uniform dose

GI  
Gastrointestinal

HD  
Hausdorff distance

HDR-BT or HDR  
High-dose-rate brachytherapy

HS  
Rigid plus image processing plus HSOF-DIR in DIRART

HSOF  
Horn-Schunck optical flow registration algorithm

IMRT  
Intensity-modulated radiation therapy

IP  
Image processing

IQR  
Interquartile range

JAC  
Jacobian determinant

LENT-SOMA  
Late effects of normal tissue - subjective, objective, management and analytic

LKB  
Lyman-Kutcher-Burman

LQ  
Linear-quadratic model

m  
LKB NTCP parameter

M  
Median

MI  
Mutual information

MD  
Median difference

MRI  
Magnetic resonance imaging

MSE  
Root of the mean-squared error

MV  
Megavoltage

n  
LKB NTCP parameter

NTCP  
Normal tissue complication probability

OAR  
Organ at risk
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>p</td>
<td>P-value</td>
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<tr>
<td>PSA</td>
<td>Prostate-specific antigen</td>
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<tr>
<td>PTV</td>
<td>Planning target volume</td>
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<tr>
<td>RADAR</td>
<td>Randomized androgen deprivation and radiotherapy trial</td>
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<td>RT</td>
<td>Radiation therapy</td>
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<tr>
<td>SDV</td>
<td>Source definition volume</td>
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<tr>
<td>sDVH</td>
<td>Spatial DVH</td>
</tr>
<tr>
<td>TD50</td>
<td>LKB NTCP parameter</td>
</tr>
<tr>
<td>TG43</td>
<td>AAPM Task Group Number 43</td>
</tr>
<tr>
<td>TPS</td>
<td>Treatment planning system</td>
</tr>
<tr>
<td>TROG</td>
<td>Trans-Tasman Radiation Oncology Group</td>
</tr>
<tr>
<td>V1</td>
<td>Rigid plus multi-pass DIR in VelocityAI</td>
</tr>
<tr>
<td>V2</td>
<td>Rigid plus scale plus multi-pass DIR in VelocityAI</td>
</tr>
<tr>
<td>V_X</td>
<td>Percentage of the rectal volume receiving at least X Gy after applying an α/β</td>
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<tr>
<td>VelocityAI</td>
<td>Velocity Advanced Imaging</td>
</tr>
<tr>
<td>Z</td>
<td>Z-value</td>
</tr>
<tr>
<td>zDVH</td>
<td>DVH modified to include axial spatial information</td>
</tr>
</tbody>
</table>
List of figures

2.1 A planning CT and rectum contour for high-dose-rate brachytherapy. 46
2.2 A planning CT and rectum contour for external beam radiotherapy. 46
2.3 A summary of the image processing, registration and evaluation process. 47
2.4 The Dice similarity coefficient results for registrations. 52
2.5 Average surface distance and Hausdorff results for registrations. 54
2.6 Ranking of registration methods according to image-similarity results. 55
S2.1 The high-dose-rate brachytherapy CT with and without image processing. 62
S2.2 The rigidly-registered external beam radiotherapy CT with and without image processing. 62
S2.3 Anatomy of the male pelvis. 63
S2.4 The medians of the percentage of voxels with a negative JAC after various registration methods. 65
S2.5 The results for the exact Wilcoxon signed-rank test of the pairwise differences in the JAC, MSE and MI metric values between various registration methods. 66
3.1 Examples of a four-field EBRT physical dose plan and HDR-BT TG43 physical dose plan. 83
3.2 Illustration and results for the three structure-overlap metrics used to assess registrations. 85
3.3 Example of the HDR-BT TG43 physical dose plan before and after registration. 87
3.4 Parameter-adding versus distribution-adding for an alpha-beta ratio of 3 Gy. 88
S3.1 An example of the heterogeneous dose regions of a four-field EBRT physical dose plan. 96
S3.2 A closer inspection of doses around the HDR-BT catheters to highlight high-dose regions. 97
S3.3 Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images. 98

XXX
4.1 Late peak toxicity grades for various toxicity types over the follow-up period (118 patients) .................................................. 114
4.2 Registration evaluation using the overlap of structures (118 patients). 116
4.3 Odds ratios from univariate ordinal regression of distribution-adding $V_X$ and peak late toxicity. ........................................... 118
4.4 Median distribution-adding $V_X$ for the toxicity and no toxicity groups.119
4.5 Median distribution-adding $D_{X\%}$ for the toxicity and no toxicity groups.120
S4.1 Example of a four-field EBRT physical dose plan with dose displayed as a colourwash. ......................................................... 136
S4.2 Example of a HDR-BT TG43 physical dose plan with dose displayed as a colourwash. ......................................................... 136
S4.3 Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images. ......................... 139
S4.4 Odds ratios from univariate ordinal regression of distribution-adding $V_X$ and peak late toxicity for completeness of evacuation and proctitis using $\alpha/\beta = 3$ Gy. ......................................................... 140
S4.5 Median distribution-adding $V_X$ for completeness of evacuation and proctitis using $\alpha/\beta = 3$ Gy. ................................. 140
S4.6 Median distribution-adding $D_{X\%}$ for completeness of evacuation, anorectal pain and proctitis using $\alpha/\beta = 3$ Gy. ................. 141
S4.7 Median parameter-adding $D_{X\%}$ for the toxicity and no toxicity groups using $\alpha/\beta = 3$ Gy. .............................................. 142
S4.8 Odds ratios from univariate ordinal regression of distribution-adding $V_X$ for $\alpha/\beta = 5.4$ Gy. .............................................. 143
S4.9 Median distribution-adding $V_X$ for the toxicity and no toxicity groups using $\alpha/\beta = 5.4$ Gy. .............................................. 144
S4.10 Median distribution-adding $D_{X\%}$ for the toxicity and no toxicity groups using $\alpha/\beta = 5.4$ Gy. ................................. 145
S4.11 Median parameter-adding $D_{X\%}$ for the toxicity and no toxicity groups using $\alpha/\beta = 5.4$ Gy. .............................................. 146
5.1 Late peak toxicity grades for various toxicity types over the follow-up period (891 patients). .................................................. 166
5.2 A comparison of the $m$, $n$, $TD50$ and alpha-beta ratio parameters for rectal bleeding in this study with other published studies. .......... 174

5.3 A comparison of the $m$, $n$ and $TD50$ parameters for non-bleeding toxicities in this study with other published studies. .......... 178

S5.1 Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images for combined EBRT/HDR-BT. ................................................................. 188

6.1 Late peak toxicity grades for various toxicity types over the follow-up period (118 patients). .............................................. 209

6.2 Structure overlap results for the 118 patients after the rigid plus multi-pass deformable image registration. ......................... 210

6.3 Median dose-surface maps for groups of patients assigned as having and not having a rectal bleeding, stool frequency and completeness of evacuation event. ................................. 217

6.4 Voxel-wise dose differences and odds ratio maps for rectal bleeding, stool frequency and completeness of evacuation. ........ 218

6.5 Voxel-wise dose differences and odds ratio maps for diarrhoea, anorectal pain, proctitis and urgency/tenesmus. .............. 219

S6.1 Example of a four-field EBRT physical dose plan with dose displayed as a colourwash. ...................................................... 229

S6.2 Example of a HDR-BT TG43 physical dose plan with dose displayed as a colourwash. ............................................................. 229

S6.3 Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images. .................. 232

S6.4 The process for constructing a 2D dose-surface map from a 3D surface dose. ................................................................. 233

S6.5 Example of an ellipse fit on a dose-surface map thresholded at 57 Gy. 234

S6.6 Median dose-surface maps for groups of patients assigned as having and not having a diarrhoea, anorectal pain, proctitis and urgency/tenesmus event. ................................. 235
S6.7 Odds ratios for measures calculated on dose-surface maps thresholded at various dose levels with patients assessed according to rectal bleeding, stool frequency and completeness of evacuation symptoms. . . . . . . 236

S6.8 Odds ratios for measures calculated on dose-surface maps thresholded at various dose levels with patients assessed according to diarrhoea, anorectal pain, proctitis and urgency/tenesmus symptoms. . . . . . . 237
List of tables

2.1 Registration comparisons via pairwise differences in the proportions of slices with the rectal alignment approved. 51

S2.1 A summary of the improvement in the Dice similarity coefficient, average surface distance and Hausdorff distance under various registration method comparisons. 64

S2.2 Results for Wilcoxon signed-rank tests of the pairwise differences in JAC, MI and MSE metric values among the various registration methods. 67

S2.3 Results for Wilcoxon signed-rank tests of the pairwise differences in the JAC metric values among the various registration methods. 68

S2.4 Results for Wilcoxon signed-rank tests of the pairwise differences in the MI and MSE metric values among the various registration methods. 69

S2.5 A summary of the registration comparison results for a smaller sample. 70

S2.6 A summary of the improvement in the Dice similarity coefficient, average surface distance and Hausdorff distance under various registration method comparisons for a smaller sample size. 70

S2.7 A summary of the improvement in the root-mean-squared error, mutual information and Jacobian determinant metrics under various registration method comparisons for a smaller sample size. 71

S3.1 The baseline clinical characteristics of 82 patients who underwent external beam radiotherapy followed by high-dose-rate brachytherapy for prostate cancer. 95

S3.2 Results of exact Wilcoxon signed-rank tests for parameter-adding versus distribution-adding. 99

4.1 Summary of which parameters (odds ratios, $V_X$ and $D_X\%$) correlate with toxicity. 121

4.2 Influence of the applied alpha-beta ratio on the findings for odds ratios, $V_X$ and $D_X\%$. 122

4.3 Summary of findings from previous studies and the current study for various late gastrointestinal toxicities. 124

XXXIV
S4.1 The baseline clinical characteristics of 118 patients who underwent external beam radiotherapy followed by high-dose-rate brachytherapy for prostate cancer. ........................................... 135
S4.2 Grading system for clinician-assessed toxicities. ............................. 137

5.1 Estimates and confidence intervals for parameters of the LKB NTCP model. ........................................................................................................... 170
5.2 Impact of a dose fractionation correction on parameters of the LKB NTCP model. .......................................................... 171

S5.1 The baseline clinical characteristics of 167 patients who underwent external beam radiotherapy followed by high-dose-rate brachytherapy for prostate cancer. ........................................... 183
S5.2 Grading system for clinician-assessed toxicities. ............................. 186

6.1 Features used to parameterise the spatial distribution. ....................... 213
6.2 Summary of DSM features which had considerable odds ratios. ....... 220

S6.1 The baseline clinical characteristics of 118 patients who underwent external beam radiotherapy followed by high-dose-rate brachytherapy for prostate cancer. ........................................... 228
S6.2 Grading system for clinician-assessed toxicities. ............................. 230

XXXV
Chapter 1:
General
introduction
1.1 Background and literature review

1.1.1 Prostate cancer

Cancer has had a considerable impact on society as it was the second leading cause of death for the year 2015 [1] and the leading cause of death in developed countries for the year 2004 [2]. In Australia, on average one in two males is expected to be diagnosed with cancer by the time he reaches 85 years of age and prostate cancer is the most commonly-diagnosed cancer [3]. Additionally, the impact of prostate cancer is considerable as it is the sixth most common cause of cancer death for men [4]. In developed countries, prostate cancer is primarily a cancer impacting on mature-aged males as approximately 75% of prostate cancer diagnoses occur for men aged 65 years or older [5]. Consequently, the burden from prostate cancer is expected to increase with population growth and aging of the population [4].

1.1.2 Radiation therapy treatments for prostate cancer

The treatment options for clinically-localised prostate cancer include watchful waiting, surgery (e.g. radical prostatectomy), radiation therapy and hormone therapy. The malignant cells can be effectively treated by radiation therapy (radiotherapy). However, the irradiation of a target at depth in the human body is also associated with the unavoidable irradiation of normal tissue cells which are also damaged by radiation. Consequently, the use of radiotherapy to eradicate tumour cells is limited by radiation toxicity in surrounding genitourinary and gastrointestinal anatomy.

One radiotherapy option is the sole use of external X-ray beams, which is commonly called external beam radiotherapy (EBRT). Two common types of EBRT are 3D Conformal Radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy (IMRT). A second treatment option is to combine EBRT with a ‘boost’ dose using brachytherapy [6], which involves the insertion of radioactive sources. A type of brachytherapy commonly used to deliver this ‘boost’ dose is high-dose-rate brachytherapy (HDR-BT), which involves the temporary insertion of a source(s) in needles that pass through the perineum and into the prostate. A third treatment option is low-dose-rate brachytherapy, which involves delivering a high dose to the tumour at a low-dose rate by permanently implanting radioactive seeds in
or around the tumour. Prostate cancer patients are also frequently treated with surgery followed by radiotherapy or radiotherapy with hormone therapy. Radiotherapy is included in the treatment of about a half of cancer patients with EBRT being the most common radiotherapy option.

The ten year mortality rates for prostate cancer patients treated with radiotherapy can be as high as 48% or as low as 0.8% depending on the treatment method, risk group, age and other clinical factors [7]. The survival rates are expected to increase with improving delivery of radiotherapy, increased consistency of treatment and an increasing focus on individualised treatments. Hence, long-term side effects as a result of radiotherapy damaging normal tissue cells are highly relevant given such survival rates and modern life expectancy. Consequently, the topic of this thesis considers late gastrointestinal toxicities due to the impact they have on long-term quality of life.

1.1.3 Side effects of prostate radiotherapy

Studies have found that higher radiation dose is associated with a lower quality of life if side effects are considerable [8]. Additionally, patients have demonstrated a preference for lower levels of side effects compared to a more aggressive treatment [9]. Consequently, the aim of radical radiotherapy is to maximise tumour control by ensuring adequate dose to the tumour while achieving an acceptable level of side effects by minimising the dose to other tissues/organs at risk. In terms of tumour control, escalating the dose to the tumour improves the freedom from biochemical and clinical progression [10–17]. However, it is impossible with current techniques and imaging to achieve adequate dose coverage of a prostate tumour without delivering some level of dose to the surrounding anatomy. Consequently, proctitis and rectal bleeding from irradiation of the rectum are limiting factors on the dose that can be delivered to the prostate [10, 14, 18]. Other commonly considered gastrointestinal and genitourinary toxicities from irradiation of the rectum and bladder include incontinence, urination frequency and dysuria [19]. Given the impact of toxicities on quality of life, constraints on the dose to organs at risk are usually applied (e.g. the maximum dose to an organ at risk or a constraint on the volume of the organ at risk that receives at least a certain dose) [19, 20].
In order to plan the treatment of the tumour and to consider dose to other tissues/organs at risk, images for regions that will receive considerable doses are acquired. A common method is the use of a computerised tomography (CT) or magnetic resonance imaging (MRI). The 3D image data sets are input to the treatment planning systems (TPS) along with the prescribed dosage to the tumour, other treatment factors and organ at risk constraints. Improvements in technology have allowed the dose to organs at risk to be reduced by increasing the conformity of dose to the tumour and sparing organs at risk [21, 22]. Technological improvements have included the use of better imaging and image guidance to ensure dose is primarily directed to the tumour in the presence of anatomical motion and set-up errors [21, 22]. Improving the delivery of radiotherapy is not the only consideration as there are a number of clinical factors which can influence the occurrence of toxicities [19, 23, 24]. Examples of clinical factors that may be relevant to the occurrence of gastrointestinal toxicities are use of anti-hypertensives, use of anti-coagulants, smoking, previous abdominal surgery, hypertension, diabetes and haemorrhoids [19, 20, 23, 24]. However, the focus of this thesis is dose-response as a current limitation of planning is that the use of dose constraints in a TPS ignores spatial information on the distribution of the dose.

1.1.4 Using a dose-volume histogram to assess a dose distribution

The TPS will output the proposed dose distribution and summarise the information from the dose distribution typically via dose-volume histograms (DVHs), dose-surface histograms (DSHs) or other dose-based histograms for the target and organs at risk. A differential DVH is a plot showing the percentage of the volume or absolute volume that receives a certain dosage. A cumulative DVH is a plot showing the percentage of the volume or absolute volume that receives at least a certain dose. Other types of dose-based histograms consider different regions of an organ at risk such as the wall. The DVH is commonly correlated with toxicity by finding those metrics which are different for groups of patients with and without complications or by determining the odds ratio (increase in the probability of a complication per unit increase in the value of the metric) [25]. For example, studies using DVH-based analysis have indicated that high doses are important for rectal bleeding observed after
EBRT and brachytherapy [19, 20, 25–29]. Reviews of such published DVH-based analysis has led to recommended dose constraints for organs at risk [19, 20].

Analysing metrics of the DVH is not the only method as studies have investigated a variety of methods for predicting normal tissue toxicity based on the whole DVH [20, 23, 30–36]. Different types of Normal Tissue Complication Probability (NTCP) models have been developed to relate the DVH to complication probabilities for organs at risk such as the logistic model, the Lyman-Kutcher-Burman (LKB) model and the relative seriality model [37, 38]. The LKB NTCP model has commonly been used to model gastrointestinal complications by calculating the probability of a complication based on the input of three parameters and the differential DVH from treatment [39–43]. For LKB models a generalised equivalent uniform dose ($gEUD$) or effective homogeneous dose ($D_{eff}$) providing the same complication probability as the non-uniform dose distributions can be calculated based on the DVH [43, 44]. The optimal parameter values for the LKB NTCP model have been reported for a variety of radiotherapy populations and toxicities [20, 24, 26, 42, 43, 45–56]. The parameters from various studies indicate that rectal bleeding is more influenced by high doses to the rectum than mean dose to the rectum [24, 26, 43, 46, 48, 51, 54, 55]. Appropriate parameter values have previously been proposed based on a meta-analysis of the optimal parameters reported by a variety of studies [20, 26]; however, the parameters should be validated for populations not included in such meta-analysis. Models based on NTCP incorporate a single scalar quantity representing the probability of a complication; however, TPS do not typically include the results of NTCP analysis when constraining the dose to organs at risk.

The inputs to the previously mentioned DVH-based and NTCP-based analyses do not contain spatial information from the dose distribution [57]. Consequently, the outputs from the DVH and NTCP methods do not indicate where low-dose regions or high-dose regions are located within the tumour or where high-dose regions are located within organs at risk [58]. Therefore, a TPS based on dose-volume constraints or even NTCP constraints for the DVH would not differentiate between dose distributions with different distributions of high-dose regions but identical DVHs. Similarly, the TPS does not differentiate between conjoint or disjoint high-dose regions. The lack of spatial information in a DVH could be significant as different
locations of high-dose regions on an organ at risk can lead to variations in toxicity outcomes [59, 60]. Additionally, the extent to which an area is a combination of conjoint high-dose regions versus high-dose regions separated by low-dose regions has been shown to be important [58, 61–63].

1.1.5 Modifications of dose-volume histograms to include spatial information

Methods have been developed to improve on the standard DVH-based analysis by performing the analysis for DVHs calculated over sub-regions of the organ at risk [25, 64]. However, the spatial information on the dose distribution for the sub-region of the organ at risk is ignored. Alternatively, several modified versions of the DVH have been proposed to include spatial information [38, 65–67]. The zDVH is a differential dose-volume histogram plotting the volume percentage versus CT slice position with a different curve for each isodose [65]. The zDVH includes axial spatial information; however, the location of high-dose and low-dose regions within each slice remains unknown. Relevant for the tumour is the DVSH which is a dose-volume scoring-function histogram where a scoring function indicates distance from the gross tumour volume edge to clinical tumour volume edge [66]. The DVSH is a plot of dose versus score with a colour scale along a curve indicating volume. Another improvement of the DVH came in the form of a spatial DVH referred to as the sDVH [38, 67]. The cumulative or differential sDVH displays the volume percentage plotted against dose with a colour code for each designated sub-volume of the tumour (and potentially the organ at risk). However, the location of low-dose and high-dose regions within each spherical sub-volume is not obtainable from the sDVH. All of the above improved methods or modifications to the DVH are constrained by a lack of information on the shape and relative location of high-dose and low-dose regions.

1.1.6 Alternatives to the DVH that include spatial information

The issue associated with the earlier mentioned methods which use a DVH is that at some level they assume homogeneous radio-sensitivity, lack spatial accuracy and do not incorporate radio-sensitive sub-regions of the organ at risk [64, 68]. Conse-
sequently, alternatives to the DVH consider certain spatial aspects of the dose distribution. One proposed method of this type is to parameterise the organ at risk prior to dose-line histogram analysis [69]. Another method involves relating distance-from-dose metrics to observed toxicity [61, 70]. More advanced methods consider the entire shape of the 3D dose distribution by relating the size of simulated clustering of damage from dose to observed toxicity [58, 63] or assess complications after simulated damage in terms of the number of functional units remaining [62]. In cluster and functional models a complication is predicted if the cluster size reaches a predetermined level of significance or if sufficient numbers of functional units are impaired. Differences in the shape of the dose distribution from patient to patient can also be directly compared by registering datasets to a common template followed by voxel-wise analysis [68, 71] or voxel-based principle component analysis [72]. However, the difficulty with applying such methods that consider the entire shape of the dose distribution is the computational complexity of the analysis and the difficulty of interpreting and applying the results.

A method which has been useful for explaining gastrointestinal toxicity in terms of spatial information and is easier to interpret than the above methods is the dose-surface map (DSM) for an organ at risk (e.g. rectum) [57, 59, 60, 63, 73–77]. A DSM is generated by virtually unfolding the 3D surface dose slice by slice into a 2D dose-surface map. Consequently, DSMs are only appropriate for organs where the tissue which is expected to be responsible for dose-response has a 2D topology (e.g. cylindrical). The vertical axis of a DSM contains the axial slice location in the inferior to superior direction. The horizontal axis contains surface locations for each inferior-superior level (e.g. posterior, right, anterior, left and back to posterior). The dose at surface locations is indicated in the DSM through a colourwash. DSMs have the ability to identify differences in accumulated doses that are not revealed by DVH-based analysis [78] and to add predictive power to the standard DVH-based analysis [57]. Comparing DSMs from patient to patient is also easier to interpret than comparing the 3D doses. One method for assessing spatial features of a DSM involves thresholding the DSM at different dose levels [76] via 0-valued pixels for doses less than the chosen level and 1-valued pixels for doses of at least the chosen level. The shape of 1-valued pixel clusters for each dose level is characterised by
fitting an ellipse to the cluster. The shape of the cluster for each dose level can be summarised through longitudinal extent, lateral extent and eccentricity of the ellipse fit. The results of Buettner et al. [76] for the application of this method indicate that low doses beyond the superior end of the rectum may be important for loose stools. Another method for assessing spatial features of a DSM is to analyse different regions of the DSM for an organ at risk [59, 60]. For example, the mean dose in different regions can be calculated or the height, width and location of isodose curves can be determined. This analysis can be conducted for patients with toxicity and then for patients without toxicity. Comparison of the analysis for patients with and without toxicity allows toxicities to be related to spatial aspects of DSMs. For example, analysis by Gianolini et al. [59] indicated that the superior portion of the rectum may be important for rectal incontinence. One complication when undertaking such spatial or dose-volume analysis for EBRT combined with a HDR-BT boost dose is how to incorporate the doses delivered with different dose per fraction for each phase.

1.1.7 Adjusting for different dose fractionation

Treatments such as combined EBRT/HDR-BT are complicated by the dose being delivered with different dose per fraction for each phase as the response of tumours and normal tissue to a dose has been shown to be dependent on dose delivered per fractionation, the total number of fractions, treatment duration and other factors [79]. The linear-quadratic (LQ) model is commonly used to model the fractionation sensitivity and other common dose-response factors [79–81]. In order to compare treatment plans involving different fraction regimes the dose data have to be converted to isoeffective doses such as equieffective dose in 2 Gy fractions ($EQD_{2α/β}$ Gy) using the LQ model with an appropriate alpha/beta ratio ($α/β$) [82]. Equation (1.1) is the Withers formula [83] for converting total dose $D$ Gy in $d$ Gy per fraction to equieffective total dose $EQDX_{α/β}$ Gy in $X$ Gy per fraction and assumes complete recovery between fractions with the same overall treatment time.

$$EQDX_{α/β} = D \frac{d + α/β}{X + α/β}$$  \hspace{1cm} (1.1)
The formula requires knowing or determining the appropriate $\alpha/\beta$, a ratio of empirical fitting parameters, for the organ at risk [84]. For late rectal bleeding, the recommended $\alpha/\beta$ is 3 Gy [26, 85]; however, the upper limit reported by other studies is around 4.8-5.4 Gy [45, 86]. Converting dose to equivalent dose fraction schemes is also important in general as the number of fractions, the dose delivered per fraction and the period over which all fractions are given varies from institution to institution and across different radiotherapy techniques such as EBRT and HDR-BT. For combined EBRT/HDR-BT, adjusting doses to 2 Gy per fraction is not the only issue as after the doses are adjusted for dose fractionation the concern is how to accumulate the doses from phases of the combined treatment.

1.1.8 Accumulating dose

The discrepancy between planned dose and delivered dose confounds previously published correlations between planned dose-volume parameters and observed toxicities [87, 88]. Hence, there has been an interest in developing methods for accumulating dose given in fractions or across phases of combined EBRT/HDR-BT [88–93]. For combined treatments, the anatomy in CTs may not coincide due to motion and variations in reference coordinate systems. One method for dealing with anatomical differences is to assume that the same volumes will receive the high doses and then to crudely sum DVH parameters (commonly called parameter-adding) [87]. However, such an assumption does not always represent a ‘worst case’ as it is possible that a volume planned to receive a specific dose from one component could receive a higher dose after adjustments for motion [87, 94] and/or intra/inter-observer contouring errors [95, 96]. Studies have attempted to manage anatomical differences between rectal anatomy in EBRT and HDR-BT planning CTs by post-planning the brachytherapy on the EBRT planning CT [97] or rigidly-registering the CTs prior to dose summation [91, 98]. However, non-rigid registration, also called deformable image registration (DIR), prior to dose summation has been recommended due to deformations and shrinkage of anatomy [92, 97, 99–102]. However, 3D summation of the deformed dose distributions (commonly called distribution-adding) [88, 103]
can only be used reliably when DIR is considered to be adequate [104].

The topic of evaluating DIR algorithms is maturing with many methods having already been proposed [105–110]. One example is evaluating registrations experimentally using deformed phantoms or image modification to include known deformations [111, 112]. The agreement between the manually-delineated structure for one CT and the DIR applied to the manually-delineated structure from the other CT is another assessment tool for DIR [105, 113]. Additionally, the reliability of DIR has been checked in terms of metrics assessing the displacement vector field and the similarity between one image and the deformed image [107]. Ultimately, clinical checks of the post-registration anatomical alignment are required for the approval of DIR in clinical situations [109, 114]. Many more evaluation methods have been proposed in recent times (e.g. [115, 116]). However, one evaluation type may be more appropriate in certain situations as there is no known ground truth when registering clinical images with anatomical differences [105, 107].

Registering the EBRT dataset to the HDR-BT dataset for combined treatments allows the datasets to be combined accurately as at the time of planning; however, inter/intra-fraction and transient rectal contents will affect the delivered dose distributions [76, 78, 87, 117–126]. It has been suggested that motion will affect current models based on spatial information from DSMs less than models based on DVHs/NTCP models [127]. The reason given is that current DSM-based methods parameterise the general shape of the DSM and the general shape is unlikely to be changed by motion. It is expected that the influence of such motion will depend on the stringency of the protocol and quality assurance for treatments.

1.2 Information on the RADAR trial

This study includes data for 891 prostate cancer patients who were accrued to the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial from 23 centres across Australia and New Zealand during the period 2003 to 2008 [128–130]. The trial registration number at ClinicalTrials.gov is NCT00193856 [131]. The RADAR trial was a phase 3 trial examining the influence of neoadjuvant androgen suppression with or without bisphosphonate treatment therapy along with all patients receiving adjuvant radio-
therapy. Centres had the option of delivering radiotherapy to each patient using EBRT or EBRT followed by a HDR-BT boost.

A 2 × 2 factorial design was used for the RADAR trial, which had specific eligibility criteria:

- Non-metastatic prostate adenocarcinoma.
- Tumour T-stage T2b-4.
- T-stage T2a if Gleason score ≥ 7 and prostate-specific antigen concentration ≥ 10 µg/L.
- No history of lymph node or systematic metastases or co-morbidities that leads to a life expectancy of less than five years.
- Patients randomised to short-term (six months) neoadjuvant androgen suppression (22.5 mg of leuprorelin intramuscularly administered every three months) or intermediate-term (18 months) neoadjuvant androgen suppression with or without 18 months of zoledronic acid (4 mg intravenously administered every three months).
- Radiotherapy started within five months of randomisation.

The patient criteria, treatment methodology and extensive quality assessments for the RADAR trial have previously been reported in detail [25, 128–134]. The main aspects of the treatment and patient follow-up are described below.

### 1.2.1 External beam radiotherapy followed by high-dose-rate brachytherapy

167 of the 891 patients included in this study were treated with EBRT followed by HDR-BT at Sir Charles Gairdner Hospital in the period 2004 to 2008. Patient criteria and treatment methodology for patients receiving combined EBRT/HDR-BT were as specied for the RADAR trial [128–130] and no patient had artificial hip joints.

The EBRT prescription dose to the prostate was 46 Gy to the International Commission on Radiation Units and Measurements 50 reference point (23 daily fractions of conventional fractionation over five weeks). The four-field three-dimensional
EBRT plan was created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden) based on the EBRT planning CT with the patient in the supine position. The combined EBRT/HDR-BT treatment process has previously been reported [120].

The HDR-BT was typically started two to five weeks after the end of EBRT. The HDR-BT treatment preparation involved the temporary insertion of metal needle HDR-BT catheters through the guidance of trans-rectal ultrasound, fluoroscopy and a perineal template while the patient was in the lithotomy position. Cystoscopy was used to ensure proper tenting of the bladder wall mucosa by catheters. The plastic template was sutured to the skin to hold the needles in place. After insertion, the HDR-BT planning CT was acquired. The HDR-BT treatment plan was created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US) based on the HDR-BT planning CT. The HDR-BT prescription dose to the prostate was 19.5 Gy delivered in three fractions using an Iridium-192 radioactive source controlled through an after-loader (Varian Oncology Systems) and covered the prostate gland and any extracapsular extensions. The HDR-BT doses were calculated by the TG43 algorithm [135]. The planned dose to the rectum from HDR-BT was limited to a maximum of 80% of the 19.5 Gy prescription dose. The HDR-BT was delivered in three fractions of 6.5 Gy across two days with the trial guidelines stipulating a maximum delivery time of 90 minutes for each fraction and a minimum of six hours between fractions. Patients were in the lithotomy position for HDR-BT treatment with cushions used to keep the patients legs in the abducted position between fractions. Reproducibility of needle positions before each fraction was ensured via reference to fiducial markers implanted before the first fraction [120].

The EBRT planning target volume (PTV) and HDR-BT source definition volume (SDV) were obtained by expanding the corresponding clinical target volume (CTV) by a 10 mm margin. The HDR-BT SDV was used to restrict dwell positions to the lengths of identified catheters covered by the SDV. The external wall of the rectum was manually delineated by treating-clinicians in the HDR-BT CTs using BrachyVision and in the EBRT CTs using the Elekta Focal contouring system (Elekta AB, Stockholm, Sweden). For rectum contouring, the inferior-superior limits of the rectum were the rectosigmoid flexure and the last slice where the ischial
tuberosities were visible.

1.2.2 External beam radiotherapy

Seven hundred and twenty-four of the 891 patients included in this study were treated with EBRT only to 66, 70 or 74 Gy (International Commission on Radiation Units and Measurements 50 reference point) across 23 centres in the period 2003 to 2008 as part of the RADAR trial [128–130]. The allowed prescription dose was 66, 70, 74 or 78 Gy; however, no patients were treated with a prescribed dose of 78 Gy. Dose-escalation was regulated as centres had to satisfy dose delivery accuracy criteria for the various prescribed doses and the stringency of the criteria increased with dose escalation. The prescription dose could be delivered in up to two phases with daily conventional fractions. Beam energy was required to be 6 MV or greater (with most delivered using 18 MV). Patient setup orientation could be prone or supine (with most in the supine position). Treatment was delivered with at least three fields (with most delivered using four fields). The dose calculation algorithms were mostly convolution, generalised pencil-beam and collapsed-cone convolution [136]. The volume of the rectum receiving at least 65, 70 and 75 Gy was constrained to at most 40%, 30%, and 5% respectively. The external wall of the rectum was manually delineated using the same definition as described earlier. The planning, treatment, patient and quality assurance details for EBRT have previously been analysed and reported in detail [25, 128–134].

1.2.3 Toxicity assessments

Patients were assessed for various gastrointestinal toxicities at baseline (randomisation) and subsequent time points after randomisation (e.g. 3, 6, 9, 12, 15, 18, 24, 30, 36, 42, 48, 54, 60, 72, 84, 96, 108 months). The median for the most recent follow-ups was 72 months (range 58-108 months) for patients receiving EBRT only and 72 months (range 12-96 months) for patients receiving combined EBRT/HDR-BT. The Late Effects of Normal Tissue - Subjective, Objective, Management and Analytic (LENT-SOMA) scales were used to assess rectal bleeding, urgency/tenesmus, stool frequency, diarrhoea, anorectal pain and completeness of evacuation [137]. Proctitis was scored by clinicians according to the Common Toxicity Criteria for Adverse
1.3 Novel aims of the study

The previous sections have detailed the impact that gastrointestinal complications have on a patients’ quality of life and the associated limitations it places on the dose that can be delivered to the prostate. Consequently, the general aim of this study was to use data from the RADAR trial to model how the distribution of dose to the rectum from combined prostate EBRT/HDR-BT relates to observed late gastrointestinal complications. As described below, relating the dose from treatment to observed complications was a three stage process with each stage containing more specific aims. The studies for the aims described below were undertaken with data that was available at the time of the study.

1.3.1 Stage I: Advanced methods to accumulate the planned dose for EBRT followed by HDR-BT

Accumulated rectal dose for combined EBRT/HDR-BT can be obtained by parameter-adding or DIR followed by distribution-adding. Parameter-adding relies on an assumption that the same volumes will receive the high doses and distribution-adding relies on DIR being sufficiently accurate. For DIR, publications are lacking in the context of registering a HDR-BT CT to a EBRT CT for patients receiving combined prostate EBRT/HDR-BT. Image-intensity based DIR algorithms that may be applied to such CTs in distribution-adding are susceptible to errors when there are major image differences [139]. This application is problematic given that the discrepancies between the CTs include varying amounts of bowel gas, rectal filling and general artefacts. Additionally, only the HDR-BT CT contains the HDR-BT needles, streak artefacts off the needles, low CT number pixels around the needles and rectal packing materials. Given the uniqueness of DIR for combined prostate EBRT/HDR-BT, one aim of the thesis was to comparatively evaluate deformable registration methods that were available to our research group for registering the rectums in EBRT and HDR-BT CTs of prostate cancer patients. Chapter 2 is the first published study to undertake such evaluations for combined prostate EBRT/HDR-BT.
A second aim of the thesis was to compare the accumulated rectal dose via the parameter-adding and distribution-adding methods. Studies have commonly compared parameter-adding dose with distribution-adding dose in the context of combined EBRT/HDR-BT for gynaecological cancers [92, 93, 100, 140–143]; however, equivalent studies for combined prostate EBRT/HDR-BT are lacking. The study in Chapter 3 would be the first published study to compare the parameter-adding and distribution-adding methods for accumulating rectal doses of prostate cancer patients treated with combined EBRT/HDR-BT as previously published methods did not use DIR [78, 91, 97, 144]. The focus of the studies in Chapters 2 and 3 is the rectum due to subsequent analysis on correlating accumulated rectal doses with gastrointestinal toxicities observed after combined prostate EBRT/HDR-BT.

1.3.2 Stage II: Associating dose-volume metrics from planned dose with symptoms

Treatment plans are clinically assessed in terms of DVH metrics and subsequent constraints which are associated with acceptable levels of normal tissue toxicity [26]. However, the complication for combined EBRT/HDR-BT is that the phases are planned separately [145] and constraints on the total planned dose from the two phases would be more appropriate for reducing normal tissue toxicity [27]. Constraints could be applied for each phase; however, as described earlier, the recommendation is to use deformable registration to obtain accumulated dose due to the anatomical differences between the planning CTs [97, 99–102]. Publications are lacking in the context of the impact of deformable registration on the correlation between DVH parameters and observed gastrointestinal toxicities after combined prostate EBRT/HDR-BT. Consequently, the aim of Chapter 4 is to correlate the rectal DVH after deformable registration with gastrointestinal toxicities observed after combined EBRT/HDR-BT. Chapter 4 will be the first published study for combined prostate EBRT/HDR-BT to outline which rectal DVH metrics obtained by the registration-based method were associated with gastrointestinal toxicities and to compare those findings with the analysis repeated for metrics obtained by the simple parameter-adding method.

Another method for associating dose-volume metrics with observed complications
is to fit the LKB NTCP model to the observed complications. The optimal LKB NTCP parameters vary across radiotherapy populations and there is a lack of studies proposing optimal parameter values for Australian and New Zealand prostate cancer patients treated with 3D conformal EBRT or combined EBRT/HDR-BT. The difficulty of applying the LKB NTCP model to combined EBRT/HDR-BT is that the phases of combined EBRT/HDR-BT are planned separately with separate DVHs [145]. As described earlier, the accumulated dose for combined EBRT/HDR-BT should be obtained using deformable registration due to variations in reference coordinate systems, displacements, deformations and shrinkage [87, 97, 100, 101]. The aim of the study in Chapter 5 was to use RADAR trial data to obtain estimates of the LKB NTCP fitting parameters for various types of gastrointestinal complications observed after combined EBRT/HDR-BT and to compare the estimates with the values determined for complications observed after EBRT only. Conceptually, the doses for different fraction schedules should also be converted to $EQD_{2,\alpha/\beta}$ Gy, at a specific ratio of the $\alpha$ and $\beta$ parameters from the LQ model of response, as this adjusts for the biologically non-equivalent fractionation schedules [82, 88, 97]. However, studies have reported that dose fraction corrections are not always useful, at least when applied to NTCP models, as dose fractionation corrections have not significantly improved the model [45, 46]. Consequently, Chapter 5 includes a correction for the different dose fractions of EBRT and HDR-BT by including the LQ model with the aim of obtaining the optimal alpha-beta ratio. The study in Chapter 5 would be the first study obtaining LKB NTCP estimates for combined prostate EBRT/HDR-BT. Additionally, it would be the first LKB NTCP study to investigate the impact of accumulating rectal dose from phases of a combined EBRT/HDR-BT prostate treatment by applying deformable registration.

1.3.3 Stage III: Using novel methods to relate spatial features of dose distributions to symptoms

Methods that correlate DVH metrics with complications or fit NTCP models to complications are neglecting spatial information for the dose distribution and the spatial arrangement of dose has been shown to influence complications [58–63, 76]. As described earlier, one method for including spatial information is to obtain 2D
dose-surface maps for the 3D rectal surface dose by virtually unfolding the rectum. For combined EBRT/HDR-BT, dose-surface maps should be obtained after dose is accumulated using deformable registration as the maps for each phase may not be aligned due to deformations, shrinkage and contouring errors [87, 95-97, 100, 101]. The aim of Chapter 6 is to relate regional (voxel-wise) features of dose-surface maps and parameterised spatial patterns to gastrointestinal complications observed after combined prostate EBRT/HDR-BT. The study in Chapter 6 would be the first published study to report dose-surface maps for combined prostate EBRT/HDR-BT and to compare findings with those from previously published studies for prostate EBRT [59, 60, 76]. Additionally, it would be the first published study reporting on dose-surface maps obtained after deformable registration. Chapter 6 also explores a number of novel ways of characterising the shapes of clusters formed by thresholding dose-surface maps.

1.4 References


K. Chao, A. I. Blanco, and J. F. Dempsey, “A conceptual model integrating spatial information to assess target volume coverage for IMRT treatment


Stage I:
Advanced methods to accumulate the planned dose for EBRT followed by HDR-BT
Chapter 2:
Image registration
2.1 Foreword for manuscript

One option for accumulating planned dose for phases of combined prostate external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) is to register the planning CTs and sum the registered doses voxel-by-voxel. This option would adjust for the anatomical differences between the planning CTs by considering shrinkage and deformation. However, there exist many registration algorithms for registering images with variable performance amongst different algorithms for the same registration circumstance and the performance of a specific algorithm varying according to the registration circumstance. Consequently, the performance of registration algorithms should be evaluated for the specific registration application before the deformed doses are used.

The published paper included in this chapter evaluates the deformable registration algorithms available to our research group at the time patient data reached a large enough sample size for a registration study. The intention of the published paper was to gather evidence for selecting the most appropriate registration algorithms available for registering the rectums in the EBRT and HDR-BT CTs. The focus was on the registration performance for the rectum as the general aim of this thesis is to relate rectal dose to gastrointestinal toxicities observed after combined prostate EBRT/HDR-BT. Deformable registration has been a popular topic in recent years. Consequently, many more registration algorithms have been developed for registering the rectum in images since this study was initially completed. Similarly, many different methods of evaluating deformable registration have been developed. It is expected that deformable registration will continue to develop and users need to be mindful of the way they evaluate any changes in algorithms as new versions of applications may require other types of evaluations.


2.2 Manuscript details

Registering prostate external beam radiotherapy with a boost from high-dose-rate brachytherapy: a comparative evaluation of deformable registration algorithms.


Publication status: Published. The manuscript in this chapter (including supplements) is a typeset of the final published article. The inclusion of published material in this chapter is allowed by the copyright agreement for the final published article [1].

2.3 Abstract

2.3.1 Background
Registering CTs for patients receiving external beam radiotherapy (EBRT) with a boost dose from high-dose-rate brachytherapy (HDR-BT) can be challenging due to considerable image discrepancies (e.g. rectal fillings, HDR-BT needles, HDR-BT artefacts and HDR-BT rectal packing materials). This study is the first to comparatively evaluate image processing and registration methods used to register the rectums in EBRT and HDR-BT CTs of prostate cancer patients. The focus is on the rectum due to planned future analysis of rectal dose-volume response.

2.3.2 Methods
For 64 patients, the EBRT CT was retrospectively registered to the HDR-BT CT with rigid registration and non-rigid registration methods in VelocityAI. Alternative non-rigid registration methods were applied in the software suite for Deformable Image Registration and Adaptive Radiotherapy Research (DIRART) using the Horn-Schunck optical flow and Demons algorithms. Image processing was undertaken on the HDR-BT CT and the rigidly-registered EBRT CT prior to the alternative non-rigid registrations in DIRART. The propagated EBRT-rectum structures were compared with the HDR-BT structure using the Dice similarity coefficient (DSC), Hausdorff distance (HD) and average surface distance (ASD). The image similarity was compared using mutual information (MI) and root-mean-squared error (MSE). The displacement vector field was assessed via the Jacobian determinant (JAC). The post-registration alignments of rectums for 21 patients were visually assessed.

2.3.3 Results
The greatest improvement in the median DSC relative to the rigid registration result was 35% for the Horn-Schunck algorithm with image processing. This algorithm also provided the best ASD results. The VelocityAI algorithms provided superior HD, MI, MSE and JAC results. The visual assessment indicated that the rigid plus deformable multi-pass method within VelocityAI resulted in the best rectal alignment.
2.3.4 Conclusions

The DSC, ASD and HD improved significantly relative to the rigid registration result if image processing was applied prior to DIRART non-rigid registrations, whereas VelocityAI without image processing provided significant improvements. Reliance on a single rectal structure-correspondence metric would have been misleading as the metrics were inconsistent with one another and visual assessments. It was important to calculate metrics for a restricted region covering the organ of interest. Overall, VelocityAI generated the best registrations for the rectum according to the visual assessment, HD, MI, MSE and JAC results.
2.4 Introduction

Radiotherapy dose-volume parameters for specific organs have been associated with normal tissue toxicity [2]. However, the correlation between planned dose-volume parameters and observed toxicities is confounded by how well the planned dose reflects the dose delivered [3]. Hence, studies have focused on developing methods for accumulating dose from daily fractions [4] or combined treatments [5, 6].

Therapies with different fractionation can be adjusted for fractionation effects by converting to equieffective dose given in 2 Gy fractions ($EQD_{2\alpha/\beta}$ Gy) [5, 7]. However, the anatomy in CTs may not coincide due to motion and variations in reference coordinate systems. Consequently, a ‘worst case’ assumption that the same volumes will receive the high doses is not necessarily valid, as it is possible that a volume planned to receive a specific dose from one component could receive a different dose after adjustments for motion [8]. A rigid registration is not sufficient as non-rigid registration, also called deformable image registration (DIR), is required due to deformations and shrinkage [6]. A total dose distribution could be obtained after DIR by performing voxel-by-voxel summation of the $EQD_{2\alpha/\beta}$ doses [5, 9]. Combining dose without applying DIR via post-planning the brachytherapy on the external beam radiotherapy (EBRT) planning CT has been explored [10] and is subject to whether post-planning the brachytherapy dose is adequate given anatomy changes.

The accuracies of DIR algorithms have been examined experimentally using deformed phantoms or image modification to include deformations [11, 12]. The reliability of DIR has been examined for each patient by checking the agreement between the manually-delineated structure for one CT and the DIR applied to the manually-delineated structure from the other CT [13, 14]. Clinical checks of the post-registration anatomical alignment can also be used [15, 16]. Additionally, metrics assessing the displacement vector field (DVF) and the similarity between one image and the deformed image have been proposed as tools for assessing the reliability of DIR [17]. One evaluation type may be more appropriate in certain situations [13, 17]. The deformed dose distribution can be used reliably when DIR is considered to be adequate [18].

Publications are lacking in the context of registering an EBRT pelvic CT to a
high-dose-rate brachytherapy (HDR-BT) pelvic CT. Image-intensity-based DIR algorithms applied to such CTs are susceptible to errors when there are major image differences [19]. This application is problematic given that the time between the HDR-BT and EBRT planning CTs can be months. The discrepancies between the CTs include varying amounts of bowel gas, rectal filling and general artefacts. Additionally, only the HDR-BT CT contains the HDR-BT needles, streak artefacts off the needles, low CT number pixels around the needles and rectal packing materials.

This study examines the performance of image processing and non-rigid registration tasks available in commercial software and customisations to an open-source package when applied to register the rectums in prostate EBRT and HDR-BT data. Specifically, how they performed in terms of the Dice similarity coefficient [13], Hausdorff distance [13], average surface distance [13], root-mean-squared error [13], mutual information [20], Jacobian determinant [13] and visual assessment [15]. We focus on the rectum due to planned future analysis of rectal dose-volume response for combined EBRT/HDR-BT prostate treatment.

2.5 Patient data

This study used treatment plans for 64 prostate cancer patients who were treated with EBRT followed by a boost dose from Iridium-192 HDR-BT via after-loading hollow metal needles at Sir Charles Gairdner Hospital in the period 2004 to 2008. Patient criteria and treatment methodology were as specified for the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [21, 22]. A planning CT was acquired at the start of each treatment component (e.g. Figures 2.1 and 2.2). The number of slices (EBRT 32-77, HDR-BT 32-59) and the voxel spacing (EBRT 0.809-0.977 mm, HDR-BT 0.242-0.566 mm) for the CTs varied; however, there was a common slice thickness (3 mm) and dimension (512 by 512 pixels).

The external wall of the rectum was manually delineated by treating clinicians in the EBRT CTs using the Elekta Focal treatment planning software (Elekta AB, Stockholm, Sweden) and in the HDR-BT CTs using the BrachyVision treatment planning software (Varian Medical Systems, Palo Alto, US). Outlines of the rectum were reviewed (by author MK) for consistency between patients. The superior border
of the rectal structures in the EBRT CTs were defined by the level that the rectum
turns horizontally into the sigmoid colon and the inferior border defined on the most
inferior axial image slice on which the ischial tuberosities were visible. Any further
references to rectal ‘structure’ refer to the 3D manual outline of the external rectal wall, while ‘contour’ refers to the 2D section of this outline on a particular image slice.

2.6 Methods

Figure 2.3 illustrates the registration and evaluation process detailed in this section.

2.6.1 Rigid registration

A manual rigid registration (global translations and rotations) was performed in Velocity Advanced Imaging 2.8.1 (Varian Medical Systems, Palo Alto, US) to align the bony anatomy in the EBRT and HDR-BT planning CTs. An automatic rigid registration was then performed to optimise the registration.
Copies of the HDR-BT CT, the re-sampled rigidly-registered EBRT CT and the rectum structures from the HDR-BT and rigidly-registered EBRT CTs were exported from Velocity Advanced Imaging (VelocityAI) in DICOM format for further image preprocessing in other applications. The other applications included MATLAB™ R2010a (The MathWorks Inc., Massachusetts, US), Computational Environment for Radiotherapy Research (CERR) version 4.1 [23] and Deformable Image Registration and Adaptive Radiotherapy Research (DIRART) version 1.0a [24]. At the time of export the rigidly-registered EBRT CTs were re-sampled to have the same voxel sizes and dimensions as the HDR-BT CTs (see earlier section on patient data), which covered a smaller field-of-view.

2.6.2 Image preprocessing

Prior to DIR in DIRART the image processing detailed below was applied as the image processing led to a considerably improved post-registration alignment of the rectum. Figures S2.1 and S2.2 in Supplement 2A provide examples of slices of the final HDR-BT and rigidly-registered EBRT CTs after image processing. The image processing steps are explained in detail in Supplement 2A. The key components are:

1. The HDR-BT needles, HDR-BT rectal-packing material and HDR-BT low CT number artefacts for the rectum were replaced with the average CT number of neighbouring tissue pixels.

2. A Gaussian smoothing and blurring process was applied to avoid features in the HDR-BT image caused by the previous pixel adjustments.

3. Rectal painting [15] with a uniform high CT number (2500) was applied to the final HDR-BT and rigidly-registered EBRT CTs.

2.6.3 Non-rigid registration (deformable image registration)

Image processing was not applied prior to DIR in VelocityAI as the post-registration alignment in VelocityAI was reasonable relative to registrations obtained in DIRART without image processing. The multi-pass DIRs in VelocityAI (version 2.8.1) were based on the B-spline algorithm with the Mattes mutual information metric [25]. Additionally, non-rigid registrations in VelocityAI were performed by applying
a global-scale registration immediately before DIR. The VelocityAI methods were rigid, rigid plus multi-pass DIR (V1) and rigid plus scale plus multi-pass DIR (V2).

The DIR in DIRART was applied to the EBRT rigidly-registered CT and the HDR-BT CT after image processing as this led to a considerably-improved post-registration alignment for the rectum and made it more comparable with the VelocityAI alignments. The original Demons and original Horn-Schunck optical flow (HSOF) algorithms were used. These DIRs use the root of the mean of the squared-intensity differences as the image-similarity metric [24]. The default settings in DIRART were used [24, 25]. The image processing and DIRs applied in DIRART were rigid plus image-processing plus HSOF-DIR (HS) and rigid plus image-processing plus Demons-DIR (D).

2.6.4 Visual assessments

The anatomical alignment for 64 patients was initially inspected by the researcher running each registration (author CRM). The post-DIR anatomical alignments for 21 of the 64 patients were inspected by a combination of in-training (author VL) and experienced (author CIT) radiation oncologists. The alignment between the rectums in the HDR-BT CT and the registered EBRT CT was graded slice-by-slice using the spyglass tool in VelocityAI. The grades were ‘approved’, ‘indifferent’ or ‘unapproved’. The grading was based on whether the misalignment was clinically relevant and was similar to the situation where an observer has to decide if a contour is sufficiently inconsistent with anatomy to warrant re-contouring. The results were assessed by calculating the proportion of slices with grades of the ‘approved’ type.

2.6.5 Structure-correspondence metrics

The Dice similarity coefficient (DSC) was calculated as the volume of overlap of the two structures and normalized by the average volume of the structures. The DSC range is zero (no overlap) to one (perfect overlap) [13]. The Hausdorff distance (HD) was calculated as the maximum of the distances from a point on one 3D structure to the closest point on the other 3D structure [13]. The average surface distance (ASD) was calculated as the average of the distances from a point on one 3D structure to the closest point on the other 3D structure [13]. Due to considerable differences in
the slice span of the rectal structures for the HDR-BT and EBRT CTs, these metrics were calculated over slices where the HDR-BT (fixed image) rectal structure existed.

2.6.6 Image-similarity metrics

Image similarity was examined via the percentage increase (decrease) in the image-similarity (dissimilarity) metric relative to that before the registration. The mutual information (MI) was used for similarity and the root of the mean-squared error (MSE) for dissimilarity [13, 20]. Using these two metrics ensured assessment with at least one image-similarity metric that was different to the metric used in the DIR algorithm to optimise the registration.

2.6.7 Displacement-vector-field metric

Physically unachievable organ deformations are indicated by negative Jacobian determinants (JAC) of the DVF [13]. Consequently, the physically-unachievable characteristics of the DVF can be summarised via the percentage of voxels with a negative JAC.

2.6.8 Statistical analysis

Paired percentage differences between the absolute DSC/ASD/HD results for different registration comparisons were tested for significance via exact Wilcoxon signed-rank tests against a zero median. The percentage JAC metric and the proportion of approved rectal-alignments for different registration comparisons were expressed in absolute difference and subject to the same test. Quantile-quantile plots showed that differences were not normally distributed. The tests were performed in R (version 2.15.2) [26] using the Coin package [27] and the Pratt method for zeros [28]. P-values were considered significant if less than 0.05.

2.7 Results

2.7.1 Visual assessments

The major misalignments after DIR were observed around the pubic symphysis, ischium near the inferior extent of the obturator foramen, superior ramus of pubis
near the obturator canal, coccyx, medial aspect of the acetabulum and anterior side of the rectum (see Figure S2.3 in Supplement 2B for labeling of anatomy).

**Table 2.1:** Registration comparisons via pairwise differences in the proportions of slices with the rectal alignment approved. N is the number of patients to whom the registrations were applied. The pairwise difference is calculated as the first mentioned registration minus the second mentioned registration. The Z-value and p-value are from the Wilcoxon signed-rank test of the pairwise differences against a median of zero (this test is not appropriate when the median difference is zero). A significant negative difference indicates the second mentioned registration is superior. See the methods section for information about D, HS, V1 and V2.

<table>
<thead>
<tr>
<th>Registration Comparison</th>
<th>N Patients</th>
<th>Comparison of Rectal Approval-proportion</th>
<th>Median Difference</th>
<th>Z-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V2 versus V1</td>
<td>21</td>
<td>Comparison of Rectal Approval-proportion</td>
<td>-0.032</td>
<td>-3.44</td>
<td>0.0002</td>
</tr>
<tr>
<td>HS versus V1</td>
<td>21</td>
<td>-0.169</td>
<td>-3.84</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HS versus V2</td>
<td>21</td>
<td>-0.124</td>
<td>-3.22</td>
<td></td>
<td>0.0006</td>
</tr>
<tr>
<td>D versus V1</td>
<td>21</td>
<td>-0.241</td>
<td>-4.02</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D versus V2</td>
<td>21</td>
<td>-0.189</td>
<td>-4.00</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D versus HS</td>
<td>21</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

The medians of pairwise differences in the proportions of slices with the alignment of the rectum approved for various DIR comparisons of the V1, V2, D and HS methods are provided in Table 2.1. According to the median differences in rectal approval-proportions between registrations, the most useful to least useful alignments came from the V1, V2 and D/HS methods respectively. The median approval-proportions for the V1, V2, D and HS methods were 0.626, 0.574, 0.385 and 0.385 respectively.

The registration package providing the best registration of the rectum according to the other metrics detailed in the following sections was consistent irrespective of whether the metrics were calculated for the 64 patients or the sub-sample used for the visual assessments (see Supplement 2D for the results when metrics are calculated for the sub-sample). Consequently, the results for the metrics when they were calculated across the full analysed data set were compared with the visual assessment results.

### 2.7.2 Structure-correspondence metrics

Figure 2.4 shows the DSCs after the HS, D, V1 and V2 methods for the 64 patients. Additionally, the median and interquartile range for the rigid registration DSCs were 0.641 and 0.142. The medians of the percentage differences between the DSC results
for most comparisons of the rigid, V1, V2, D and HS registrations were significantly different from zero given the Wilcoxon test Z-values and p-values. The significant differences for the HS, D, V1 and V2 registration comparisons are indicated in Figure 2.4. The HS method achieved the best DSC results in terms of percentage differences with the other methods (Figure 2.4).

Figure 2.4: The Dice similarity coefficient (DSC) results for registrations applied to 64 patients. The figure includes the median (thick horizontal line), interquartile ranges (large boxes), maximums/minimums without outliers (vertical lines from large boxes) and raw data points (filled circles). The median pairwise percentage difference (%Diff) between the indicated registrations is provided alongside the Z-values (Z) and p-values (p) from exact Wilcoxon signed-rank tests of a median of zero for the pairwise percentage difference. The difference was calculated as the registration on the left minus the registration on the right and this difference was expressed as a percentage of the registration on the right. A significant positive percentage difference in DSC indicates that the registration on the left is superior. See the methods section for information about D, HS, V1 and V2.

Figures 2.5(a) and 2.5(b) show the ASD and HD results after the HS, D, V1 and V2 registration methods for the 64 patients. The significant differences for the HS, D, V1 and V2 registration comparisons via Wilcoxon signed-rank tests on pairwise percentage differences are indicated in Figures 2.5(a) and 2.5(b). The ASDs for the HS method were significantly smaller (smaller average shape discrepancy) than those for the D, V1 and V2 methods [Figure 2.5(a)]. However, the HDs for the V1 and V2 methods were significantly smaller (smaller extreme shape discrepancy) than those for HS and D methods [Figure 2.5(b)].
All non-rigid registration methods led to a significant percentage improvement of the DSC, ASD and HD from the rigid registration result (see Table S2.1 in Supplement 2C for statistical results).

2.7.3 Image-similarity metrics

Figure 2.6 summarises the image similarity results by ranking the V1, V2, D and HS methods according to the MI and MSE values for the 64 patients (alternatively, see Figure S2.4 in Supplement 2C for the values). The registrations with insignificant pairwise differences in metric values according to Wilcoxon signed-rank tests were assigned the same ranking in Figure 2.6. Alternatively, see Figure S2.5, Table S2.2 and Table S2.4 in Supplement 2C for the statistical results.

Considering similarity over the entire images, the HS method led to the best change (greatest percentage reduction) in the median MSE relative to the rigid registration value (Figure 2.6), whereas the HS/V1/V2 methods inseparably led to the best change (greatest percentage increase) in the median MI for similarity over the entire images (Figure 2.6). However, the V1 and V2 methods inseparably provided the best changes in the median MSE and median MI when considering similarity within the 3D bounding box enclosing both the HDR-BT CT and rigidly-registered EBRT CT rectal structures (Figure 2.6). For the DIRART methods, the MI decreased (deteriorated) relative to the rigid registration result and the MSE increased (deteriorated) relative to the rigid result when considering similarity in the 3D bounding box (Figure S2.4 in Supplement 2C).

2.7.4 Displacement-vector-field metrics

To determine orderings, Wilcoxon signed-rank tests of the pairwise differences in the percentage of voxels with a negative JAC between the HS, D, V1 and V2 methods were performed for the 64 patients. When the V2, V1, HS and D methods were compared for the DVF across the whole image, the ordering of methods according to increasing percentage of voxels with a negative JAC was D, V2 and V1/HS. However, the medians of the percentages of voxels with a negative JAC were zero for the VelocityAI methods when calculations were restricted to the region contained by the volume of the rigidly-registered EBRT rectal structure. For this region, the
Figure 2.5: (a) Average surface distance (ASD) and (b) Hausdorff (HD) results for registrations applied to 64 patients. The figures include the median (thick horizontal line), interquartile ranges (large boxes), maximums/minimums without outliers (vertical lines from large boxes) and raw data points (filled circles). The median pairwise percentage difference (%Diff) between the indicated registrations is provided alongside the Z-values (Z) and p-values (p) from exact Wilcoxon signed-rank tests of a median of zero for the pairwise percentage difference. The difference was calculated as the registration on the left minus the registration on the right and this difference was expressed as a percentage of the registration on the right. A significant negative percentage difference in ASD indicates that the registration on the left is superior. A significant positive percentage difference in HD indicates that the registration on the right is superior. See the methods section for information about D, HS, V1 and V2.
ordering of registrations in terms of increasing percentages of voxels with a negative JAC was V1/V2, D and HS. Alternatively, Figure S2.4 in Supplement 2C provides values with the test results detailed in Figure S2.5, Table S2.2 and Table S2.3.

![Ranking of Registrations](image)

**Figure 2.6:** Ranking of registration methods according to image-similarity results for registrations applied to 64 patients. The medians of the percentage changes in the root-mean-squared error (MSE) and mutual information (MI) were calculated via 100\times after/before-100. Increasing ranking indicates less image similarity and more image dissimilarity. Some registrations share the same ranking due to insignificant (p > 0.05) paired differences for metric values (alternatively, see Figures S2.4 and S2.5 in Supplement 2C for metric values and the results of the statistical significance tests). The MSE and MI metrics were calculated for two regions of interest, which were the entirety of the images and the bounding box enclosing both the HDR-BT CT and rigidly-registered EBRT CT rectal structures. See the methods section for information about D, HS, V1 and V2.

### 2.8 Discussion

#### 2.8.1 Visual assessments were important

The V1 method was superior to the V2, HS and D methods in terms of significant differences in the proportions of slices with the rectal-alignment approved according to the visual assessments. Additionally, the VelocityAI methods (V1 and V2) resulted in superior rectal alignment approval-proportions compared to the DIRART methods. This was inconsistent with the structure-correspondence metric results, where the HS and D methods achieved better DSCs with worse HDs. The inconsistency between the results of metrics and visual assessments has been identified before [29]. Additionally, in this case it supports the current practice that a sole structure-correspondence metric cannot be used for the remaining registrations of the larger dataset as a filtering measure in lieu of a slice-by-slice visual assessment by expert observers.

The visual assessment results can be confounded by intra-observer and inter-observer assessment variations [29]; however, the impact of these variations was reduced by conducting the analysis via paired registration differences and the same observer assessing the four registrations per patient in a consecutive manner.
2.8.2 Deformable image registration improved the rigid registration results

DIR was useful as, for example, the DSC, ASD and HD results were improved by applying DIR methods after rigid registration. The improvement in the median DSC was 35% for the HS algorithm with image processing as compared to rigid registration. This compares well with the 31% improvement in the mean DSC obtained by a study using the same algorithm with similar image processing tasks in the context of registering daily mega-voltage CT images to treatment planning kilovoltage CT images [30]. The results and comparisons are confounded by inter/intra-observer variations in contouring [31].

2.8.3 The choice of metrics and the way they were calculated were important

The results for the structure-correspondence metrics indicate that the selection of structure-correspondence metrics should be made carefully. The HS method was superior to the D, V1 and V2 methods in terms of a better structure-volume match (DSC) and less overall shape discrepancy (ASD). The V1 and V2 methods were superior to the HS and D methods in terms of extreme shape discrepancy (HD). The inconsistency of these metrics contrasts with another study where they were useful for evaluations [13]. In this case, the most extreme shape discrepancy (HD) is important from a dosimetric perspective as the anterior side of the registered rectal-structure could deviate from the fixed structure by extending over the brachytherapy high-dose area. Consequently, the correlation between the most extreme shape discrepancy and the high-dose parameters after registration may be useful when checking the validity of deformed dose.

It is important to calculate metrics over a restricted region that covers the area of concern or the organ at risk rather than the whole image when assessing whether the registration is acceptable in that area or for the organ at risk. The reason is that the registration is optimised over a region of interest and the performance can vary locally. For example, the V1/V2 methods provided optimum results for the rectum in terms of MI and MSE calculated in the region defined by the volume of the rigidly-registered EBRT rectal structure, whereas the HS method provided the best
MSE result when calculated over the whole image. Additionally, unlike the DIRART algorithms the VelocityAI algorithms led to improvements in the image-similarity metrics calculated across the rectum relative to the rigid registration result. The choice of metrics can be important as elsewhere the MSE was found to be not useful for evaluation [13].

2.8.4 The B-splines-based registration resulted in the best registration of the rectum

The results for the rectum were sufficiently different to distinguish the best-performing VelocityAI registration from the best-performing DIRART registration. Relative to the DIRART algorithms, the VelocityAI algorithms did achieve better image similarity and visual alignment over the region contained by the volume of the rectal structure. Additionally, the VelocityAI algorithms appeared to do so with less physically-unrealistic displacements (smaller percentage of displacements with negative JACs) and less extreme shape discrepancy between the fixed and propagated rectal structures (smaller HD). As there was no image processing prior to the VelocityAI algorithms, the VelocityAI algorithms achieved these superior results whilst exposed to rectal discrepancies. As such, this study demonstrates the VelocityAI DIRs (B-splines-based) appeared to result in the best alignment of the rectum and achieve DVF's with the least physically-unrealistic displacements.

This evaluation is based on the algorithms in the form they were released. Also, the user cannot change the registration parameters in VelocityAI. If the parameters in both packages were adjustable, it would be a useful and difficult task to find optimum performance [25].

The comparative evaluations of registrations from different registration systems is important for adequately accumulating dose for combined EBRT/HDR-BT prostate cancer treatment and correlating it with observed gastrointestinal toxicities. The assessment of impact of image registration on dose-outcomes correlation will provide additional validation of the alternative approaches, and this is the subject of ongoing investigation.
2.8.5 Recommendations and future considerations

- Registrations may benefit from images immediately prior to the HDR-BT insertion of needles as this may allow changes over the preceding months to be separated from changes due to HDR-BT needles and treatment positioning.

- It would be useful to evaluate registrations after applying methods which could better manage image discrepancies such as a recently-developed penalty term minimising the volume of missing information [19], algorithms that exclude discrepancies in rectal filling [32, 33] or applying other image-similarity metrics within DIRART (e.g. mutual information).

- Evaluation of registrations customised for the urethra, bladder, prostate and seminal vesicles would be useful as they require work on considerable image issues (e.g. HDR-BT needles in the prostate and the urethra catheter balloon in the bladder).

- Registration evaluation for patients can be difficult and involve a variety of methods as there is no direct measure of registration error due to no known ground truth. Information obtained from other evaluation methods such as landmarks, phantoms and deformed dose uncertainty [25, 34–37] would be useful if applied to HDR-BT CTs, given the image contents.

2.9 Conclusions

This study demonstrated that structure correspondence, image similarity and visual assessments are useful for assessing registrations applied to EBRT and HDR-BT CTs of prostate cancer patients. We found that using non-rigid registrations in VelocityAI or image processing plus non-rigid registrations in DIRART improved the alignment of the rectum according to visual assessment and various metrics. It would have been misleading to use a structure-correspondence metric as a sole indicator of the alignment of the rectum, given that such metrics were inconsistent with other metrics and visual assessments. It is recommended that image-similarity and displacement-vector-field metrics be calculated for a restricted region covering the organ of interest instead of using global values. Applying the DIR methods in VelocityAI provided
the optimum registration result for the rectum as assessed by the greatest rectal alignment approval-proportion, the least extreme shape discrepancy between rectal structures and the optimum rectal image similarity. We encourage the development of registrations for the prostate and urethra in EBRT and HDR-BT CTs as doses to the prostate and urethra are key clinical concerns in the RADAR trial.

2.10 Declarations

2.10.1 Ethics approval and consent to participate

The TROG 03.04 RADAR Trial is registered with the National Institutes of Health Clinical Trials Registry (number NCT00193856). This trial has approval from the Hunter New England Human Research Ethics Committee (Trial ID. 03/06/11/3.02), the Sir Charles Gairdner Group Human Research Ethics Committee (2003-050) and the University of Western Australia Human Research Ethics Office (RA/4/1/5601). Patients participating in the trial signed consent forms.

2.10.2 Consent for publication

The signed patient consent forms for the trial informed patients that their medical information may be used in the published results of the study. In accordance with the signed patient consent forms, this publication includes only anonymous information and does not include information identifying any patient.

2.10.3 Competing interests

The authors declare that they have no competing interests.

2.10.4 Authors’ contributions

CRM, MJH, CIT and MAE have made substantial contributions to design of analysis. CRM, VL, CIT, MK, DJJ, JWD and MAE have made substantial contributions to acquire the data. CRM, MJH, VL, CIT and MAE contributed substantially to analysis and interpretation of data. CRM has been involved in drafting the manuscript. MJH, VL, CIT, DJJ, JWD and MAE revised it critically for important
and correct content. JWD and DJJ were involved in the design and coordination of the RADAR trial. All authors read and approved the version to be published.

2.10.5 Acknowledgements

We acknowledge funding from the National Health and Medical Research Council (300705, 455521, 1006447), the University of Western Australia, an Australian Postgraduate Award, an Ana Africh Scholarship, the Hunter Medical Research Institute, the Health Research Council (New Zealand), Abbott Laboratories and Novartis Pharmaceuticals. We thank Annette Haworth and radiation oncology staff at Sir Charles Gairdner Hospital for their contributions.

2.11 Supplements 2A-2D

2.11.1 Supplement 2A

This supplement provides additional detail on the image-processing algorithm and examples of images before and after applying the process.

Image processing details:

1. HDR-BT needles were detected by thresholding CT numbers (≥3500). For each axial slice, a boundary was extracted from the outermost detected points. It was empirically determined that dilating the boundary in each axial slice by 6 voxels radially allowed the entirety of the HDR-BT needles and associated artefacts to be contained. The pixels in the interior of the new boundaries were checked for a CT number above that of muscle/tissue (1200) or below that of fat/tissue (800). The detected pixels were replaced with the average CT number of neighbouring undetected pixels. A binary mask was created from these detected pixels. The Hounsfield number is the CT number minus 1000.

2. For the HDR-BT CTs, the rectal-packing material extended beyond the superior-inferior extent of the HDR-BT rectal structure. As such, pixels beyond the superior-inferior extent of the HDR-BT structure that contained rectal-packing material (≥1200) and low CT number artefacts (≤800) were
detected and replaced with the average CT number of neighbouring undetected pixels. The earlier mentioned binary mask was updated to include these detected pixels.

3. The following Gaussian smoothing and blurring process resulted in balanced HDR-BT CT ($I_{balanced}$) and was applied to avoid features in the image caused by the pixel adjustments in steps 1 and 2:

   (a) A smoothed image ($I_{smoothed}$) was obtained by passing the adjusted HDR-BT image ($I_{adjusted}$) through a Gaussian low pass-filter ($\sigma = 2$ voxels).

   (b) A blurred binary mask ($M_{blurred}$) was obtained by applying a Gaussian low-pass filter ($\sigma = 2$ voxels) to the binary mask.

   (c) A balanced HDR-BT image ($I_{balanced}$) was obtained from the adjusted image ($I_{adjusted}$), smoothed image ($I_{smoothed}$) and the blurred binary mask ($M_{blurred}$) according to (S2.1).

   $$I_{balanced} = I_{adjusted} \times (1 - M_{blurred}) + I_{smoothed} \times M_{blurred} \quad \text{(S2.1)}$$

4. An approach for dealing with inconsistent contents between the rectal structures for the EBRT and HDR-BT CTs is to paint the contents of the rectal structures with a uniform CT number. The contents of rectal structures were replaced with a high CT number (2500), which was empirically determined as separating the rectum from surrounding tissue. The final HDR-BT and rigidly-registered EBRT CTs were obtained by applying this rectal structure-painting to the balanced HDR-BT CT ($I_{balanced}$) and the rigidly-registered EBRT CT.
Figure S2.1: The high-dose-rate brachytherapy (HDR-BT) CT with and without image processing (IP). The contour is in black.

Figure S2.2: The rigidly-registered external beam radiotherapy (EBRT) CT with and without image processing (IP). The contour is in black.
2.11.2 Supplement 2B

This supplement provides an illustration of the anatomy in the male pelvis.

**Figure S2.3:** (a) Male pelvis with the coccyx (A), femoral heads (B), femoral necks (C) and pubic symphysis (D) marked (Source: University of Rochester Medical Center [38], Creative Commons CC-BY). (b) Hip bone with the ischium near the inferior extent of the obturator foramen (E), superior ramus of pubis near the obturator canal (F) and medial aspect of the acetabulum (G) marked (Source: OpenStax College [39], Creative Commons CC-BY). The major anatomy misalignments for rigid registrations were observed around the coccyx, ischium near the inferior extent of the obturator foramen, superior ramus of pubis near the obturator canal, femoral heads and femoral necks. The rigid registration was observed in the majority of slices to provide unacceptable alignment of the rectum and soft tissue surrounding the rectum. After DIR, the major anatomy misalignments were observed around the pubic symphysis, ischium near the inferior extent of the obturator foramen, superior ramus of pubis near the obturator canal, coccyx and the medial aspect of the acetabulum.
2.11.3 Supplement 2C

This supplement contains additional results for the 64 patient sample.

Table S2.1: A summary of the improvement in the Dice similarity coefficient (DSC), average surface distance (ASD) and Hausdorff distance (HD) under various registration method comparisons for 64 patients via the median of percentage changes \([X \text{ versus } Y = 100\times(X/Y-1)]\) and exact Wilcoxon signed-rank tests of medians of zero. A positive percentage difference in DSC indicate that the first mentioned registrations is superior as it had the larger DSC and a larger DSC indicates more contour overlap. A negative percentage difference in ASD indicate that the first mentioned registration is superior as it had the smaller ASD and a smaller ASD indicates closer overall contour shape matching. A negative percentage difference in HD indicate that the first mentioned registration is superior as it had the smaller HD and a smaller HD indicates a less extreme contour shape discrepancy.

<table>
<thead>
<tr>
<th>Registration Comparison</th>
<th>DSC Results</th>
<th>ASD Results</th>
<th>HD Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change (%)</td>
<td>Z-value</td>
<td>P-value</td>
</tr>
<tr>
<td>V1 versus Rigid</td>
<td>19.4</td>
<td>6.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>V2 versus Rigid</td>
<td>22.6</td>
<td>6.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D versus Rigid</td>
<td>26.8</td>
<td>6.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HS versus Rigid</td>
<td>32.0</td>
<td>6.96</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Figure S2.4: The medians of the percentage of voxels with a negative JAC after various registration methods applied to 64 patients. Additionally, the medians of the percentage changes (e.g. $100 \times \text{after/before} - 100$) in the MSE and MI image-similarity metrics due to registrations applied to 64 patients. The percentage changes in the MSE and MI are the values after DIR relative to values after rigid registration. Consequently, a negative change in MI or a positive change in MSE indicate that the DIR has not improved upon the image similarity achieved by the rigid registration. For each metric, read horizontally to get the metric values for the various registrations indicated by symbols. The JACs were calculated across the entire displacement vector field and the region contained by the volume of the rigidly-registered EBRT rectal structure. The MSE and MI metrics were calculated for the entirety of the images and a bounding box enclosing both the HDR-BT CT and rigidly-registered EBRT CT rectal structures.
Figure S2.5: The results for the exact Wilcoxon signed-rank test of the pairwise differences in the JAC, MSE and MI metric values between various registration methods applied to 64 patients. The JACs were calculated across the entire displacement vector field and the rigidly-registered EBRT CT rectal structure volume. The MSE and MI metrics were calculated for the entirety of the images and a bounding box enclosing both the HDR-BT CT and rigidly-registered EBRT CT rectal structures. For each metric, read horizontally to get the Z-values for tests on the paired difference against a median of zero. The p-values associated with the Z-values are provided by a colour-fill of the plot markers.
Table S2.2: Results for Wilcoxon signed-rank tests of the pairwise differences in JAC, MI and MSE metric values among the various registration methods applied to 64 patients. The JACs, MIs and MSEs were calculated across the whole image (entire displacement vector field). The paired metric comparison (difference method) is median absolute difference (M = X – Y) for metrics already in percentage format. The Z-values (Z) and p-values (p) from the tests that the medians are zero are included. A positive difference in the percentage of voxels with a negative JAC or change in MSE after DIR indicates that the second mentioned registration has fewer physically-unachievable displacements or less image dissimilarity respectively. A positive difference for the change in MI after DIR indicates that the first mentioned registration has superior image similarity.

<table>
<thead>
<tr>
<th>Registration Comparison</th>
<th>Metric (Whole Image)</th>
<th>Median of the Percentage of Voxels with a Negative JAC</th>
<th>Median MSE Change After DIR (%)</th>
<th>Median MI Change After DIR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS3 - V2</td>
<td>M: 0.567</td>
<td>-0.097</td>
<td>0.00915</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: 3.91</td>
<td>-4.13</td>
<td>-1.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.288</td>
<td></td>
</tr>
<tr>
<td>HS3 - V1</td>
<td>M: 0.313</td>
<td>-0.116</td>
<td>0.154</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: 1.61</td>
<td>-5.81</td>
<td>-0.0869</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: 0.110</td>
<td>&lt;0.0001</td>
<td>0.934</td>
<td></td>
</tr>
<tr>
<td>D3 - V2</td>
<td>M: -0.288</td>
<td>0.185</td>
<td>-0.429</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: -2.88</td>
<td>6.57</td>
<td>-5.51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: 0.00361</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>D3 - V1</td>
<td>M: -0.668</td>
<td>0.169</td>
<td>-0.340</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: -4.07</td>
<td>5.87</td>
<td>-4.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HS3 - D3</td>
<td>M: 6.83</td>
<td>0.293</td>
<td>0.327</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: 6.83</td>
<td>6.96</td>
<td>6.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>V2 - V1</td>
<td>M: -0.155</td>
<td>-0.0121</td>
<td>0.0684</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: -4.61</td>
<td>-4.84</td>
<td>4.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Difference Method       Absolute       Absolute       Absolute
Table S2.3: Results for Wilcoxon signed-rank tests of the pairwise differences in the JAC metric values among the various registration methods applied to 64 patients. The JACs were calculated in the region contained by the volume of the rigidly-registered EBRT rectal structure. The paired metric comparison (difference method) is median absolute difference ($M = X - Y$) for metrics already in percentage format. The $Z$-values ($Z$) and $p$-values ($p$) from the tests that the medians are zero are included. A positive difference in the percentage of voxels with a negative JAC indicates that the second mentioned registration has fewer physically-unachievable displacements.

<table>
<thead>
<tr>
<th>Registration Comparison</th>
<th>Metric (Rectal Volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median of the Percentage of Voxels with a Negative JAC</td>
</tr>
<tr>
<td>HS3 - V2</td>
<td>M: 5.84</td>
</tr>
<tr>
<td></td>
<td>Z: 6.91</td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
</tr>
<tr>
<td>HS3 - V1</td>
<td>M: 5.41</td>
</tr>
<tr>
<td></td>
<td>Z: 6.59</td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
</tr>
<tr>
<td>D3 - V2</td>
<td>M: 0.644</td>
</tr>
<tr>
<td></td>
<td>Z: 5.17</td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
</tr>
<tr>
<td>D3 - V1</td>
<td>M: 0.615</td>
</tr>
<tr>
<td></td>
<td>Z: 4.60</td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
</tr>
<tr>
<td>HS3 - D3</td>
<td>M: 4.53</td>
</tr>
<tr>
<td></td>
<td>Z: 6.84</td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
</tr>
<tr>
<td>V2 - V1</td>
<td>M: 0.0000</td>
</tr>
<tr>
<td></td>
<td>Z: 1.12</td>
</tr>
<tr>
<td></td>
<td>p: 0.300</td>
</tr>
</tbody>
</table>

Difference Method: Absolute
Table S2.4: Results for Wilcoxon signed-rank tests of the pairwise differences in the MI and MSE metric values among the various registration methods applied to 64 patients. The MI and MSEs were calculated across a bounding box enclosing both the HDR-BT CT and rigidly-registered EBRT CT rectal structures. The paired metric comparison (difference method) is median absolute difference ($M = X - Y$) as the metrics are already in percentage format. The Z-values (Z) and p-values (p) from the tests that the medians are zero are included. A positive difference in the change in MSE after DIR indicates that the second mentioned registration has less image dissimilarity. A positive difference for the change in MI after DIR indicates that the first mentioned registration has superior image similarity.

<table>
<thead>
<tr>
<th>Registration Comparison</th>
<th>Metric (Box Around Rectum)</th>
<th>Median MSE Change After DIR (%)</th>
<th>Median MI Change After DIR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS3 - V2</td>
<td>M: 0.0932</td>
<td>-0.534</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: 5.83</td>
<td>-5.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HS3 - V1</td>
<td>M: 0.105</td>
<td>-0.570</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: 4.98</td>
<td>-4.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>D3 - V2</td>
<td>M: 0.298</td>
<td>-0.603</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: 6.89</td>
<td>-6.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>D3 - V1</td>
<td>M: 0.313</td>
<td>-0.602</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: 6.11</td>
<td>-5.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HS3 - D3</td>
<td>M: -0.200</td>
<td>0.0511</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: -6.93</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: &lt;0.0001</td>
<td>0.307</td>
<td></td>
</tr>
<tr>
<td>V2 - V1</td>
<td>M: -0.00191</td>
<td>-0.00596</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z: -1.81</td>
<td>-0.221</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: 0.0713</td>
<td>0.829</td>
<td></td>
</tr>
</tbody>
</table>

Difference Method Absolute Absolute
2.11.4 Supplement 2D

This supplement contains the metric results for the case of the 21 patient subsample.

Table S2.5: A summary of the registration comparison results provided in Tables S2.6 and S2.7 for 21 patients. The table includes which package (DIRART or VelocityAI) provided the best performing registration for the rectum according to different metrics. The metrics used to assess performance were the Dice similarity coefficient (DSC), average surface distance (ASD), Hausdorff distance (HD), root-mean-squared error (MSE), mutual information (MI) and Jacobian determinant (JAC) as calculated in Tables S2.6 and S2.7.

<table>
<thead>
<tr>
<th>Metric Assessing Performance</th>
<th>Package Providing Best Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSC</td>
<td>DIRART</td>
</tr>
<tr>
<td>HD</td>
<td>VelocityAI</td>
</tr>
<tr>
<td>ASD</td>
<td>DIRART</td>
</tr>
<tr>
<td>MSE</td>
<td>VelocityAI</td>
</tr>
<tr>
<td>MI</td>
<td>VelocityAI</td>
</tr>
<tr>
<td>JAC</td>
<td>VelocityAI</td>
</tr>
</tbody>
</table>

Table S2.6: A summary of the improvement in the Dice similarity coefficient (DSC), average surface distance (ASD) and Hausdorff distance (HD) under various registration method comparisons for 21 patients via the median of pairwise percentage changes \([X \text{ versus } Y = 100 \times (X/Y-1)]\). A positive percentage difference in DSC indicates that the first mentioned registration is superior as it had the larger DSC and a larger DSC indicates more contour overlap. A negative percentage difference in ASD indicates that the first mentioned registration is superior as it had the smaller ASD and a smaller ASD indicates closer overall contour shape matching. A negative percentage difference in HD indicates that the first mentioned registration is superior as it had the smaller HD and a smaller HD indicates a less extreme contour shape discrepancy.

<table>
<thead>
<tr>
<th>Registration Comparison</th>
<th>DSC Results</th>
<th>HD Results</th>
<th>ASD Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change (%)</td>
<td>Change (%)</td>
<td>Change (%)</td>
<td></td>
</tr>
<tr>
<td>V1 versus Rigid</td>
<td>19.9</td>
<td>-14.1</td>
<td>-34.0</td>
</tr>
<tr>
<td>V2 versus Rigid</td>
<td>20.0</td>
<td>-12.6</td>
<td>-32.5</td>
</tr>
<tr>
<td>D versus Rigid</td>
<td>24.5</td>
<td>-1.15</td>
<td>-46.5</td>
</tr>
<tr>
<td>HS versus Rigid</td>
<td>34.5</td>
<td>-9.14</td>
<td>-64.8</td>
</tr>
<tr>
<td>HS versus D</td>
<td>5.58</td>
<td>-3.48</td>
<td>-21.8</td>
</tr>
<tr>
<td>HS versus V1</td>
<td>12.1</td>
<td>2.93</td>
<td>-45.1</td>
</tr>
<tr>
<td>HS versus V2</td>
<td>10.3</td>
<td>4.73</td>
<td>-44.3</td>
</tr>
<tr>
<td>D versus V1</td>
<td>2.85</td>
<td>19.0</td>
<td>-13.5</td>
</tr>
<tr>
<td>D versus V2</td>
<td>2.78</td>
<td>20.1</td>
<td>-11.6</td>
</tr>
</tbody>
</table>
Table S2.7: A summary of the improvement in the root mean squared error (MSE), mutual information (MI) and Jacobian determinant (JAC) metrics under various registration method comparisons for 21 patients. The MSE and MI image-similarity metrics were calculated as the percentage changes in values from before and after DIR (e.g. $100 \times \text{after/before} - 100$). The JAC metric was calculated as the percentage of voxels with a negative JAC. The reported medians are the median of the absolute pairwise difference between various registration methods [X versus Y = X-Y]. The MIs and MSEs were calculated across a bounding box enclosing both the HDR-BT CT and rigidly-registered EBRT CT rectal structures. A positive (negative) difference in the change in MSE after DIR indicates that the second (first) mentioned registration has less image dissimilarity. A positive (negative) difference for the change in MI after DIR indicates that the first (second) mentioned registration has superior image similarity. The JACs were calculated in the region contained by the volume of the rigidly-registered EBRT rectal structure. A positive difference in the percentage of voxels with a negative JAC indicates that the second mentioned registration has fewer physically-unachievable displacements.

<table>
<thead>
<tr>
<th>Registration Comparison</th>
<th>MSE Results</th>
<th>MI Results</th>
<th>JAC Results</th>
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<tr>
<td></td>
<td>Change After DIR(%)</td>
<td>Change After DIR(%)</td>
<td>Percentage of JACs &lt; 0 (%)</td>
</tr>
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<td>HS versus D</td>
<td>-21.9</td>
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<td>3.71</td>
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<td>D versus V1</td>
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<td>D versus V2</td>
<td>26.3</td>
<td>-60.0</td>
<td>0.625</td>
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References


Chapter 3:
Dose accumulation
3.1 Foreword for manuscript

The previous chapter recommended that metrics assessing registration performance should be used in combination with visual checks of the registrations. Consequently, registered images were visually checked before being included in the studies that are described in the remaining chapters of this thesis. The previous chapter also determined that the deformable multi-pass registration algorithm in Velocity Advanced Imaging was the preferred registration algorithm for registering the rectums in external beam radiotherapy (EBRT) and high-dose-rate brachytherapy (HDR-BT) CTs. However, it has been common for studies on combined EBRT/HDR-BT to accumulate rectal dose without using deformable registration by simple addition of the dose-volume histogram (DVH) parameters. The question is then: how different are the rectal DVH parameters obtained by registration-based distribution-adding and DVH-based parameter-adding? That is, are the differences between the dose accumulation methods of clinical relevance?

For HDR-BT, the rectal DVH parameters of interest for gastrointestinal toxicities are typically high-dose metrics due to the closeness of the anterior rectal wall to the high-dose gradients from the HDR-BT catheters. Consequently, the manuscript in this chapter investigates whether differences between high-dose metrics for rectal dose accumulated using the distribution-adding and parameter-adding methods are significant and clinically relevant. One intention of the study in this chapter is to gain insight into whether the differences between the methods are large enough for the choice of method to be a confounding factor for subsequent correlations of accumulated rectal dose with observed gastrointestinal toxicities. Such dose-toxicity correlations are the subject of subsequent chapters and the second two stages of the thesis.
3.2 Manuscript details

Accumulation of rectum dose-volume metrics for prostate external beam radiotherapy combined with brachytherapy: Evaluating deformably-registered dose distribution addition using parameter-based addition.


Publication status: In press. The manuscript in this chapter (including supplements) is a typeset of the version submitted to the journal for peer review. The inclusion of published material in this chapter is allowed by the copyright agreement for the in press article [1].

3.3 Abstract

3.3.1 Background

To investigate the accuracy of deriving rectal dose-volume histogram (DVH) parameters from deformably-registered data by comparing values with the simple addition of rectal DVHs from each phase of a combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) prostate treatment.

3.3.2 Methods

82 patients received EBRT in 23 fractions of 2 Gy and HDR-BT TG43 in three fractions of 6.5 Gy. The HDR-BT CT was deformably-registered to the EBRT CT. The $D_{0.1cc}$, $D_{1cc}$, $D_{2cc}$ and $D_{10cc}$ for the rectum were calculated in two ways. (1) Parameter-adding: the EBRT DVH parameters (or the EBRT prescription dose) were added to the unregistered HDR-BT DVH parameters. (2) Distribution-adding: the parameters were extracted after the EBRT doses were 3D-summed with the registered HDR-BT doses. Resulting differences between the parameters were investigated.

3.3.3 Results

The $D_{0.1cc}$, $D_{1cc}$ and $D_{2cc}$ from parameter-adding were 21.3% ($p<0.001$), 6.3% ($p<0.001$) and 3.5% ($p<0.001$) smaller than those from distribution-adding. The $D_{10cc}$ was 2.2% ($p=0.015$) larger for distribution-adding.

3.3.4 Conclusions

Distribution-adding was confounded by unsystematic inter/intra-observer rectum-contouring errors and registration accuracy near the anterior rectal wall. Consequently, clinical use of distribution-adding to assess rectal doses requires careful contour and registration evaluation.
3.4 Introduction

For accurate planning and reporting of combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT), dose-volume histogram (DVH) parameters [2, 3] from each treatment phase should be combined [4, 5]. The biological non-equivalence of the fractionation schedules can be managed by converting the doses or DVHs to equieffective doses given in 2 Gy fractions [5–7]. Accumulated dose parameters can then be obtained by simply adding the EBRT prescription dose to the HDR-BT DVH parameters or full addition of EBRT and HDR-BT DVH parameters [4, 8, 9]. However, crude addition of doses or parameters may not be accurate where there is anatomical deformation and shrinkage [4, 10, 11]. Deformable image registration (DIR) can be applied to adjust for deformation and shrinkage [10, 12–14]. Accumulated dose parameters can then be obtained via addition of deformably-registered dose distributions [4, 15]. The assumption that DVH-based addition provides the ‘worst possible’ peak rectal doses [4] should be investigated in the presence of localised contouring inconsistencies and registration inaccuracies, which could lead to registrations providing greater near-maximum doses.

The variation in accumulated rectal doses obtained via the DVH-based addition and registration-based distribution addition methods is a concern for combined EBRT/HDR-BT as the planning CTs contain substantial anatomical changes (e.g. HDR-BT rectal-packing material and variable rectal filling) [16]. The difference between the methods has been reported for cervical cancer treatments [4, 12, 17–20] and endometrial cancer treatments [21]. However, such studies are lacking in the context of combined EBRT/HDR-BT prostate cancer treatments where dose accumulation for the rectum [7, 15, 22, 23] has not yet progressed to include deformable image registration.

This study aimed to assess registration-based distribution addition via comparison with DVH-based addition when accumulating dose to the rectum for prostate EBRT followed by a HDR-BT boost.
3.5 Methods

3.5.1 Patient data

This study included 82 prostate cancer patients (tumour T stage ≥ 2a) who were treated with neoadjuvant androgen deprivation therapy and radiotherapy at Sir Charles Gairdner Hospital in the period 2004 to 2008. The radiotherapy consisted of HDR-BT commencing two to five weeks after the completion of EBRT. Patient criteria and treatment methodology were as specified for the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) trial [24, 25]. The standard HDR-BT treatment has previously been described [26]. Additional patient characteristics and HDR-BT treatment details are given in Supplement 3A.

The EBRT prostate prescription dose was 46 Gy (23 daily fractions) to the International Commission on Radiation Units and Measurements reference point [27]. The HDR-BT prostate prescription dose of 19.5 Gy (three fractions across two days) was delivered by Iridium-192 using metal after-loading catheters with the trial guidelines requiring the delivery time to be less than 90 minutes for each fraction and the time between fractions to be at least 6 hours. Using the EBRT planning CT, a four-field conformal EBRT plan was created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden) with the patient in the supine position. Using the HDR-BT planning CT acquired prior to the first fraction, a three-fraction HDR-BT plan was created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US). Additional CT scans were not acquired for fractions two and three, as the protocol in place at the time of the trial required fiducial markers to be implanted before the first fraction and these markers were used to ensure reproducibility of HDR-BT catheter positions before each fraction [26]. The HDR-BT doses were calculated using the TG43 formalism [28] with a maximum rectal dose of 80% of the prescription dose and the prescription dose covering the prostate gland/extracapsular extensions.

The clinical target volume (CTV) and external wall of the rectum were manually delineated by treating-clinicians in the HDR-BT CTs using BrachyVision and in the EBRT CTs using the Elekta Focal contouring system (Elekta AB, Stockholm,
Outlines of the rectum were reviewed (by author MK) for consistency between patients. The rectum was contoured from the rectosigmoid flexure to the most inferior axial image slice on which the ischial tuberosities were visible. Bowel preparation was not commonly required. The EBRT planning target volume (PTV) and HDR-BT source definition volume (SDV) were obtained by expanding the corresponding CTV (10 mm margin). The HDR-BT SDV was used to restrict dwell positions to the lengths of identified catheters covered by the SDV. Figure 3.1 provides examples of the EBRT and HDR-BT TG43 physical dose plans. Figures S3.1 and S3.2 in Supplement 3B provide examples of regions of heterogeneous dose within the EBRT PTV and high doses around the HDR-BT catheters respectively.

Figure 3.1: (A) A four-field EBRT physical dose plan with dose displayed as a colourwash up to 46 Gy. (B) A HDR-BT TG43 physical dose plan with dose displayed as a colourwash up to 19.5 Gy. The CTV, SDV and rectal structures are in yellow, red and green respectively. Source: [29], Creative Commons CC-BY.

3.5.2 Evaluating the registrations

Rigid registration followed by DIR was performed in Velocity Advanced Imaging 2.8.1 (Varian Medical Systems, Palo Alto, US) to register the HDR-BT planning CT (day 1) to the EBRT planning CT (day 1) [30]. The algorithm performs the registration in multiple passes from low resolution to high resolution using a B-splines algorithm with the Mattes mutual information metric and the limited-memory Broyden-Fletcher-Goldfarb-Shanno optimiser. The DIR is described in additional detail elsewhere [16, 30]. A detailed evaluation of the registration, including qualitative visual inspection by experts, has previously been reported [16].
The registration of patient images is associated with registration uncertainties due to image discrepancies; however, visual inspections for the 82 patients included in this study did not identify any major registration misalignments of the rectum (e.g. Figure S3.3 in Supplement 3C). The registrations were quantitatively evaluated for each patient in this study using the following three structure-overlap metrics (see Figure 3.2 for an illustration of the overlap metrics and results).

1. This metric assesses the alignment of EBRT and registered HDR-BT rectal volumes. The overlap of the EBRT rectum and registered HDR-BT rectum was calculated and then expressed as a percentage of the volume of the registered HDR-BT rectum. A larger overlap indicates better general alignment.

2. This metric assesses alignment of the HDR-BT prostate doses closer to or further (posteriorly) into the EBRT anterior rectal wall. The overlap of the EBRT rectum and registered HDR-BT SDV was calculated and expressed as a percentage of the volume of the EBRT rectum. A larger overlap indicates the HDR-BT prostate has been registered with more high-dose gradients aligned over the anterior rectal wall.

3. This metric assesses alignment of the HDR-BT prostate doses further away (anteriorly) from the EBRT anterior rectal wall. The overlap of the EBRT CTV and registered HDR-BT rectum was calculated and expressed as a percentage of the volume of the EBRT rectum. A larger overlap indicates the HDR-BT prostate has been registered with less high-dose gradients aligned over the anterior rectal wall.

The three structure-overlap metrics were used as they evaluate different types of registration misalignment using different structures which were contoured at different times in the combined treatment. Consequently, directly comparing the results for the different metrics would be confounded by the use of different structures.

3.5.3 Obtaining dose-volume parameters

The EBRT, unregistered HDR-BT and registered HDR-BT 3D-doses were imported into MATLAB™ R2010a (The MathWorks Inc., Massachusetts, US) and the Computational Environment for Radiotherapy Research (CERR) version 4.1 [31]. The
unregistered HDR-BT and registered HDR-BT 3D-doses were from plans based on the unregistered and registered HDR-BT planning CT (day 1) respectively. The voxel doses were converted to equireffective doses given in 2 Gy per fraction using the linear-quadratic model [6, 32] with an alpha-beta ratio (\(\alpha/\beta\)) of 3 Gy for the rectum [2]. The analysis was also performed for an alpha-beta ratio of 5.4 Gy to check the sensitivity of results to the upper limit published for the rectum [33]. The rectal DVH parameters calculated from these doses were the \(D_{X_{cc}}\), which are minimum doses to the most irradiated \(X\) cubic centimetres (cc) of the rectum. The focus is on the \(D_{0.1cc}, D_{1cc}, D_{2cc}\) and \(D_{10cc}\) as studies have investigated the correlation of high- and intermediate-dose parameters with gastrointestinal toxicities [34]. Three methods were used to calculate the \(D_{0.1cc}, D_{1cc}, D_{2cc}\) and \(D_{10cc}\) for the rectum.

Figure 3.2: Illustration and results for the three structure-overlap metrics used to assess registrations. (A) Metric assessing major alignment of rectal volume. (B) Metric assessing alignment of the HDR-BT prostate doses closer to or further (posteriorly) into the EBRT anterior rectal wall. (C) Metric assessing alignment of the HDR-BT prostate doses further away (anteriorly) from the EBRT anterior rectal wall. Metrics are described in the methods section.

1. Partial parameter-adding: The unregistered HDR-BT \(D_{X_{cc}}\) was calculated us-
ing the corresponding dose and rectal structure. The method then assumes the EBRT rectum homogeneously receives the 46 Gy prescribed to the prostate. Hence, 46 Gy was added to the HDR-BT $D_{Xcc}$.

2. Full parameter-adding: The EBRT $D_{Xcc}$ and unregistered HDR-BT $D_{Xcc}$ were calculated using the corresponding doses and rectal structures. The EBRT $D_{Xcc}$ was added to the HDR-BT $D_{Xcc}$.

3. Distribution-adding: The EBRT dose was summed voxel-by-voxel with the registered HDR-BT dose (i.e. accumulated). The $D_{Xcc}$ was calculated using the total dose and the EBRT rectal structure.

The distribution-adding value was subtracted from the parameter-adding value for each of the 82 patients and expressed as a percentage of the distribution-adding value. Given that published studies have obtained rectal dose using the partial parameter-adding method and/or the full parameter-adding method, the two methods for parameter-adding were included to allow reliable comparisons with such studies [4, 12].

3.5.4 Statistical analysis

Exact two-sided Wilcoxon signed-rank tests of percentage differences against a median of zero were performed in R (version 2.15.2) [35] using the Coin package (version 1.0.23) [36] and the Pratt method for zeros [37]. The differences were not normally distributed according to quantile-quantile plots. Differences were considered significant if the p-values (p) were less than 0.05.

3.6 Results

The results for registration quality as assessed by structure-overlap metrics are provided in Figure 3.2. The median overlap is 81.9% for alignment of EBRT/registered HDR-BT rectal structure volumes [Figure 3.2(A)] with 70% considered the starting point for a satisfactory general structure overlap [38]. The median overlap is 3.0% for the EBRT rectum/registered HDR-BT SDV structures [Figure 3.2(B)] and 0.2% for the EBRT CTV/registered HDR-BT rectal structures [Figure 3.2(C)]. Figure 3.3
provides an example of a HDR-BT TG43 physical dose before and after registration. For the registration in Figure 3.3, the overlap metrics assessing general rectal volume-correspondence and registration of the HDR-BT prostate doses further into the anterior wall of the EBRT rectum were 94.5% and 0.3% respectively. For Figure 3.3, there is greater separation between the HDR-BT CTV and HDR-BT rectum in Figure 3.3(A) relative to the separation between the EBRT CTV and EBRT rectum in Figure 3.3(B). For the registration and structures in Figure 3.3, the total rectal \( D_{2cc} \) for distribution-adding and parameter-adding were 67.0 \( EQD2 \) Gy and 64.8 \( EQD2 \) Gy respectively.

Figure 3.3: (A) A HDR-BT CT and TG43 physical dose plan with dose displayed as a colourwash between 2.5 and 13.9 Gy. (B) The physical HDR-BT TG43 dose from (A) after registration and overlaid on the EBRT CT with dose displayed as a colourwash between 2.5 and 13.9 Gy. The CTV and rectal structures for the corresponding CT are in yellow and green respectively.

Figure 3.4(A) provides the medians for the rectal \( D_{0.1cc} \), \( D_{1cc} \), \( D_{2cc} \) and \( D_{10cc} \) obtained by partial and full parameter-adding with an alpha-beta ratio of 3 Gy (see Table S3.2 in Supplement 3D for consistent results for the alternative alpha-beta ratio of 5.4 Gy). The rectal \( D_{0.1cc} \), \( D_{1cc} \) and \( D_{2cc} \) for full parameter-adding were greater than those for partial parameter-adding in terms of medians (e.g. 70.9, 65.2 and 62.1 Gy versus 70.2, 65.0 and 62.0 Gy). The \( D_{10cc} \) was less for full parameter-adding (e.g. 52.7 Gy versus 53.8 Gy). The median paired-differences between partial parameter-adding and full parameter-adding were less than -0.7% (\( p<0.001 \)), -0.4% (\( p<0.001 \)), -0.3% (\( p=0.07 \)) and 2% (\( p<0.001 \)) for the \( D_{0.1cc} \), \( D_{1cc} \), \( D_{2cc} \) and \( D_{10cc} \) respectively.

In Figure 3.4(B) the relative differences between parameter-adding and distribution-adding are reported for an alpha-beta ratio of 3 Gy. The median per-
Figure 3.4: (A) The median rectal $D_X$ obtained by applying two alternative parameter-adding methods to the EBRT and HDR-BT TG43 doses with an $\alpha/\beta=3$ Gy for 82 patients. (B) The median paired-differences between the parameter-adding and distribution-adding methods (as percentages of the distribution-adding values) with an $\alpha/\beta=3$ Gy for 82 patients. The vertical lines in figures represent the 25th and 75th percentiles. The p-values (p) are from exact Wilcoxon signed-rank tests (alternatively, see Supplement 3D for full statistical results, which include the 95% confidence intervals). Parameters and statistical tests are explained in the methods section.

The percentage differences between full parameter-adding and distribution-adding are negative, significant and considerable for the $D_{0.1cc}$ (e.g. -21.3%, $p<0.001$). Additionally, the median percentage differences between full parameter-adding and distribution-adding are negative, significant and low for the rectal $D_{1cc}$ and $D_{2cc}$ (e.g. -6.3% and -3.5% with $p<0.001$). However, the 25th percentiles for the differences associated with the rectal $D_{1cc}$ and $D_{2cc}$ are largely negative (e.g. -22.3% and -12.5%).

The differences between full parameter-adding and distribution-adding for the $D_{10cc}$ are positive and significant; however, these differences are small (e.g. 2.2%, $p=0.015$). The differences between partial parameter-adding and distribution-adding for the $D_{0.1cc}$, $D_{1cc}$, $D_{2cc}$ and $D_{10cc}$ were similar to the differences when full parameter-adding was applied [Figure 3.4(B)].

3.7 Discussion

This study is the first to compare rectal dose accumulation using registration-based distribution-addition with DVH-based parameter-addition methods in the context of combined EBRT/HDR-BT prostate cancer treatment. Studies [7, 15] have explored EBRT/HDR-BT rectal dose accumulation without deformable image registration; however, Kikuchi et al. [7] acknowledged that deformable image registration should be part of a more accurate method of accumulating the dose to the rectum.
This study improved upon these studies by including a larger sample size of 82 patients, applying deformable image registration and comparing parameter-adding and distribution-adding. The context of this study is also important as it should not be assumed the comparisons of parameter-adding and distribution-adding reported for non-prostate cancer treatments [4, 12, 17–21] set a precedent for prostate cancer treatments, as the contouring, registration, anatomy, protocol and treatment circumstances are different and require verification.

The two methods for parameter-adding generate estimates of the accumulated rectal dose through the addition of unregistered-dose metrics. However, such estimates can only be considered to be maximum estimates for accumulation if it is assumed that the same elements of tissue receive the highest doses from each treatment phase [8]. Additionally, partial parameter-adding assumes that the dose to the EBRT rectum is homogeneous at the prescription dose for EBRT and that the prescription dose is the peak dose regardless of any high-dose hot-spots that may extend into the rectal contour [4]. Consequently, partial parameter-adding only represents a ‘worst possible’ case if the EBRT prescription dose is equal to or greater than any peak-dose hot-spots in the EBRT dose [4]. However, Figure S3.1 in Supplement 3B shows that for patients in this study there are heterogeneous regions of EBRT dose within the PTV with dose greater than the prescription dose. Additionally, the $D_{0.1cc}$ from partial parameter-adding was less than the corresponding full parameter-adding value for 69 of the 82 patients in this study. Consequently, partial parameter-adding does not provide conservative estimates of peak dose for all cases compared to full parameter-adding as it is based on assumptions. Overall, the percentage differences between partial parameter-adding and full parameter-adding were small for the high-dose metrics, e.g. -0.7%, -0.4% and -0.3% for the $D_{0.1cc}$, $D_{1cc}$ and $D_{2cc}$ respectively. The differences between parameter-adding and full parameter-adding are small enough that it is inconsequential which method is used and subsequently the high-dose metrics for distribution-adding can be reliably compared with those from either of the parameter-adding methods. The results indicate distribution-adding versus full parameter-adding is conservative as it provides the closest comparison.

The assumption that full parameter-adding provides a conservative estimate of
peak dose compared to distribution-adding is faulty in certain situations. Full parameter-adding will represent the ‘worst possible’ case for peak dose when the dose distribution is invariant between fractions [8] and the rectum has been contoured without any inter/intra-observer errors [39]. However, peak rectal doses can be different if there are errors in the contouring of the anterior rectal wall or motion after the planning CT. Hence, inter/intra-fraction motion [18] or violation of the no inter/intra-observer rectal-contouring errors assumption could lead to either smaller or larger parameter-adding estimates at high doses relative to distribution-adding. Ideally, imaging over the duration of treatment would be acquired to allow an assessment of the impact of intra/inter-fraction motion. However, it is common for retrospective studies, such as this one, to be constrained by resources and protocols in place at the time patients were treated. The potential influence of inter/intra-fraction motion on rectal doses for patients in this study who received combined prostate EBRT/HDR-BT has previously been discussed in more detail [29].

Inaccuracy in registrations could also influence the difference between parameter-adding and distribution-adding estimates. For the patients in this study, the visual inspections of registrations did not indentify any major misalignments of rectum walls. However, it is difficult to evaluate registrations and quantify the registration inaccuracy for patients, as there is no known ground truth [8]. As such, distribution-adding is also subject to uncertainties regarding anatomical accuracy achieved by the registrations. Misalignment after registrations could lead to smaller or larger distribution-adding estimates. Alternatively, it is plausible that smaller or non-systematically-larger distribution-adding estimates across a patient sample could be obtained for distribution-adding relative to parameter-adding if a perfect registration was associated with inter/intra-observer rectal-contouring errors. The problem is further compounded by the difficulty of separating the contouring and registration contributions at a localised level within the anatomy as a systematic bias of either was not observed. Parametric and non-parametric regressions of overlap metrics with differences between distribution-adding and parameter-adding were performed in attempts to further scrutinise the impact of registration accuracy. However, the fits for such regressions were poor, which may be a result of the non-systematic nature of the differences as well as the visual assessments excluding poor registra-
tions from inclusion in the study. Given that the confounding factors cannot be isolated, it is important for distribution-adding and parameter-adding estimates to be published for a variety of studies to allow a multi-institutional comparison of findings and the confounding factors associated with specific prostate cancer treatment techniques, contouring circumstances and registration applications. Centres looking to accumulate the dose for EBRT/HDR-BT data may benefit from additional imaging between the start of EBRT and start of HDR-BT to assess the influence of contouring, motion and registration.

Applying registration and 3D-dose summation to combined EBRT/HDR-BT prostate cancer treatment plans resulted in greater median rectal $D_{0.1cc}$, $D_{1cc}$ and $D_{2cc}$ compared to parameter-adding (e.g. 21%, 6% and 4% for the $D_{0.1cc}$, $D_{1cc}$ and $D_{2cc}$). Additionally, patients in the 25th percentile for the differences had considerably greater $D_{0.1cc}$, $D_{1cc}$ and $D_{2cc}$ values for distribution-adding compared to parameter-adding. Studies have provided results consistent with the plausibility of higher rectal dose parameters from distribution-adding when there is heterogeneity in the dose distribution, contouring inconsistencies and/or intra/inter-fraction motions [4, 21]. For example, Sabater et al. [21] found that distribution-adding of endometrial cancer HDR-BT fractions overstated the rectal $D_{0.1cc}$ by 3% compared to plans which simply scale the dose from the first HDR-BT fraction by the number of fractions and consequently did not consider motion. Additionally, Van de Kamer et al. [4] reported that the distribution-adding $D_{2cc}$ for combined cervical EBRT/HDR-BT exceeded parameter-adding values by 0.7% when there are rectal structures for each phase as well as heterogeneity in the dose distribution due to the parametrium boost dose. The differences reported in the study by Van de Kamer et al. [4] may be smaller than the differences reported in this study due to the proximity of the rectal wall to the target volume being different for a parametrium boost dose compared to prostate boost dose. Additionally, the degree and coverage of heterogeneities in dose distributions will be different. Studies in a variety of registration contexts are warranted, as it is important to determine the clinical usefulness of distribution-adding given that the above mentioned studies [4, 21] contrast with other cervical cancer studies [12, 17, 19] where the parameter-adding $D_{2cc}$ was reported to be larger by 0% to 4%.
In this current study, possible errors in contouring and registration accuracy will confound parameters obtained via distribution-adding. For example, the total rectal $D_{2cc}$ for distribution-adding (67.0 $EQD2$ Gy) was greater than that from full parameter-adding (64.8 $EQD2$ Gy) for the patient in Figure 3.3. However, there was greater separation between the HDR-BT CTV and HDR-BT rectum in Figure 3.3(A) compared to the EBRT CTV and EBRT rectum in Figure 3.3(B). The difference in separation could be explained by anatomical changes and/or contouring variations. Additionally, the EBRT rectum has been contoured close to the EBRT CTV in Figure 3.3(B) while the high-dose region of the HDR-BT dose has been registered partially over the anterior wall of the EBRT rectum in Figure 3.3(B). This registration result is confounded by potential registration inaccuracies for the prostate/rectum interface. Consequently, in some cases distribution-adding could be sensitive to contouring variations for the anterior rectal wall and/or registration inaccuracies for the prostate/rectum interface. The overlap results for the registration in Figure 3.3(B) would generally indicate a good registration (e.g. 94.5% and 0.3% for the metrics assessing general rectal volume-correspondence and registration of the HDR-BT prostate further over the anterior wall of the EBRT rectum respectively). A median overlap of 82% for the rectal volume-correspondence across all patients would also indicate that the registrations are satisfactory. However, the proximity of the HDR-BT rectum to the HDR-BT catheters makes distribution-adding sensitive to small localised variations in contouring and/or registration accuracy across the prostate/rectum interface. When comparing the addition methods there were three concerns for combined EBRT/HDR-BT. (1) The HDR-BT catheters located close to the anterior side of the HDR-BT CT rectal wall can be registered closer to the corresponding EBRT CT rectum. (2) The HDR-BT prostate to be registered further anteriorly (away) from the EBRT rectum. (3) Inconsistency in contouring the HDR-BT rectum less anteriorly and/or the EBRT rectum more anteriorly would lead to lower estimates for parameter-adding, as the parameters for the HDR-BT DVH would be lower and/or the EBRT rectum would extend further into the registered HDR-BT dose. For this study, distribution-adding requires a careful consideration of (1) and (3) as they have the potential to lead to the larger values that were observed for distribution-adding relative to parameter-adding. The median structure
overlap results for (1) and (2) were 3% and 0.2% respectively; however, direct comparison of these metrics is confounded as they contain different structures which were contoured at different times in the combined treatment.

Distribution-adding and the associated considerations are less appealing for the $D_{10\text{cc}}$ and other intermediate-dose parameters, as parameter-adding provides larger $D_{10\text{cc}}$ estimates and it is questionable whether the 25th percentile for the differences between parameter-adding and distribution-adding is clinically actionable.

Given this is the first study to compare the choice of methods for combined EBRT/HDR-BT prostate cancer treatments, we encourage more centres to undertake more prostate cancer studies to assess the accuracy of dose accumulation using similar methods to those applied for combined EBRT/HDR-BT cervical cancer treatment [4, 12, 17]. Software developers and treatment-planning vendors have the opportunity to contribute considerably to this advanced accumulation-based EBRT/HDR-BT treatment by customising registrations for this context. Studies at other institutions regarding the choice of methods for prostate cancer treatments would be useful for assessing the influence of confounding factors on the discrepancies between the methods and reporting the comparisons for a variety of registration algorithms. Such studies would also be important for obtaining a consensus on the clinical usefulness of distribution-adding. It would be useful to subsequently determine what impact differences between methods have on dose-volume modelling [9] and dose-shape toxicity modelling [40].

### 3.8 Conclusions

This is the first published study for prostate EBRT combined with a HDR-BT boost to find that parameter-based addition resulted in smaller (larger) median $D_{0.1\text{cc}}$, $D_{1\text{cc}}$ and $D_{2\text{cc}}$ ($D_{10\text{cc}}$) values compared to distribution-based addition. The differences in the $D_{0.1\text{cc}}$, $D_{1\text{cc}}$ and $D_{2\text{cc}}$ values for parameter-adding versus distribution-adding were large enough in the 25th percentile of patients to warrant clinical consideration. However, comparisons of parameter-adding and distribution-adding are confounded by heterogeneously-distributed high-dose, inter/intra-observer rectal-contouring errors, potential intra/inter-fraction motion and registration accuracy around the anterior rectal wall. Consequently, attempts to accurately accumulate rectal dose by apply-
ing the more advanced method of distribution-adding have to include careful contour, motion and registration checks, as associated uncertainties in the high-dose region could lead to inaccurately-reported rectal parameters and clinically unusable parameters. Distribution-adding and subsequent checks were less appealing for intermediate-dose parameters as parameter-adding provided conservative estimates.

3.9 Acknowledgements

We appreciate the ideas from Annette Haworth and radiation oncology staff at Sir Charles Gairdner Hospital. We are grateful for funding from the University of Western Australia, an Australian Postgraduate Award, an Ana Africh Postgraduate Scholarship, the National Health and Medical Research Council (grants 300705, 455521, 1006447), the Health Research Council (New Zealand), the Hunter Medical Research Institute, Novartis Pharmaceuticals and Abbott Laboratories. We acknowledge the TROG 03.04 RADAR Trial is registered (under number NCT00193856) with the National Institutes of Health Clinical Trials Registry. The RADAR trial has approval from the Sir Charles Gairdner Group Human Research Ethics Committee (2003-050), the University of Western Australia Human Research Ethics Office (RA/4/1/5601) and the Hunter New England Human Research Ethics Committee (Trial ID. 03/06/11/3.02).

3.10 Supplements 3A-3D

3.10.1 Supplement 3A

This supplement provides additional detail on patient characteristics and treatment protocol.

The additional details on the standard HDR-BT treatment process are:

- The temporary metal needle HDR-BT catheters were inserted with trans-rectal ultrasound, fluoroscopy and perineal template guidance while the patient was in the lithotomy position.
• Needle catheters were inserted and cystoscopy was used to ensure proper tenting of the bladder wall mucosa by catheters.

• A plastic template was sutured to the skin to hold the needles in place.

• The patient was then taken to have a HDR-BT planning CT and a three-fraction HDR-BT plan was created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US) based on this CT.

• Patients were in the lithotomy position for HDR-BT treatment with cushions used to keep the patients’ legs in the abducted position between fractions.

• No patient had artificial hip joints.

**Table S3.1:** The baseline clinical characteristics of 82 patients who underwent external beam radiotherapy followed by high-dose-rate brachytherapy for prostate cancer. Abbreviations: PSA = Prostate-specific antigen; HDR-BT = High-dose-rate brachytherapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspect of characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median</td>
<td>67.5</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>61.3-72.3</td>
</tr>
<tr>
<td>PSA</td>
<td>PSA &lt; 10</td>
<td>22 (26.8%)</td>
</tr>
<tr>
<td></td>
<td>10 ≤ PSA &lt; 20</td>
<td>30 (36.6%)</td>
</tr>
<tr>
<td></td>
<td>PSA ≥ 20</td>
<td>30 (36.6%)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>&lt; 7</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td></td>
<td>= 7</td>
<td>29 (35.4%)</td>
</tr>
<tr>
<td></td>
<td>≥ 8</td>
<td>51 (62.2%)</td>
</tr>
<tr>
<td>Tumour classification</td>
<td>T2b</td>
<td>10 (12.2%)</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>8 (9.8%)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>63 (76.8%)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Risk group</td>
<td>Medium</td>
<td>23 (28%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>59 (72%)</td>
</tr>
<tr>
<td>Number of HDR-BT catheters</td>
<td>12</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>67 (81.7%)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>9 (11.0%)</td>
</tr>
</tbody>
</table>
3.10.2 Supplement 3B

This supplement provides additional examples of planned doses.

**Figure S3.1:** A four-field EBRT physical dose plan with dose displayed as a colourwash between 45.9 and 47.4 Gy (the maximum dose) to highlight heterogeneous dose regions. Physical dose between 40.1 and 45.9 Gy is uniformly displayed as dark blue to illustrate dose coverage of the PTV. Physical dose below 40.1 Gy is not displayed. The rectal $D_{1cc}$ was 47.3 Gy for the physical EBRT dose and 47.8 Gy for equieffective EBRT dose given in 2 Gy per fraction. The EBRT CTV, PTV and rectal structures are in yellow, red and green respectively.
Figure S3.2: A closer inspection of doses around the HDR-BT catheters with physical dose displayed as a colourwash between 7 and 47 Gy to highlight high-dose regions. Physical doses below 7 Gy are not displayed. The HDR-BT CTV, SDV and rectal structures are in yellow, red and green respectively.
3.10.3 Supplement 3C

This supplement provides an example of the visual check on registration alignment.

Figure S3.3: Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images. The EBRT images are in the background. Regions of the HDR-BT images after a rigid plus multi-pass deformable image registration are contained within the yellow outlined rectangular spyglass box. This box can be resized and moved around (e.g. left image versus right image). The EBRT CTV, PTV and rectal structures are in purple, red and green respectively. Source: [29], Creative Commons CC-BY.
3.10.4 Supplement 3D

This supplement provides results for statistical tests and a comparison with the results for $\alpha/\beta = 5.4$ Gy.

**Table S3.2:** Results of exact Wilcoxon signed-rank tests applied for 82 patients when alpha-beta ratios of 3 Gy and 5.4 Gy were used. The median percentage differences (MD) are reported along with the interquartile range (IQR), 95% confidence interval (CI) and Z-value (Z)/p-value (p) from the Wilcoxon test.

<table>
<thead>
<tr>
<th>Difference description</th>
<th>$D_X$</th>
<th>MD</th>
<th>IQR</th>
<th>95% CI</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full parameter-adding versus distribution-adding with $\alpha/\beta = 3$ Gy</td>
<td>$D_{0.1cc}$</td>
<td>-21.3</td>
<td>(-50.3, -4.0)</td>
<td>(-30.9, -18.5)</td>
<td>-6.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{1cc}$</td>
<td>-6.3</td>
<td>(-22.3, 1.5)</td>
<td>(-30.9, -18.5)</td>
<td>-6.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{2cc}$</td>
<td>-3.5</td>
<td>(-12.5, 3.3)</td>
<td>(-30.9, -18.5)</td>
<td>-6.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{10cc}$</td>
<td>2.2</td>
<td>(-1.7, 3.6)</td>
<td>(-30.9, -18.5)</td>
<td>-6.58</td>
<td>0.015</td>
</tr>
<tr>
<td>Full parameter-adding versus distribution-adding with $\alpha/\beta = 5.4$ Gy</td>
<td>$D_{0.1cc}$</td>
<td>-17.9</td>
<td>(-44.6, -3.4)</td>
<td>(-27.3, -16.0)</td>
<td>-6.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{1cc}$</td>
<td>-5.2</td>
<td>(-18.7, 1.2)</td>
<td>(-10.8, -4.1)</td>
<td>-4.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{2cc}$</td>
<td>-2.9</td>
<td>(-10.5, 2.9)</td>
<td>(-6.3, -1.6)</td>
<td>-3.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{10cc}$</td>
<td>2.0</td>
<td>(-1.6, 3.1)</td>
<td>(0.3, 2.2)</td>
<td>2.47</td>
<td>0.013</td>
</tr>
<tr>
<td>Partial parameter-adding versus distribution-adding with $\alpha/\beta = 3$ Gy</td>
<td>$D_{0.1cc}$</td>
<td>-22.4</td>
<td>(-50.7, -4.6)</td>
<td>(-31.6, -19.3)</td>
<td>-6.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{1cc}$</td>
<td>-7.0</td>
<td>(-22.5, 1.8)</td>
<td>(-13.3, -5.6)</td>
<td>-4.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{2cc}$</td>
<td>-3.5</td>
<td>(-12.6, 3.0)</td>
<td>(-7.8, -2.3)</td>
<td>-3.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{10cc}$</td>
<td>4.0</td>
<td>(-0.6, 7.2)</td>
<td>(2.4, 5.0)</td>
<td>4.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial parameter-adding versus distribution-adding with $\alpha/\beta = 5.4$ Gy</td>
<td>$D_{0.1cc}$</td>
<td>-19.1</td>
<td>(-45.0, -4.0)</td>
<td>(-28.0, -16.8)</td>
<td>-6.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{1cc}$</td>
<td>-5.8</td>
<td>(-19.0, 1.5)</td>
<td>(-11.2, -4.7)</td>
<td>-4.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{2cc}$</td>
<td>-2.8</td>
<td>(-10.7, 2.7)</td>
<td>(-6.5, -1.9)</td>
<td>-3.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$D_{10cc}$</td>
<td>3.8</td>
<td>(-0.6, 6.5)</td>
<td>(2.2, 4.6)</td>
<td>4.99</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
3.11 References


[22] J. E. Scaife, S. J. Thomas, K. Harrison, et al., “Accumulated dose to the rectum, measured using dose-volume histograms and dose-surface maps, is different from planned dose in all patients treated with radiotherapy for...


Stage II:

Associating dose-volume metrics from planned dose with symptoms
Chapter 4:
Dose-volume histogram analysis
4.1 Foreword for manuscript

The previous chapter determined that the medians of high-dose metrics from distribution-adding are greater than the corresponding medians from parameter-adding and that the discrepancies for sub-groups of patients containing 25% of the largest differences warrant clinical consideration. The previous chapter also explained that the differences between the methods are confounded by registration and contouring uncertainties near the anterior rectal wall where the dose gradients from the high-dose-rate brachytherapy (HDR-BT) are high. Consequently, the manuscript in this chapter correlated both the high-dose parameter-adding dose-volume histogram (DVH) parameters and high-dose distribution-adding DVH parameters with gastrointestinal toxicities observed after combined external beam radiotherapy (EBRT)/HDR-BT. Additionally, the published paper included in this chapter outlines which DVH parameters demonstrate the greatest dose-response in terms of odds ratios.

The intention of the manuscript in this chapter is to determine whether DVH parameters determined as important for complications after combined EBRT/HDR-BT are consistent with DVH parameters reported in the literature as being important for patients receiving EBRT or combined EBRT/HDR-BT. Another motivation for the study in this chapter is to gain knowledge of the important DVH parameters for comparison with subsequent normal tissue complication probability analysis (Chapter 5). Additionally, the findings for DVH parameters are required for comparison with more advanced models that include spatial information on the dose distribution (Chapter 6).
4.2 Manuscript details

Prostate external beam radiotherapy combined with high-dose-rate brachytherapy: dose-volume parameters from deformably-registered plans correlate with late gastrointestinal complications.


Publication status: Published. The manuscript in this chapter (including supplements) is a typeset of the final published article. The inclusion of published material in this chapter is allowed by the copyright agreement for the final published article [1].

4.3 Abstract

4.3.1 Background

The derivation of dose-volume which will subsequently be used in toxicity modelling can be difficult for multi-modal treatments due to the perceived need for voxel-by-voxel dose accumulation. With data available for a single-institution cohort with long follow-up, an investigation was undertaken into rectal dose-volume effects for gastrointestinal toxicities after deformably-registering each phase of a combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) prostate treatment.

4.3.2 Methods

118 patients received EBRT in 23 fractions of 2 Gy and HDR-BT (TG43 algorithm) in three fractions of 6.5 Gy. Results for the Late Effects of Normal Tissues - Subjective, Objective, Management and Analytic toxicity assessments were available with a median follow-up of 72 months. The HDR-BT CT was deformably-registered to the EBRT CT. Doses were corrected for dose fractionation. Rectal dose-volume histogram (DVH) parameters were calculated in two ways. (1) Distribution-adding: parameters were calculated after the EBRT dose distribution was 3D-summed with the registered HDR-BT dose distribution. (2) Parameter-adding: the EBRT DVH parameters were added to HDR-BT DVH parameters. Logistic regressions and Mann-Whitney U-tests were used to correlate parameters with late peak toxicity (dichotomised at grade 1 or 2).

4.3.3 Results

The 48-80, 40-63 and 49-55 Gy dose regions from distribution-adding were significantly correlated with rectal bleeding, urgency/tenesmus and stool frequency respectively. Additionally, urgency/tenesmus and anorectal pain were associated with the 25-26 Gy and 44-48 Gy dose regions from distribution-adding respectively. Parameter-adding also indicated the low-mid dose region was significantly correlated with stool frequency and proctitis.
4.3.4 Conclusions

This study confirms significant dose-histogram effects for gastrointestinal toxicities after including deformable registration to combine phases of EBRT/HDR-BT prostate cancer treatment. The findings from distribution-adding were in most cases consistent with those from parameter-adding. The mid-high dose range and near maximum doses were important for rectal bleeding. The distribution-adding mid-high dose range was also important for stool frequency and urgency/tenesmus. We encourage additional studies in a variety of institutions using a variety of dose accumulation methods with appropriate inter-fraction motion management.
4.4 Introduction

External beam radiotherapy (EBRT) with a high-dose-rate brachytherapy (HDR-BT) boost dose is used to treat prostate cancer patients [2]. This treatment and other radiotherapy treatments are planned with consideration of the dose-volume parameters and subsequent constraints associated with acceptable levels of normal tissue toxicity [3]. However, typically the phases of combined EBRT/HDR-BT are planned separately [4]. Constraints on the total planned dose from the two phases would be appropriate for reducing normal tissue toxicity [5]. Constraints could be applied for each phase; however, this is susceptible to anatomical differences between the planning CTs.

When adjustments for anatomical changes are not included, the relevance of plans based on dose-volume constraints depends on how well the planned dose reflects the delivered dose [6]. Hence, studies in other radiotherapy contexts have incorporated dose accumulation [7, 8]. Simple crude addition of the separately planned doses from two modalities is not valid as the anatomy in the CT image study sets may be misaligned due to variations in reference coordinate systems, displacements, deformations and shrinkage [9]. Consequently, a rigid registration is used to align the reference coordinate systems and then deformable image registration (DIR) is applied to adjust for deformations and shrinkage [10, 11]. Additionally, the doses for different fraction schedules should be converted to the equieffective doses given in a reference $X$ Gy per fraction ($EQDX_{\alpha/\beta}$ Gy), as this adjusts for the biologically non-equivalent fractionation schedules [6, 12, 13].

Adjusting for anatomical differences between planning CTs and subsequently accumulating the phases of planned dose more accurately may allow dose-volume parameters to be more appropriately correlated with toxicity [3, 14]. Studies accumulating the rectal dose from phases of a combined EBRT/HDR-BT prostate treatment by applying deformable registration are lacking. This study uses data from combined EBRT/HDR-BT prostate cancer treatments, which were subject to multicentre trial guidelines, to assess whether the rectal dose-histogram parameters extracted after applying deformable registration are correlated with late gastrointestinal toxicities.
4.5 Methods

4.5.1 Patient data

This study included 118 prostate cancer patients (tumour T stage $\geq 2a$) who were treated with EBRT followed by HDR-BT at Sir Charles Gairdner Hospital in the period 2004 to 2008. These patients were treated as part of the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [15, 16]. The patient criteria and treatment methodology for the RADAR trial have previously been detailed [15, 16]. Aspects of the combined EBRT/HDR-BT treatment process have previously been described [17]. The four-field EBRT plans for a prescription dose of 46 Gy in 23 daily fractions were created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden). The HDR-BT plans for a prescription dose of 19.5 Gy in three fractions across two days were created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US) using the TG43 formalism [18]. Supplement 4A provides additional patient and treatment details.

The external wall of the rectum was manually delineated by treating-clinicians in the HDR-BT CTs using BrachyVision and in the EBRT CTs using the Elekta Focal contouring system (Elekta AB, Stockholm, Sweden). Author with initials MK reviewed outlines of rectums for consistency between patients. For contouring the rectum, the inferior-superior limits of the rectum were the rectosigmoid flexure and the last slice where the ischial tuberosities were visible. Patients did not commonly require bowel preparation. Examples of the planning CTs and structures for EBRT and HDR-BT TG43 physical dose plans are provided by Figures S4.1 and S4.2 in Supplement 4B.

4.5.2 Toxicity outcomes

Patients were assessed for various gastrointestinal toxicities at baseline (randomisation) and subsequent time points after randomisation. The median of the most recent patient follow-ups was 72 months (range 12-96 months). The Late Effects of Normal Tissue - Subjective, Objective, Management and Analytic (LENT-SOMA) scales were used to assess rectal bleeding, urgency and tenesmus, stool frequency, di-
Late peak toxicity was calculated for the period onwards from three months after radiation therapy. Figure 4.1 provides a summary of the late peak toxicity event rates for the follow-up period. Patients were classified to a toxicity group if the late peak toxicity was at least a certain grade (threshold for dichotomisation). In the interest of modelling a moderate severity of toxicity, the threshold was grade 2 for rectal bleeding, stool frequency and completeness of evacuation. The threshold was grade 1 for diarrhoea, anorectal pain, proctitis, urgency and tenesmus due to low toxicity rates for grade \( \geq 2 \) toxicity and/or a lack of significance for grade \( \geq 2 \) toxicity. Alternatively, the chosen thresholds for toxicities are indicated in Figure 4.1. The analysis was repeated using the prevalence of toxicity at 36 months post-randomisation. This did not reveal any additional trends for dose-histogram effects...
and so is reported no further.

### 4.5.3 Registration process

The HDR-BT CT was registered to the EBRT CT using rigid registration followed by a B-splines multi-pass DIR in Velocity Advanced Imaging 2.8.1 (Varian Medical Systems, Palo Alto, US) [21]. The registration process has been described in detail previously [21, 22]. Visual inspections for the 118 patients were undertaken by authors (initials CRM, VL and CIT) and did not identify any major registration misalignments (e.g. Figure S4.3 in Supplement 4D). The registrations were quantitatively evaluated for each patient in this study using the overlap of the EBRT rectum and registered HDR-BT rectum (expressed as a percentage of the volume of the registered HDR-BT rectum). As illustrated in Figure 4.2, the median overlap is 80.4% for alignment of EBRT/registered HDR-BT rectal structure volumes. A general structure overlap of 70% is considered to be the starting point for satisfactory structure-correspondence in the radiotherapy context [23, 24]. The registrations have also previously been extensively evaluated using structure-correspondence metrics, image-similarity metrics and qualitative visual inspection by authors (initials CRM, VL and CIT) [22].

### 4.5.4 Obtaining dose-volume histograms

The EBRT and registered HDR-BT 3D-doses were imported into MATLAB™ R2010a (The MathWorks Inc., Massachusetts, US) and the Computational Environment for Radiotherapy Research (CERR, version 4.1) [25]. The voxel doses were converted to equieffective doses given in a reference 2 Gy per fraction using the linear-quadratic model [12] with an alpha-beta ratio ($\alpha/\beta$) of 3 Gy for the rectum [3]. The analysis was also performed for an alpha-beta ratio of 5.4 Gy to check the sensitivity of results to the upper limit published for the rectum [26]. The EBRT dose was summed voxel-by-voxel with the registered HDR-BT dose (i.e. accumulated). The rectal dose-volume histograms (DVH) in 1 Gy bins from 1-80 Gy were extracted for the total registered dose (with EBRT rectal structure), the unregistered EBRT dose (with EBRT rectal structure) and the unregistered HDR-BT dose (with the HDR-BT rectal structure). The parameters extracted from the rectal...
Figure 4.2: Registration evaluation using the overlap of structures. Illustration of the structure-overlap metric used to assess major misalignment of rectal volume (Top). Overlap of the EBRT rectum/registered HDR-BT rectum was expressed as a percentage of the volume of the registered HDR-BT rectum. Structure overlap results for the 118 patients after the rigid plus multi-pass DIR are provided (Bottom).

DVHs were the $V_X$ (percentage of the rectal volume receiving at least $X$ Gy after applying an alpha-beta ratio) and $D_{X\%}$ (minimum dose to the most irradiated $X$ percent of the rectal volume after applying an alpha-beta ratio). The $V_X$ and $D_{X\%}$ were calculated using the total registered dose and the EBRT rectal structure (‘distribution-adding’). Additionally, the $D_{X\%}$ was alternatively calculated by adding the EBRT $D_{X\%}$ to the unregistered HDR-BT $D_{X\%}$ using the corresponding rectal structures (‘parameter-adding’).

4.5.5 Response modelling

For each type of toxicity, univariate logistic regression was applied at each $V_X$ to obtain an odds ratio (OR) for the increase in toxicity probability per 5% absolute increase in volume [27]. 95% confidence intervals (CI) for odds ratios were calcu-
lated using bootstrapping with 10,000 resamples from the toxicity and no toxicity groups. Odds ratios were considered significant if the 95% CIs did not include the value of one. Mann-Whitney U-tests were used to determine whether the median $V_X$ (or $D_{X\%}$) values for the toxicity and no toxicity groups were significantly different (p-value < 0.05). This analysis was performed in MATLAB$^\text{TM}$ R2010a (The MathWorks Inc., Massachusetts, US).

Clinical risk factors were not included in dose-response modelling as a previously published analysis determined that clinical covariates did not significantly influence late toxicities for patients in the RADAR trial [28]. An equivalent analysis for the 118 patients in this study confirmed that clinical covariates did not significantly influence late toxicities and are thus not reported any further. The clinical factors considered were age, tumour T stage, Gleason score, initial PSA, risk group, number of HDR-BT catheters, colorectal disorders, hypertension, diabetes, smoking, use of statins, ACE inhibitors and anti-coagulants.

4.6 Results

Unless it is stated otherwise, all figures and tables in this section report distribution-adding dose values in a reference 2 Gy per fraction using an $\alpha/\beta = 3$ Gy.

Figure 4.3 provides the logistic regression odds ratio results for late rectal bleeding, stool frequency, diarrhoea, anorectal pain, urgency and tenesmus respectively. Figure 4.3 includes an indication for distribution-adding dose levels where the 95% confidence intervals for the odds ratio did not include a value of one. For completeness of evacuation and proctitis, the odds ratios are not significantly different from one at any dose levels (Figure S4.4 in Supplement 4E).

Figure 4.4 provides the distribution-adding $V_X$ results for late rectal bleeding, stool frequency, diarrhoea, anorectal pain, urgency and tenesmus. Figure 4.5 provides the corresponding distribution-adding $D_{X\%}$ results for late rectal bleeding, stool frequency, diarrhoea, urgency and tenesmus. Figures 4.4 and 4.5 include an indication of dose and volume levels for which there was a significant difference between the toxicity and no toxicity groups (p-value < 0.05). For completeness of evacuation and proctitis, there are no significant differences between the toxicity and no toxicity group results at any distribution-adding $V_X$ (Figure S4.5 in Supple-
Figure 4.3: Odds ratios from univariate ordinal regression of distribution-adding $V_X$ and peak late toxicity. The toxicities are rectal bleeding (A), stool frequency (B), diarrhoea (C), anorectal pain (D) and urgency/tenesmus (E). The peak late toxicities for rectal bleeding and stool frequency were dichotomised at grade 2 whereas diarrhoea, anorectal pain and urgency/tenesmus were dichotomised at grade 1. A red dot is used to indicate the doses at which odds ratios are significantly different from a value of one (95% confidence intervals do not include one). Abbreviations: $V_X$, percentage of the rectal volume receiving at least $X$ Gy after applying an $\alpha/\beta = 3$ Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy; 95% CI, 95% confidence interval.

For completeness of evacuation, anorectal pain and proctitis, there are no significant differences between the toxicity and no toxicity group results at any distribution-adding $D_{X\%}$ (Figure S4.6 in Supplement 4E).

Table 4.1 summarises the important distribution-adding doses for the odds ratios and the important distribution-adding doses (volumes) for the $V_X$ ($D_{X\%}$) results. Additionally, Table 4.1 summarises the important volumes for the $D_{X\%}$ obtained by parameter-adding (alternatively, see Figure S4.7 Supplement 4F for full results.
Figure 4.4: Median distribution-adding $V_X$ for the toxicity and no toxicity groups. The toxicity groups are based on peak late toxicity. The peak late toxicities for rectal bleeding (A) and stool frequency (B) were dichotomised at grade 2 whereas diarrhoea (C), anorectal pain (D) and urgency/tenesmus (E) were dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $V_X$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $V_X$, percentage of the rectal volume receiving at least X Gy after applying an $\alpha/\beta = 3$ Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy.

for the $D_{X\%}$ obtained by parameter-adding). The $D_{8-13\%}$ and $D_{5-38\%}$ become important for diarrhoea and urgency/tenesmus respectively when distribution-adding is used instead of parameter-adding. The parameter-adding $D_{59-70\%}$ and $D_{58-73\%}$, which were significant for proctitis and stool frequency respectively, are not significant when distribution-adding is used. However, the $D_{36-74\%}$ becomes important for urgency/tenesmus when distribution-adding is used instead of parameter-adding. Similar trends for significance of $D_{X\%}$ are found for all other toxicities regardless of
Figure 4.5: Median distribution-adding $D_{X\%}$ for the toxicity and no toxicity groups. The peak late toxicities for rectal bleeding (A) and stool frequency (B) were dichotomised at grade 2 whereas diarrhoea (C) and urgency/tenesmus (D) were dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $D_{X\%}$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $D_{X\%}$, minimum dose to the most irradiated $X$ percentage of rectal volume after applying an $\alpha/\beta = 3$ Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy.

Table 4.2 summarises the influence of using an $\alpha/\beta$ ratio of 5.4 Gy instead of 3 Gy. Alternatively, Figures S4.8, S4.9 and S4.10 in Supplement 4G provide the odds ratio, $V_X$ and $D_{X\%}$ results when distribution-adding and an $\alpha/\beta$ of 5.4 Gy are used. Also, Figure S4.11 in Supplement 4H alternatively provides the $D_{X\%}$ results obtained by parameter-adding with an $\alpha/\beta$ of 5.4 Gy. The odds ratio at $EQD2_{\alpha/\beta}$ 51 Gy for diarrhoea is no longer significant if an $\alpha/\beta$ of 5.4 Gy is used instead of 3 Gy. However, similar trends for significance of odds ratios, $V_X$ and $D_{X\%}$ are found for all other toxicities regardless of whether the $\alpha/\beta$ is 3 or 5.4 Gy.
Table 4.1: Summary of which parameters (odds ratios, \(V_X\) and \(D_{X\%}\)) correlate with toxicity. The statistical test results indicate doses at which odds ratios were significantly different from a value of one, doses at which the median \(V_X\) for toxicity and no toxicity groups were significantly different and volumes at which the median \(D_{X\%}\) for toxicity and no toxicity groups were significantly different. Abbreviations: \(V_X\), percentage of the rectal volume receiving at least \(X\) EQD2 Gy after applying an \(\alpha/\beta = 3\) Gy; \(D_{X\%}\), minimum EQD2 Gy dose to the most irradiated \(X\) percentage of rectal volume after applying an \(\alpha/\beta = 3\) Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using \(\alpha/\beta = 3\) Gy; \(\alpha/\beta\), alpha-beta ratio.

<table>
<thead>
<tr>
<th>Toxicity type</th>
<th>Odds ratio</th>
<th>(V_X)</th>
<th>(D_{X%})</th>
<th>(D_{X%})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>01-05, 48-80 Gy</td>
<td>48-80 Gy</td>
<td>01-25, 68-78 %</td>
<td>01-25, 62-78 %</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>49-55 Gy</td>
<td>49-57 Gy</td>
<td>07-18 %</td>
<td>02-24, 58-73 %</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>51 Gy</td>
<td>50-59 Gy</td>
<td>08-13 %</td>
<td>None</td>
</tr>
<tr>
<td>Completeness of evacuation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Anorectal pain</td>
<td>44-48 Gy</td>
<td>45-48 Gy</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Urgency/tenesmus</td>
<td>25-26, 40-63 Gy</td>
<td>25-27, 43-64 Gy</td>
<td>05-38, 56-74 %</td>
<td>None</td>
</tr>
<tr>
<td>Proctitis</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>59-70 %</td>
</tr>
</tbody>
</table>
Table 4.2: Influence of the applied alpha-beta ratio on the findings for odds ratios, $V_X$ and $D_{X\%}$. That is, whether significance still exists when an $\alpha/\beta$ of 5.4 Gy is used instead of 3 Gy. Abbreviations: $V_X$, percentage of the rectal volume receiving at least $X$ EQD2 Gy after applying an $\alpha/\beta = 3$ or 5.4 Gy; $D_{X\%}$, minimum EQD2 Gy dose to the most irradiated $X$ percentage of rectal volume after applying an $\alpha/\beta = 3$ or 5.4 Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ or 5.4 Gy; $\alpha/\beta$, alpha-beta ratio.

<table>
<thead>
<tr>
<th>Toxicity type</th>
<th>Findings for $\alpha/\beta = 5.4$ Gy versus $\alpha/\beta = 3$ Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>Similar trends</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>Similar trends</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Odds ratios not significant for $\alpha/\beta = 5.4$ Gy</td>
</tr>
<tr>
<td>Completeness of evacuation</td>
<td>No significance for $\alpha/\beta = 3$ Gy or $\alpha/\beta = 5.4$ Gy</td>
</tr>
<tr>
<td>Anorectal pain</td>
<td>Similar trends</td>
</tr>
<tr>
<td>Urgency/tenesmus</td>
<td>Similar trends</td>
</tr>
<tr>
<td>Proctitis</td>
<td>Similar trends</td>
</tr>
</tbody>
</table>

4.7 Discussion

4.7.1 It is important to explore dose-toxicity modelling in a variety of registration contexts

This study is the first to use registration-based distribution-addition to obtain accumulated rectal dose-histogram parameters for combined EBRT/HDR-BT prostate cancer treatment and to then correlate the resulting parameters with gastrointestinal toxicities. Studies have estimated the accumulated rectal dose for combined EBRT/HDR-BT prostate cancer treatment without applying deformable registration [4, 8]. However, Kikuchi et al. [13] acknowledged that deformable image registration should be part of a more accurate method of accumulating the rectal dose. This current study improved upon these studies by applying deformable image registration and then correlating accumulated rectal dose with various gastrointestinal toxicities. This study acknowledges the uncertainties of deformable image registration. Subsequently, it compares the findings for distribution-adding with the findings for parameter-adding. Given the potential uncertainties of deformable registration, it is important for registration-based dose-toxicity modelling to be published for a variety of studies. This would allow a multi-institutional comparison of findings to include the confounding factors associated with different registration algorithms, registration circumstances, associated inter-fraction motion constraints and diversity in treatment techniques.
4.7.2 Studies had identified important dose-volume metrics for a variety of prostate radiotherapy techniques

The volume receiving certain doses and the magnitude of dose delivered to volumes have been associated with late gastrointestinal toxicities, typically rectal bleeding, scored after a number of prostate radiotherapy techniques including EBRT only, HDR-BT only, low-dose-rate brachytherapy (LDR-BT) only, combined EBRT/HDR-BT and combined EBRT/LDR-BT [3–5, 27, 29–46]. Table 4.3 summarises the important dose-response findings for the previously mentioned studies and the findings for this study.

The previously mentioned studies commonly suggested that the incidence of late rectal bleeding following prostate radiotherapy can be reduced by constraining the volume of the rectum receiving high doses (e.g. [5, 29, 43, 44, 47]). Additionally, some of the studies have correlated the mid- and low-mid-dose regions with late rectal bleeding [29, 31, 33, 34] and stool frequency/urgency/tenesmus [27, 31, 33, 38] respectively. Consequently, the mid-high rectal doses in prostate EBRT are typically managed through constraints on the $V_{40−75\text{Gy}}$ [29, 47], whereas treatments involving prostate brachytherapy (HDR-BT or LDR-BT) should consider the high rectal doses via the $V_{70−100\%}$, $D_{1cc}$, $D_{2cc}$ and/or near-maximum dose [5, 48–50] due to high-dose hot spots associated with radioactive sources. For treatments involving prostate HDR-BT, the importance of low-dose regions has been explained in terms of considerable inter-patient variation in rectal gas and the distance from the prostate to the anterior rectal wall [46]. The instances where the $V_{50\text{Gy}}$ and $V_{90\text{Gy}}$ have been identified as important for prostate cancer treatments involving EBRT only were related to homogeneous irradiation of volumes with hypofractionated doses [46]. The sections to follow will discuss the findings of this study, summarised in Table 4.3, relative to findings of the previously mentioned dose-response studies, which are also summarised in Table 4.3.
Table 4.3: Summary of findings from previous studies and the current study for various late gastrointestinal toxicities (Note: the table continues on the next page). Abbreviations: RT, radiotherapy; EBRT, external beam radiotherapy; HDR-BT, high-dose-rate brachytherapy; LDR-BT, low-dose-rate brachytherapy; $V_{X Gy}$, percentage of the rectal volume receiving at least $X$ Gy; $V_{X\%}$, percentage of the rectal volume receiving at least $X\%$ of the prescription dose; $D_{X\%}$, minimum dose to the most irradiated $X\%$ of rectal volume; $D_{X cc}$, minimum dose to the most irradiated $X$ cubic centimetres of rectal volume; cc, cubic centimetres.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose-volume consideration</th>
<th>Reference</th>
<th>RT technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal toxicity</td>
<td>Constrain the $V_{30-70 Gy}$</td>
<td>[29, 35–37]</td>
<td>HDR-BT, EBRT</td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{40 Gy}$ and $V_{65-80 Gy}$</td>
<td>[38]</td>
<td>EBRT</td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{100%}$</td>
<td>[39]</td>
<td>HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Limit the $D_{1 cc-10 cc}$</td>
<td>[35]</td>
<td>HDR-BT</td>
</tr>
<tr>
<td></td>
<td>$D_{5%-90%}$ were not significant</td>
<td>[35]</td>
<td>HDR-BT</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>Limit the high/near maximum doses</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Limit doses $&gt; 48$ Gy</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Some association with low doses ($0-5$ Gy)</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{40-80 Gy}$</td>
<td>[3, 27, 29–32, 38, 40–42]</td>
<td>EBRT</td>
</tr>
<tr>
<td></td>
<td>Limit the $D_{2 cc}$ and near maximum doses</td>
<td>[5, 43, 44]</td>
<td>EBRT+HDR-BT/LDR-BT</td>
</tr>
<tr>
<td></td>
<td>Near maximum doses were not significant</td>
<td>[4]</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Limit doses $&gt; 30$ Gy</td>
<td>[29, 31, 33, 34]</td>
<td>EBRT</td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{30%}$, $V_{50%}$, $V_{80%}$ and $V_{90%}$</td>
<td>[45]</td>
<td>EBRT</td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{10%}$, $V_{30%}$ and $V_{50%}$</td>
<td>[46]</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>Limit the mid-high dose range ($49-57$ Gy)</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td>Symptom</td>
<td>Association Range</td>
<td>Study Type</td>
<td>Treatment Modalities</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>-------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Some association with mid-high doses (50-59 Gy)</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Limit the low-mid doses (22-32 Gy)</td>
<td>[31] EBRT</td>
<td></td>
</tr>
<tr>
<td>Completeness of evacuation</td>
<td>No dose range is significant</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Limit the low-mid doses (12-36 Gy)</td>
<td>[31] EBRT</td>
<td></td>
</tr>
<tr>
<td>Anorectal pain</td>
<td>Some association with mid-dose range (45-48 Gy)</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td>Urgency/tenesmus</td>
<td>Limit the mid-high doses (43-64 Gy)</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Some association with low doses (25-27 Gy)</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{40-60Gy}$</td>
<td>[27] EBRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{25-75Gy}$</td>
<td>[38] EBRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limit the low-mid doses (5-38 Gy)</td>
<td>[31] EBRT</td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>No dose range is significant</td>
<td>Current study</td>
<td>EBRT+HDR-BT</td>
</tr>
<tr>
<td></td>
<td>Constrain the $V_{40-70Gy}$</td>
<td>[27] EBRT</td>
<td></td>
</tr>
</tbody>
</table>
4.7.3 The findings indicate a serial response for rectal bleeding

In agreement with other studies [3, 29–31], the high-dose metrics for the rectum were significantly correlated with rectal bleeding for both distribution-adding and parameter-adding. The significant correlation between near-maximum dose metrics for the rectum and rectal bleeding indicates that the dose-volume effects follow a serial response. The confirmation of the expected importance of near-maximum doses after registration is important, as a previous study without registration did not find any significance for near-maximum doses [4] and the GEC/ESTRO recommendation is to limit the $D_{2cc}$ to 75 Gy [5]. Additionally, the identified serial response is consistent with the suggestion that rectal bleeding is associated with epithelial damage and mucositis as a result of exposure of parts of the rectal wall to near-maximum doses [32].

4.7.4 The mid-dose region is important for bleeding/non-bleeding toxicities

Studies have also demonstrated that the mid-dose region (> 30 Gy) is important for rectal bleeding [29, 31, 33, 34]. In this study, the importance is shifted to relatively higher doses in the mid-high dose range for both distribution-adding and parameter-adding. An influencing factor for the lack of importance of the lower end of the mid-dose range could be that the combined EBRT/HDR-BT treatments were subject to the constraint that the maximum rectal dose from HDR-BT should not exceed 80% of the 19.5 Gy prescription dose for HDR-BT. Consequently, in the context of the total EBRT/HDR-BT dose, this constraint effectively applies more to the lower end of the mid-dose range after adjusting for dose fractionation than it does to the high-dose region. The importance of the high-dose and near-maximum dose regions could also be related to the steepness of dose gradients associated with HDR-BT treatments, as it has been proposed that a focused high-dose region could aid healing of the vascular sclerosis in high-dose regions via cell migration from the low-dose region [51]. Consequently, it would be useful to determine optimum rectal dose constraints for combined EBRT/HDR-BT based on accumulated dose. A larger sample size containing patients from a variety of institutions would allow for a feasible application of multivariate and cut-point analysis.
The upper end of the mid-high dose range after distribution-adding was important for the non-bleeding toxicities of stool frequency and urgency/tenesmus. This result could support the earlier suggestion that the rectal dose constraint for HDR-BT effectively applies a constraint to the lower end of the mid-dose range when the total EBRT/HDR-BT dose is considered. The dose constraint in one dose region leading to other dose regions becoming important is consistent with a previous study focusing on patients within the trial who received EBRT only [31]. The study indicated that the low-mid dose range was important for stool frequency, urgency and tenesmus in the presence of high-dose constraints [31]. More optimised dose constraints for the mid-high dose range based on accumulated dose could be useful for reducing the toxicities associated with these doses. Such constraints could be relatively more important for urgency/tenesmus compared to stool frequency given the higher toxicity rate in this patient sample compared to the other toxicities.

4.7.5 Toxicity is also influenced by low doses and the lower end of the mid-dose range

The association of urgency/tenesmus with distribution-adding doses at the lower end of the mid-dose range is consistent with the finding from another study where violation of the $V_{40Gy}$ dose constraint was important for urgency [27]. Additionally, the results indicate that the lower end of the mid-dose range and the low doses may be associated with anorectal pain and rectal bleeding respectively. The correlation of toxicities with low doses and the lower end of the mid-dose range is possible, as it is plausible that a low-dose bath to a large volume will be associated with detriment. However, these findings of association should be considered with respect to toxicity event rates, sample size and the potential of random discovery.

4.7.6 Software developments to improve contour consistency and registration accuracy for the prostate/rectum interface would be of great benefit

Analysis based on contouring and registration is associated with uncertainties. However, the dose regions indicated as being important for toxicity after distribution-adding were in most cases consistent with those indicated as important after
parameter-adding. The low-mid dose range for parameter-adding was significantly associated with proctitis and stool frequency. In contrast, these regions after distribution-adding were not identified as important. However, distribution-adding did indicate additional regions as important compared to regions identified by the parameter-adding results. For example, the analysis for parameter-adding did not indicate any significant dose regions for diarrhoea and urgency/tenesmus, whereas analysis after distribution-adding indicated the mid-high dose range was important. The alpha-beta ratio is an additional uncertainty for diarrhoea correlations as the mid-high dose range was only important for an alpha-beta ratio of 3 Gy. Further studies for a variety of contouring and registration contexts would be useful for gathering data for the purpose of determining whether registration and distribution-adding reveals correlations which were not identified by parameter-adding.

When considering the distribution-adding findings in isolation, it should be noted that errors in contouring and registration accuracy will confound the distribution-adding parameters that have been correlated with toxicity. A median overlap of 80.4% for the rectal volume correspondence across all patients would indicate that the registrations are satisfactory, as a general structure overlap of 70% is considered to be the starting point for satisfactory structure-correspondence in the radiotherapy context [23, 24]. The proximity of the HDR-BT rectum to the HDR-BT catheters makes parameters obtained by registration and distribution-adding sensitive to small localised variations in contouring and/or registration accuracy across the prostate/rectum interface. Given that this is the first study to accumulate the rectal dose for combined EBRT/HDR-BT prostate cancer treatments using deformable registration and then to correlate the doses with toxicity, we encourage more prostate cancer studies to assess the importance of dose-volume metrics using a variety of registration algorithms. Software developers and treatment-planning vendors have the opportunity to greatly improve planning and the reliability of dose-toxicity modelling after registration by improving contouring and registration accuracy for the prostate/rectum interface.
4.7.7 Inter-fraction motion should be considered

A common uncertainty associated with EBRT, HDR-BT and other radiotherapy techniques is inter-fraction motion of patient anatomy [52–55]. In response to this uncertainty, it is becoming more common for institutions to adopt repeat imaging over the course of prostate cancer treatment in order to correct for inter-fraction motions and improve the correspondence between planned dose and delivered dose [54, 56]. However, many studies, including this study, do not contain repeat imaging due to the retrospective nature of studies, where long follow-up is required to correlate dose with late toxicities. Consequently, studies are constrained by treatments performed in the past with the associated resources and protocols of their times.

A consideration for prostate EBRT in this study is rectal motion and variable rectal contents confounding the accuracy of rectal dose-distributions obtained from single static planning CTs [53, 57, 58]. A variety of methods have been used to estimate the impact of inter-fraction motion on rectal dose parameters and dose-response modelling for prostate EBRT [9, 53, 59–62]. To obtain appropriate mean estimates for the difference in EBRT rectal dose between the single CT based values and the motion-corrected values, this study analysed the results of another study [53] that used the same registration software and registration algorithm. Consequently, compared to the motion-corrected values, the single CT-based values may be conservative estimates by 3.9% for the $D_{2\%}$ and 5.8% for the equivalent uniform dose [53].

An important consideration for inter-fraction motion during prostate brachytherapy is the movement of the anterior rectal wall relative to the prostate [55, 63]. A variety of methods have been used to estimate inter-fraction motion in prostate HDR-BT [17, 55] and the subsequent impact on rectal dose parameters for prostate brachytherapy [55, 64–66]. Simnor et al. [55] calculated that the catheter mean caudal displacements of 7.9 mm and 3.8 mm prior to fractions 2 and 3 were associated with mostly systematic increases to the $D_{2\%}$ of 0.69 Gy ($\approx6.6\%$) and 0.76 Gy ($\approx7.2\%$) respectively. For HDR-BT at the institution where patients in this study were treated, the displacement of catheters was checked prior to each of the three fractions using an anterior-posterior radiograph and corrected for using a rigid external holding device as described by Tiong et al. [17]. The catheter mean caudal
displacements after this advancement process were reported as 1.7 mm, 1.1 mm and 0.8 mm for fractions 1, 2 and 3 respectively [17]. Consequently, the inter-fraction motion increases to the $D_{2cc}$ reported by Simnor et al. [55] may be appropriate conservative estimates for the inter-fraction motion of HDR-BT catheters that could be expected for this study.

It is possible that the above mentioned inter-fraction motion could remove the significance of dose ranges. However, shifting of dose values identified as significant is likely as the single CT-based estimates were mostly identified as being systematically different to the motion-corrected values [53, 55]. The influence of inter-fraction on delivered doses is likely to be important when considering dose constraints recommended by studies where planned dose tends to be less than delivered dose. Consequently, it would be useful to confirm the importance of published dose-volume constraints after registration is applied for repeat daily imaging.

4.7.8 Avenues and recommendations for further analysis

- Given this is the first study to apply deformable registration prior to correlating combined EBRT/HDR-BT dose with toxicity, it is important that the model and findings be validated in other contexts with standardised contouring, implanting and planning guidelines for EBRT and HDR-BT.

- A larger sample size would make it feasible to explore models that incorporate multiple toxicity events over the follow-up period [67] or include the persistence of toxicity rather than peak late toxicity [68].

- Image-guided radiotherapy or further imaging could improve the reliability of accumulated dose-histogram metrics [14].

- Customised registration algorithms for accurately handling the catheters within the HDR-BT prostate or data for treatments which use plastic HDR-BT catheters are encouraged as prostate and urethra doses are key clinical concerns in the RADAR trial [28].

- It would also be useful to determine whether other aspects of the total registered dose-distribution add predictive capability to dose-toxicity modelling, e.g. including dose-shape toxicity modelling [61].
• Exploring the association between toxicity and doses to other organs or regions may be useful for further explaining the incidence of toxicity (e.g. doses to the bowel and gastrointestinal tract could be associated with toxicity [47, 69]).

### 4.8 Conclusions

A number of significant dose-histogram effects were revealed for gastrointestinal toxicities after applying deformable registration to adjust for the anatomical differences between planning CTs for each phase of a combined EBRT/HDR-BT prostate cancer treatment. The findings for distribution-adding were in most cases consistent with those for parameter-adding. The mid-high dose range and near-maximum doses were important for rectal bleeding. The distribution-adding mid-high dose range was also important for stool frequency and urgency/tenesmus. The anorectum doses which were important for toxicity are reported so as to guide and encourage future planning of combined EBRT/HDR-BT prostate cancer treatments based on accumulated phases with appropriate inter-fraction motion management. We encourage other studies to report on important dose-histogram effects and spatial aspects of accumulated dose distributions for combined EBRT/HDR-BT.

### 4.9 Declarations

#### 4.9.1 Ethics approval and consent to participate

The TROG 03.04 RADAR Trial is registered with the National Institutes of Health Clinical Trials Registry (number NCT00193856). This trial has approval from the Hunter New England Human Research Ethics Committee (Trial ID. 03/06/11/3.02), the Sir Charles Gairdner Group Human Research Ethics Committee (2003-050) and the University of Western Australia Human Research Ethics Office (RA/4/1/5601). Patients participating in the trial signed consent forms.

#### 4.9.2 Consent for publication

The signed patient consent forms for the trial informed patients that their medical information may be used in the published results of the study. In accordance with the
signed patient consent forms, this publication includes only anonymous information and does not include information identifying any patient.

4.9.3 Availability of data and material

Not applicable.

4.9.4 Competing interests

The authors declare that they have no competing interests.

4.9.5 Funding

We acknowledge funding from the National Health and Medical Research Council (300705, 455521, 1006447), the University of Western Australia, an Australian Postgraduate Award, an Ana Africh Scholarship, the Hunter Medical Research Institute, the Health Research Council (New Zealand), Abbott Laboratories and Novartis Pharmaceuticals.

4.9.6 Authors’ contributions

CRM, MJH, CIT and MAE have made substantial contributions to design of analysis. CRM, VL, CIT, MK, DJJ, JWD and MAE have made substantial contributions to acquire the data. CRM, MJH, VL, CIT and MAE contributed substantially to analysis and interpretation of data. CRM has been involved in drafting the manuscript. MJH, VL, CIT, DJJ, JWD and MAE revised it critically for important and correct content. JWD and DJJ were involved in the design and coordination of the RADAR trial. All authors read and approved the version to be published.

4.9.7 Acknowledgements

We thank Annette Haworth and radiation oncology staff at Sir Charles Gairdner Hospital for their contributions. We also appreciate the support of the RADAR centres and the Trans-Tasman Radiation Oncology Group.
4.10 Supplements 4A-4H

4.10.1 Supplement 4A

This supplement provides additional detail on patient characteristics and treatment protocol.

The 118 prostate cancer patients were initially treated with neoadjuvant androgen deprivation therapy at Sir Charles Gairdner Hospital in the period 2004 to 2008. Then they received EBRT followed by HDR-BT. Patient criteria and treatment methodology were as specified for the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [15, 16]. The standard HDR-BT planning and treatment process has previously been described [17]. The important details are:

- The EBRT prescription dose to the prostate for the 118 patients was 46 Gy to the International Commission on Radiation Units and Measurements 50 reference point (23 daily fractions of conventional fractionation over five weeks).

- The four-field three-dimensional EBRT plan was created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden) based on the planning CT with the patient in the supine position.

- The prescription dose to the prostate was 19.5 Gy for HDR-BT delivered by Iridium-192 after-loading catheters (Varian Oncology Systems).

- The HDR-BT prescription dose covered the prostate gland and any extracapsular extensions.

- The HDR-BT was delivered in three fractions of 6.5 Gy across two days with trial guidelines stipulating a maximum delivery time of 90 minutes for each fraction and a minimum of six hours between fractions.

- The dose to the rectum from HDR-BT was limited to a maximum of 80% of the 19.5 Gy prescription dose.

- The HDR-BT was typically started two to five weeks after the end of external beam radiotherapy.
- The temporary metal needle HDR-BT catheters were inserted with trans-rectal ultrasound, fluoroscopy and perineal template guidance while the patient was in the lithotomy position.

- Needle catheters were inserted and cystoscopy was used to ensure proper tenting of the bladder wall mucosa by catheters.

- A plastic template was sutured to the skin to hold the needles in place.

- The patient was then taken to have a HDR-BT planning CT and a three fraction HDR-BT plan was created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US) based on this CT.

- The HDR-BT doses were based on the standard TG43 format [18].

- Patients were in the lithotomy position for HDR-BT treatment with cushions used to keep the patients’ legs in the abducted position between fractions.

- No patient had artificial hip joints.

- The EBRT planning target volume (PTV) and HDR-BT source definition volume (SDV) were obtained by expanding the corresponding clinical target volume (CTV) by a 10 mm margin. The HDR-BT SDV was used to restrict dwell positions to the lengths of identified catheters covered by the SDV.

Table S4.1 summarises the patient characteristics at baseline.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspect of characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median</td>
<td>66.6</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>61.0-71.4</td>
</tr>
<tr>
<td>PSA</td>
<td>PSA &lt; 10</td>
<td>31 (26.3%)</td>
</tr>
<tr>
<td></td>
<td>10 $\leq$ PSA &lt; 20</td>
<td>42 (35.6%)</td>
</tr>
<tr>
<td></td>
<td>PSA $\geq$ 20</td>
<td>45 (38.1%)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>&lt; 7</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>= 7</td>
<td>41 (34.7%)</td>
</tr>
<tr>
<td></td>
<td>$\geq$ 8</td>
<td>75 (63.6%)</td>
</tr>
<tr>
<td>Tumour classification</td>
<td>T2b</td>
<td>14 (11.9%)</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>16 (13.6%)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>87 (73.7%)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Risk group</td>
<td>Medium</td>
<td>29 (24.6%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>89 (75.4%)</td>
</tr>
<tr>
<td>Number of HDR-BT catheters</td>
<td>12</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3 (2.5%)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>96 (81.4%)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>13 (11.0%)</td>
</tr>
</tbody>
</table>
4.10.2 Supplement 4B

This supplement provides additional examples of planned doses.

Figure S4.1: A four-field EBRT physical dose plan with dose displayed as a colourwash up to the prescription dose of 46 Gy. The EBRT clinical target volume, planning target volume and rectal structures are in yellow, red and green respectively.

Figure S4.2: A HDR-BT TG43 physical dose plan with dose displayed as a colourwash up to the prescription dose of 19.5 Gy. The HDR-BT clinical target volume, source definition volume and rectal structures are in yellow, red and green respectively.
### 4.10.3 Supplement 4C

This supplement provides information on the criteria for grading the different types of toxicities.

**Table S4.2:** Toxicity grading system for clinician-assessed rectal bleeding, stool frequency, diarrhoea, completeness of evacuation, anorectal pain, urgency and tenesmus, and CTC proctitis (Note: the table continues on the next page).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>Never</td>
<td>Occult</td>
<td>&gt; 2/week</td>
<td>Daily</td>
<td>Gross haemorrhaging</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>&lt; 2/day</td>
<td>2-4/day</td>
<td>5-8/day</td>
<td>&gt; 8/day</td>
<td>Uncontrolled diarrhoea</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>None</td>
<td>Increase &lt; 4</td>
<td>Increase of 4-6</td>
<td>Increase of ≥ 7</td>
<td>Physiologic consequences requiring intensive care; haemodynamic collapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stools/day</td>
<td>stools/day or</td>
<td>stools/day or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nocturnal stools</td>
<td>incontinence or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>parenteral support</td>
<td></td>
</tr>
<tr>
<td>Compleness of evacuation</td>
<td>Complete</td>
<td>Occasional multiple evacuations (“about one week feel like you’re not ‘all done’”)</td>
<td>Frequent multiple evacuations (“more than once a week feel like you’re not ‘all done’”)</td>
<td>Requires enema to obtain complete emptying</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(“requires one movement to completely empty bowel or feel you’re all done”)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on the next page)
<table>
<thead>
<tr>
<th>Anorectal pain</th>
<th>Never</th>
<th>Occasional and mild</th>
<th>Intermittent and tolerable</th>
<th>Persistent and intense</th>
<th>Refractory and excruciating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency and tenesmus</td>
<td>Never</td>
<td>Occasional</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Refractory</td>
</tr>
<tr>
<td>CTC proctitis</td>
<td>None</td>
<td>Increased stool frequency, occasional bleeding or rectal discomfort not requiring medication</td>
<td>Increased stool frequency, bleeding mucous discharge or rectal discomfort requiring medication, anal fissure</td>
<td>Increased stool frequency/diarrhoea requiring parenteral support, rectal bleeding requiring transfusion, or persistent mucous discharge necessitating pads</td>
<td>Perforation, bleeding or necrosis or other life threatening complication requiring surgical intervention</td>
</tr>
</tbody>
</table>
4.10.4 Supplement 4D

This supplement provides an example of the visual check on registration alignment.

Figure S4.3: Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images. The EBRT images are in the background. Regions of the HDR-BT images after a rigid plus multi-pass deformable image registration are contained within the yellow outlined rectangular spyglass box. This box can be resized and moved around (e.g. left image versus right image). The EBRT clinical target volume, planning target volume and rectal structures are in purple, red and green respectively.
4.10.5 Supplement 4E

This supplement provides distribution-adding results which were not significant for other end points with $\alpha/\beta = 3$ Gy.

![Figure S4.4: Odds ratios from univariate ordinal regression of distribution-adding $V_X$ and peak late toxicity for completeness of evacuation (A) and proctitis (B)\.(\text{A})](image1)

![Figure S4.5: Median distribution-adding $V_X$ for the toxicity and no toxicity groups. The groups are based on peak late toxicity for completeness of evacuation (A) and proctitis (B).\(\text{(B)}\)](image2)

Figure S4.4: Odds ratios from univariate ordinal regression of distribution-adding $V_X$ and peak late toxicity for completeness of evacuation (A) and proctitis (B). The peak late toxicities for completeness of evacuation were dichotomised at grade 2 whereas proctitis was dichotomised at grade 1. A red dot is used to indicate the doses at which odds ratios are significantly different from a value of one (95% confidence intervals do not include one). Abbreviations: $V_X$, percentage of the rectal volume receiving at least $X$ Gy after applying an $\alpha/\beta = 3$ Gy; $E_{QD}2$ Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy; 95% CI, 95% confidence interval.

Figure S4.5: Median distribution-adding $V_X$ for the toxicity and no toxicity groups. The groups are based on peak late toxicity for completeness of evacuation (A) and proctitis (B). The peak late toxicities for completeness of evacuation were dichotomised at grade 2 whereas proctitis was dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $V_X$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $V_X$, percentage of the rectal volume receiving at least $X$ Gy after applying an $\alpha/\beta = 3$ Gy; $E_{QD}2$ Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy.
Figure S4.6: Median distribution-adding $D_{X\%}$ for the toxicity and no toxicity groups. The groups are based on peak late toxicity for completeness of evacuation (A), anorectal pain (B) and proctitis (C). The peak late toxicities for completeness of evacuation were dichotomised at grade 2 whereas anorectal pain and proctitis were dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $D_{X\%}$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $D_{X\%}$, minimum dose to the most irradiated X percentage of rectal volume after applying an $\alpha/\beta = 3$ Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy.
4.10.6 Supplement 4F

This supplement provides the parameter-adding results for $\alpha/\beta = 3$ Gy.

**Figure S4.7:** Median parameter-adding $D_{X\%}$ for the toxicity and no toxicity groups. The peak late toxicities for rectal bleeding (A), stool frequency (B) and completeness of evacuation (D) were dichotomised at grade 2 whereas diarrhoea (C), anorectal pain (E), proctitis (G) and urgency/tenesmus (F) were dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $D_{X\%}$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $D_{X\%}$, minimum dose to the most irradiated X percentage of rectal volume after applying parameter-adding and an $\alpha/\beta = 3$ Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy.
4.10.7 Supplement 4G

This supplement provides the distribution-adding results for $\alpha/\beta = 5.4$ Gy.

Figure S4.8: Odds ratios from univariate ordinal regression of distribution-adding $V_X$ and peak late toxicity for rectal bleeding (A), stool frequency (B), diarrhoea (C), completeness of evacuation (D), anorectal pain (E), urgency/tenesmus (F) and proctitis (G). The peak late toxicities for rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2 whereas diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1. A red dot is used to indicate the doses at which odds ratios are significantly different from a value of one (95% confidence intervals do not include one). Abbreviations: $V_X$, percentage of the rectal volume receiving at least $X$ Gy after applying an $\alpha/\beta = 5.4$ Gy; $EQD2$ Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 5.4$ Gy; 95% CI, 95% confidence interval.
Figure S4.9: Median distribution-adding $V_X$ for the toxicity and no toxicity groups. The groups are based on peak late toxicity for rectal bleeding (A), stool frequency (B), diarrhoea (C), completeness of evacuation (D), anorectal pain (E), urgency/tenesmus (F) and proctitis (G). The peak late toxicities for rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2 whereas diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $V_X$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $V_X$, percentage of rectal volume receiving at least $X$ Gy after applying an $\alpha/\beta = 5.4$ Gy; $EQD2$ Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 5.4$ Gy.
Figure S4.10: Median distribution-adding $D_{X\%}$ for the toxicity and no toxicity groups. The groups are based on peak late toxicity for rectal bleeding (A), stool frequency (B), diarrhoea (C), completeness of evacuation (D), anorectal pain (E), urgency/tenesmus (F) and proctitis (G). The peak late toxicities for rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2 whereas diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $D_{X\%}$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $D_{X\%}$, minimum dose to the most irradiated X percentage of rectal volume after applying an $\alpha/\beta = 5.4$ Gy; EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 5.4$ Gy.
This supplement provides the parameter-adding results for $\alpha/\beta = 5.4$ Gy.

**Figure S4.11:** Median parameter-adding $D_{X\%}$ for the toxicity and no toxicity groups. The peak late toxicities for rectal bleeding (A), stool frequency (B) and completeness of evacuation (D) were dichotomised at grade 2 whereas diarrhoea (C), anorectal pain (E), proctitis (G) and urgency/tenesmus (F) were dichotomised at grade 1. The red curve and p-value axis indicate doses at which median $D_{X\%}$ values for the toxicity and no toxicity groups are significantly different (p-value < 0.05). Abbreviations: $D_{X\%}$, minimum dose to the most irradiated $X$ percentage of rectal volume after applying parameter-adding and an $\alpha/\beta = 5.4$ Gy; $EQD2$ Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 5.4$ Gy.
4.11 References


radiation therapy for prostate cancer: results from 2 prospective cohorts,”


Chapter 5:
Complication
probability
5.1 Foreword for manuscript

The previous chapter determined that the findings for correlating dose-volume histogram (DVH) parameters with gastrointestinal complications were mostly consistent between the two methods of accumulating the parameters (parameter-adding versus distribution-adding). Additionally, a number of dose regions were identified as important for gastrointestinal complications. Consequently, it would be useful to know what parameter values would be appropriate for the Lyman-Kutcher-Burman (LKB) model of normal tissue complication probability when applying it to combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) data from Australian and New Zealand populations. The manuscript in this chapter reports appropriate parameter values for the LKB model of normal tissue complication probability when applied to registered EBRT/HDR-BT data. Additionally, the manuscript in this chapter compares the optimum parameter values for combined EBRT/HDR-BT with those calculated for patients who received EBRT. The parameter values derived from Australian and New Zealand populations are then compared with parameter values reported for other trials which are based on prostate cancer patients in other countries.

The calculated parameter values for the LKB model of normal tissue complication probability can be interpreted such that they provide information on whether high or low dose regions are important for gastrointestinal complications. Consequently, the discussions and findings in this chapter could be compared with the findings in the previous chapter which were based on directly correlating the DVH parameters with toxicities. Similarly, the findings of this chapter could be compared with dose regions identified as important after including spatial information on the dose distribution which is performed in Chapter 6. Such comparisons of findings from different chapters are covered in the general discussion for the thesis (Chapter 7). The analysis in this chapter is the most recent of the analyses in this thesis and consequently includes the largest amount of registered data.
5.2 Manuscript details

Parameter estimates for the Lyman-Kutcher-Burman model of late rectal toxicities observed after two prostate radiotherapy techniques in an Australian and New Zealand trial.


Publication status: Submitted. The manuscript in this chapter (including supplements) is a typeset of the version submitted to a journal for peer review. The candidate will ensure that any subsequent copyright agreement for the future final published article will agree with the inclusion of published material in this thesis. Sections 5.5.1, 5.5.2, 5.5.4, 5.5.5, 5.5.6, 5.9.1, 5.9.3 and 5.9.4 are based on the publication for Chapter 4 [1].
5.3 Abstract

5.3.1 Purpose

The Lyman-Kutcher-Burman (LKB) model of Normal Tissue Complication Probability (NTCP) was applied to late rectal toxicities in an Australian and New Zealand trial. The parameter values are compared with parameter values reported for trials in other countries.

5.3.2 Methods

724 patients received 66, 70 or 74 Gy of prostate external beam radiotherapy (EBRT) and 167 patients received 46 Gy of prostate EBRT followed by 19.5 Gy of prostate high-dose-rate brachytherapy (HDR-BT). For patients receiving EBRT, dose-volume histogram (DVH) parameters were obtained. For combined EBRT/HDR-BT, the HDR-BT CT was deformably-registered to the EBRT CT and then DVH parameters were obtained from the unregistered EBRT and registered HDR-BT dose distributions. For each patient, the NTCP was calculated for every combination in a parameter space. The maximum log-likelihood estimates and 95% confidence intervals were determined. The impact of dose fractionation was considered by converting to equieffective doses at 2 Gy/fraction using a range of alpha-beta ratios.

5.3.3 Results

Rectal bleeding was influenced by high doses with a greater sensitivity to high doses for higher grade bleeding [i.e. the $n$ ($TD_{50}$) values decreased (increased) as the bleeding criteria was increased]. Non-bleeding toxicities had larger $n$ values than rectal bleeding (i.e. less influenced by high doses). The $TD_{50}$ values were smaller for non-bleeding toxicities after combined EBRT/HDR-BT compared to EBRT.

5.3.4 Conclusions

The estimates for the $n$ and $TD_{50}$ parameters were in most cases consistent with published studies. However, the slope of the dose-response curve ($1/m$) was smaller than in most of the published studies. Including a correction for dose fractionation
only significantly improved the maximum log-likelihood for urgency/tenesmus after combined EBRT/HDR-BT. Validation studies are recommended for combined EBRT/HDR-BT.
5.4 Introduction

External beam radiotherapy (EBRT) with or without a high-dose-rate brachytherapy (HDR-BT) boost dose is used to treat prostate cancer [2]. Treatments are typically evaluated both with respect to curative efficacy and expected levels of normal tissue toxicity [3]. Consequently, studies have investigated a variety of methods for predicting normal tissue toxicity [4–12]. The Lyman-Kutcher-Burman (LKB) model of normal tissue complication probability (NTCP) is one method that has commonly been used to derive parameters for predicting gastrointestinal toxicities from prostate radiotherapy [13–16]. The LKB NTCP model calculates the probability of a complication based on the input of three parameters and the differential dose-volume histogram (DVH) from treatment [17].

One difficulty when applying the LKB NTCP model to combined EBRT/HDR-BT is that the phases of combined EBRT/HDR-BT are planned separately with separate DVHs [18]. Simple crude addition of the DVHs from the two modalities planned at different times is not valid as the anatomy in the CT image study sets may be misaligned due to variations in reference coordinate systems, displacements, deformations and shrinkage [19]. Consequently, a rigid registration is used to align the reference coordinate systems and then deformable image registration (DIR) is recommended due to deformations and shrinkage [20–22]. Additionally, it is expected that the doses for different fraction schedules should be converted to equieffective doses given in a reference $X$ Gy per fraction ($EQDX_{\alpha/\beta}$ Gy), at a specific ratio of the $\alpha$ and $\beta$ parameters from the linear-quadratic model of response, as this adjusts for the biologically non-equivalent fractionation schedules [23, 24]. However, studies have reported that applying a dose fractionation correction for the LKB NTCP model does not significantly improve the model [25, 26].

The parameter values for the best fit of the LKB NTCP model have varied across radiotherapy populations [3, 5, 16, 17, 25–37]. Consequently, meta-analysis on the optimum parameters reported by such studies has been used to incorporate a variety of populations [3] and to recommend appropriate parameters to adopt when using the LKB NTCP model [3, 5]. In terms of consistency, it is useful to have such recommendations; however, for predicting late toxicities of Australian and New Zealand prostate cancer patients, it would be useful to know how such recommendations
compare with parameter values for EBRT and combined EBRT/HDR-BT derived using Australian and New Zealand populations.

There is a lack of published studies applying the LKB NTCP model to various gastrointestinal toxicities after 3D conformal EBRT and combined EBRT/HDR-BT for Australian and New Zealand prostate cancer patients. Additionally, LKB NTCP models have not previously investigated the impact of accumulating the rectal dose from phases of a combined EBRT/HDR-BT prostate treatment by applying deformable registration. This study uses data from combined EBRT/HDR-BT prostate cancer treatments and EBRT only prostate cancer treatments, which were subject to multicentre trial guidelines, to determine optimum LKB NTCP model parameters for late gastrointestinal toxicities in Australian and New Zealand populations.

5.5 Methods

5.5.1 Trial details

This study includes 891 prostate cancer patients who were accrued to the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial from 23 centres across Australia and New Zealand during the period 2003 to 2008 [38, 39]. The patient criteria, treatment methodology and extensive quality assessments for the RADAR trial have previously been described [38–43]. Centres had the option of treating each participant with EBRT or EBRT followed by a HDR-BT boost.

5.5.2 External beam radiotherapy followed by high-dose-rate brachytherapy

167 of the 891 patients included in this study were treated with EBRT followed by HDR-BT at Sir Charles Gairdner Hospital. For the combined EBRT/HDR-BT treatments, the four-field 3D conformal EBRT plans (46 Gy in 23 daily fractions) and HDR-BT plans (19.5 Gy in three fractions across two days) were created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden) and BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US)
respectively. The HDR-BT dose was planned using the TG43 formalism [44]. The combined EBRT/HDR-BT treatment process has previously been detailed [45]. Supplement 5A provides additional patient and treatment details for patients who received combined EBRT/HDR-BT.

The external wall of the rectum was manually delineated by treating-clinicians in the HDR-BT CTs using BrachyVision and in the EBRT CTs using the Elekta Focal contouring system (Elekta AB, Stockholm, Sweden). For contouring the rectum, the inferior-superior limits of the rectum were the rectosigmoid flexure and the last slice where the ischial tuberosities were visible. The maximum dose to the HDR-BT rectum was constrained to less than 80% of the HDR-BT prescription dose.

5.5.3 External beam radiotherapy

724 of the 891 patients included in this study were treated with EBRT only to 66, 70 or 74 Gy. The external wall of the rectum was manually delineated using the same definition as described earlier. The volume of the EBRT rectum receiving at least 65, 70 and 75 Gy was constrained to at most 40%, 30% and 5% respectively. The patient and treatment characteristics for the 724 patients in the RADAR trial who received EBRT only have previously been described [38–43]. Supplement 5B provides the relevant treatment details for patients who received EBRT only.

5.5.4 Toxicity scoring

Patients were assessed for various gastrointestinal toxicities at baseline (randomisation) and subsequent time points after randomisation (e.g. 3, 6, 9, 12, 15, 18, 24, 30, 36, 42, 48, 54, 60, 72, 84, 96, 108 months). The median for the most recent follow-ups was 72 months (range 58-108 months) for patients receiving EBRT only and 72 months (range 12-96 months) for patients receiving combined EBRT/HDR-BT. The Late Effects of Normal Tissue - Subjective, Objective, Management and Analytic (LENT-SOMA) scales were used to assess rectal bleeding, urgency/tenesmus, stool frequency, diarrhoea, anorectal pain and completeness of evacuation [46]. Proctitis was scored by clinicians according to the Common Toxicity Criteria for Adverse Events (CTCAE version 2) [47]. Table S5.2 in Supplement 5C provides a summary of the grading systems.
Late peak toxicity was calculated for the period onwards from three months after radiation therapy. Figure 5.1 provides a summary of the late peak toxicity event rates for the follow-up period. Patients were classified to a toxicity group if the late peak toxicity was at least a certain grade (threshold for dichotomisation). In the interest of modelling a moderate severity of toxicity, the threshold was at least grade 2 for rectal bleeding, stool frequency and completeness of evacuation. The grade 2 and 3 thresholds are abbreviated as G2 and G3 respectively. The threshold was grade 1 for diarrhoea, anorectal pain, proctitis, urgency and tenesmus due to low toxicity rates for grade $\geq 2$ toxicity and/or a lack of significant difference between DVH parameters for grade $\geq 2$ toxicity. The grade 1 threshold is abbreviated as G1. Alternatively, the thresholds applied to toxicities are indicated in Figure 5.1.

5.5.5 Registration process for patients receiving combined EBRT/HDR-BT

For the 167 patients receiving combined EBRT/HDR-BT, the HDR-BT CT was registered to the EBRT CT using rigid registration followed by a B-splines multi-pass DIR in Velocity Advanced Imaging 2.8.1 (Varian Medical Systems, Palo Alto, US) [48]. The EBRT and registered HDR-BT 3D-doses were then imported into MATLAB™ R2010a (The MathWorks Inc., Massachusetts, US) and the Computational Environment for Radiotherapy Research (CERR, version 4.1) [49] for further analysis.

The registration process has been described in detail previously [48, 50]. The registrations have also previously been extensively evaluated using structure-correspondence metrics, image-similarity metrics and qualitative visual inspection by authors (initials CRM, VL and CIT) [50]. Visual inspections did not identify any major registration misalignments (e.g. Figure S5.1 in Supplement 5D). The median overlap of the EBRT rectum and registered HDR-BT rectum (expressed as a percentage of the volume of the registered HDR-BT rectum) was 72.6%.

5.5.6 Dose-volume histogram data

For patients receiving combined EBRT/HDR-BT, the rectal differential DVHs in 0.1 Gy bins from 0-300 Gy were extracted from the EBRT dose (with the EBRT
Figure 5.1: Late peak toxicity grades for various toxicity types over the follow-up period for 724 patients who received EBRT only (A) and 167 patients who received EBRT followed by HDR-BT (B). The toxicity types (abbreviation) are rectal bleeding (bleeding), CTC proctitis (proctitis), stool frequency (frequency), diarrhoea, urgency/tenesmus (urgency), anorectal pain (pain) and completeness of evacuation (evacuation). The toxicity rates are cumulative percentages. The thresholds applied for grouping patients into toxicity/no toxicity groups are indicated by red lines.

For patients receiving EBRT only, the rectum differential DVH in 0.1 Gy bins from 0-100 Gy was extracted from the EBRT dose (with the EBRT rectal structure). The rectal structure) and the registered HDR-BT dose (with the EBRT rectal structure).
5.5.7 Normal tissue complication probability

NTCP ranges from zero (0% probability of a complication) to one (100% probability of a complication) [17, 25]. Studies have demonstrated that the Lyman-Kutcher-Burman model of NTCP is useful for explaining the dose-response of gastrointestinal toxicities in terms of a sigmoidal function with three fitting parameters ($TD_{50}$, $m$ and $n$) and the differential DVH data with $k$ bins ($D_i$ and $v_i$) [17, 25]:

$$NTCP = \frac{1}{2\pi} \int_{-\infty}^{t} e^{-u^2/2} du$$

(5.1)

$$t = \frac{D_{eff} - TD_{50}}{m \times TD_{50}}$$

(5.2)

$$D_{eff} = \left( \sum_{i=1}^{k} D_i^{1/n} \times v_i \right)^n$$

(5.3)

The $TD_{50}$ parameter is the homogeneous dose to an organ which results in a 50% complication probability [17]. A larger $TD_{50}$ value represents greater dose tolerance. The $m$ parameter is related to the slope of the dose-response curve [17]. Smaller $m$ and larger $1/m$ values are associated with steeper dose-response curves. The $n$ parameter represents the volume effect for the organ [17] and determines the importance of mean/maximum dose when reducing a heterogeneous dose distribution represented by the differential DVH to an effective homogeneous dose ($D_{eff}$). The maximum dose or serial response is important when the $n$ value is zero, whereas mean dose or parallel response is important when the $n$ value is one [17]. Some studies use an alternative parameter labelled $a$ instead of $n$ as the generalised equivalent uniform dose ($gEUD$) for parameter $a$ is equivalent to the effective dose ($D_{eff}$) for parameter $n = 1/a$ [17, 51]. The $D_i$ is the dose in each bin of the differential DVH. The $v_i$ is the fractional volume that received the dose in each bin of the differential DVH.

For patients receiving EBRT only, the effective homogeneous dose ($D_{eff}$) is obtained by inputting the $D_i$ and $v_i$ from the differential DVH into Equation (5.3). For patients receiving combined EBRT/HDR-BT, the effective homogeneous dose ($D_{eff}$) is the sum of the $D_{eff}$ for each phase. The $D_{eff}$ for each phase is obtained
by inputting the $D_i$ and $v_i$ from the appropriate EBRT or registered HDR-BT differential DVH into Equation (5.3).

The best fit values for the $TD_{50}$, $m$ and $n$ parameters were determined for each of the combined EBRT/HDR-BT and EBRT only samples by assigning patients to toxicity ($tox = 1$) and no toxicity groups ($tox = 0$) based on thresholded late peak toxicity and applying maximum log-likelihood estimation to the NTCP values. The likelihood process used the following log-likelihood ($LLH$) function [17]:

$$LLH(TD_{50}, m, n) = \sum_{tox=1} \ln [NTCP(TD_{50}, m, n)] + \sum_{tox=0} \ln [1 - NTCP(TD_{50}, m, n)]$$  (5.4)

The parameter combination providing the maximum log-likelihood for each of the combined EBRT/HDR-BT and EBRT only samples was determined by grid searching a parameter space for the maximum of the log-likelihood function which is calculated according to Equation (5.4). The parameter space was defined to extend to the edges of the confidence intervals reported in other studies [31, 34, 52]. Consequently, the parameter space was defined as $TD_{50} = 33 - 137$ (increment=1), $m = 0 - 0.6$ (increment=0.01) and $n = 0.02 - 0.8$ (increment=0.01). 95% confidence intervals (CI) for the best fit values were determined by profile likelihood estimation [25, 53].

### 5.5.8 Impact of the dose fraction correction

The impact of dose fractionation corrections were investigated by converting the dose bins of the physical-dose-based DVHs to equieffective doses given in a reference 2 Gy per fraction using the alpha-beta ratio ($\alpha/\beta$) within the linear-quadratic model [24]. The alpha-beta ratio for the rectum has been reported as 3 Gy [3, 54] with an upper limit of 4.8-5.4 Gy [25, 55]. Consequently, the previously described LKB NTCP model analysis was repeated with the alpha-beta ratio as an additional parameter. The parameter range for the alpha-beta ratio was conservatively set at $\alpha/\beta = 0.1 - 10$ (increment=0.1) as 1 and 10 Gy are typical values for late and early response respectively [55]. To test whether the inclusion of the linear-quadratic correction resulted in better fits, the likelihood ratio test was applied to compare
the log-likelihood from the physical-dose-based LKB model with the log-likelihood from the linear-quadratic adjusted LKB model [56, 57]. Code for the NTCP modelling and statistical analysis was created and run in MATLAB™ R2015a (The MathWorks Inc., Massachusetts, US). Due to the size of the parameter space, the computationally intensive modelling was coded to run on an advanced workstation (64-bit PC with a 6 core Intel i7 3.33 GHz CPU and 24 GB RAM).

5.6 Results

Table 5.1 provides the maximum likelihood estimates for parameters of the physical-dose-based LKB NTCP model applied to various late gastrointestinal toxicities observed after EBRT and combined EBRT/HDR-BT. Table 5.1 also includes the 95% CI for parameters of the physical-dose-based LKB NTCP model. Table 5.2 details the estimates obtained after including a linear-quadratic dose fraction correction which contains the alpha-beta ratio parameter. Additionally, Table 5.2 provides the p-value for the test of whether including a dose fractionation correction improves the model in terms of maximum log-likelihood.

As detailed in the following sections, the estimates for the $m$, $n$ and $TD_{50}$ parameters varied across the different toxicities (Table 5.1). Additionally, for most toxicities including a dose fractionation correction did not significantly improve the maximum log-likelihood obtained by the physical-dose-based LKB NTCP model (Table 5.2). The only significant result for the dose fractionation correction was for the LKB NTCP model applied to urgency/tenesmus after combined EBRT/HDR-BT (Table 5.2).
Table 5.1: Estimates and confidence intervals for parameters of the LKB NTCP model applied to various late gastrointestinal toxicities observed after EBRT and combined EBRT/HDR-BT. The late toxicities were dichotomised at either grade 1, 2 or 3 with the thresholds subsequently abbreviated as G1, G2 and G3 respectively. The 95% confidence intervals were obtained via the profile likelihood estimation method [25, 53]. Abbreviations: Bleeding, rectal bleeding; CI, confidence interval; EBRT, external beam radiotherapy; Evacuation, completeness of evacuation; Frequency, stool frequency; HDR-BT, high-dose-rate brachytherapy; LKB NTCP, Lyman-Kutcher-Burman model of normal tissue complication probability; Pain, anorectal pain; RT, radiotherapy technique; Urgency, urgency/tenesmus.

<table>
<thead>
<tr>
<th>Toxicity (threshold)</th>
<th>RT technique</th>
<th>m Value</th>
<th>95% CI</th>
<th>n Value</th>
<th>95% CI</th>
<th>TD50 (Gy) Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding (G3)</td>
<td>EBRT</td>
<td>0.20</td>
<td>0.13-0.40</td>
<td>0.13</td>
<td>0.05-0.41</td>
<td>79</td>
<td>72-115</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.24</td>
<td>0.15-0.45</td>
<td>0.09</td>
<td>0.02-0.50</td>
<td>97</td>
<td>66-137</td>
</tr>
<tr>
<td>Bleeding (G2)</td>
<td>EBRT</td>
<td>0.28</td>
<td>0.18-0.54</td>
<td>0.16</td>
<td>0.06-0.42</td>
<td>69</td>
<td>64-82</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.47</td>
<td>0.27-0.60</td>
<td>0.19</td>
<td>0.02-0.80</td>
<td>79</td>
<td>52-137</td>
</tr>
<tr>
<td>Frequency (G2)</td>
<td>EBRT</td>
<td>0.44</td>
<td>0.32-0.58</td>
<td>0.80</td>
<td>0.26-0.80</td>
<td>101</td>
<td>77-137</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.41</td>
<td>0.23-0.60</td>
<td>0.80</td>
<td>0.02-0.80</td>
<td>71</td>
<td>51-137</td>
</tr>
<tr>
<td>Diarrhoea (G1)</td>
<td>EBRT</td>
<td>0.60</td>
<td>0.49-0.60</td>
<td>0.25</td>
<td>0.02-0.75</td>
<td>65</td>
<td>56-87</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.60</td>
<td>0.33-0.60</td>
<td>0.67</td>
<td>0.12-0.80</td>
<td>48</td>
<td>41-73</td>
</tr>
<tr>
<td>Evacuation (G2)</td>
<td>EBRT</td>
<td>0.60</td>
<td>0.43-0.60</td>
<td>0.53</td>
<td>0.02-0.80</td>
<td>103</td>
<td>80-137</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.51</td>
<td>0.27-0.60</td>
<td>0.31</td>
<td>0.02-0.80</td>
<td>81</td>
<td>53-137</td>
</tr>
<tr>
<td>Pain (G1)</td>
<td>EBRT</td>
<td>0.60</td>
<td>0.44-0.60</td>
<td>0.36</td>
<td>0.02-0.80</td>
<td>91</td>
<td>75-130</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.60</td>
<td>0.37-0.60</td>
<td>0.78</td>
<td>0.14-0.80</td>
<td>49</td>
<td>42-73</td>
</tr>
<tr>
<td>Urgency (G1)</td>
<td>EBRT</td>
<td>0.60</td>
<td>0.51-0.60</td>
<td>0.51</td>
<td>0.21-0.80</td>
<td>39</td>
<td>36-44</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.60</td>
<td>0.47-0.60</td>
<td>0.36</td>
<td>0.10-0.58</td>
<td>33</td>
<td>33-45</td>
</tr>
<tr>
<td>Proctitis (G1)</td>
<td>EBRT</td>
<td>0.60</td>
<td>0.40-0.60</td>
<td>0.11</td>
<td>0.02-0.29</td>
<td>56</td>
<td>49-65</td>
</tr>
<tr>
<td></td>
<td>EBRT+HDR-BT</td>
<td>0.60</td>
<td>0.44-0.60</td>
<td>0.37</td>
<td>0.10-0.80</td>
<td>40</td>
<td>33-56</td>
</tr>
</tbody>
</table>
Table 5.2: Impact of a dose fractionation correction on parameters of the LKB NTCP model applied to various late gastrointestinal toxicities observed after EBRT and combined EBRT/HDR-BT. The late toxicities were dichotomised at either grade 1, 2 or 3 with the thresholds subsequently abbreviated as G1, G2 and G3 respectively. The parameters were obtained after correcting dose-volume histograms for dose fractionation using the linear-quadratic model with a range of alpha-beta ratios. The likelihood ratio test [56, 57] was used to test whether the likelihood from the physical-dose-based model was increased after including the dose fractionation correction. Stat is the log-likelihood ratio test statistic [56, 57], Stat = -2 x (log-likelihood without \( \alpha/\beta \) - log-likelihood with \( \alpha/\beta \)). The p-value is from the log-likelihood ratio test [56, 57]. Abbreviations: \( \alpha/\beta \), alpha-beta ratio; Bleeding, rectal bleeding; EBRT, external beam radiotherapy; Evacuation, completeness of evacuation; Frequency, stool frequency; HDR-BT, high-dose-rate brachytherapy; LKB NTCP, Lyman-Kutcher-Burman model of normal tissue complication probability; LQ, linear-quadratic model; Pain, anorectal pain; RT, radiotherapy technique; Urgency, urgency/tenesmus.

<table>
<thead>
<tr>
<th>Toxicity (threshold)</th>
<th>RT technique</th>
<th>LQ-adjusted parameters</th>
<th>Importance of ( \alpha/\beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( m ) ( n )</td>
<td>( TD50 (\text{Gy}) )</td>
</tr>
<tr>
<td>Bleeding G3</td>
<td>EBRT</td>
<td>0.24 0.18</td>
<td>76 0.1</td>
</tr>
<tr>
<td>Bleeding G2</td>
<td>EBRT+HDR-BT</td>
<td>0.34 0.20</td>
<td>65 0.1</td>
</tr>
<tr>
<td>Bleeding G1</td>
<td>EBRT+HDR-BT</td>
<td>0.60 0.41</td>
<td>96 1.3</td>
</tr>
<tr>
<td>Frequency G2</td>
<td>EBRT</td>
<td>0.45 0.80</td>
<td>100 10.0</td>
</tr>
<tr>
<td>Frequency G1</td>
<td>EBRT+HDR-BT</td>
<td>0.49 0.80</td>
<td>86 10.0</td>
</tr>
<tr>
<td>Diarrhoea G1</td>
<td>EBRT</td>
<td>0.60 0.02</td>
<td>82 10.0</td>
</tr>
<tr>
<td>Diarrhoea G2</td>
<td>EBRT+HDR-BT</td>
<td>0.60 0.80</td>
<td>47 10.0</td>
</tr>
<tr>
<td>Evacuation G2</td>
<td>EBRT</td>
<td>0.60 0.56</td>
<td>99 10.0</td>
</tr>
<tr>
<td>Evacuation G1</td>
<td>EBRT+HDR-BT</td>
<td>0.60 0.46</td>
<td>91 10.0</td>
</tr>
<tr>
<td>Pain G1</td>
<td>EBRT</td>
<td>0.60 0.33</td>
<td>90 10.0</td>
</tr>
<tr>
<td>Pain G2</td>
<td>EBRT+HDR-BT</td>
<td>0.60 0.80</td>
<td>49 10.0</td>
</tr>
<tr>
<td>Urgency G1</td>
<td>EBRT</td>
<td>0.60 0.48</td>
<td>38 10.0</td>
</tr>
<tr>
<td>Urgency G2</td>
<td>EBRT+HDR-BT</td>
<td>0.60 0.46</td>
<td>33 10.0</td>
</tr>
<tr>
<td>Proctitis G1</td>
<td>EBRT</td>
<td>0.60 0.12</td>
<td>54 2.2</td>
</tr>
<tr>
<td>Proctitis G2</td>
<td>EBRT+HDR-BT</td>
<td>0.60 0.61</td>
<td>37 10.0</td>
</tr>
</tbody>
</table>
5.6.1 Rectal bleeding

For a moderate severity of rectal bleeding (G2), the \( n \) value is less than 0.20 and the \( TD50 \) value is less than 79 Gy (Table 5.1). Regardless of radiotherapy technique, the estimates for the \( m \), \( n \) and \( TD50 \) parameters decrease, decrease and increase respectively with increasing severity of rectal bleeding (G2 to G3 in Table 5.1). Additionally, the \( TD50 \) values are smaller for EBRT compared to combined EBRT/HDR-BT (Table 5.1). Including a dose fractionation correction resulted in an optimum alpha-beta ratio of 3.1 Gy for severe rectal bleeding (G3) following combined EBRT/HDR-BT (Table 5.2). However, including the correction did not significantly increase the maximum log-likelihood for the model (p-value > 0.05 in Table 5.2). Additionally, including a dose fractionation correction increased the optimum \( n \) and \( TD50 \) for combined EBRT/HDR-BT (Tables 5.1 and 5.2).

5.6.2 Non-bleeding toxicities

For all non-bleeding toxicities, the \( m \) values for EBRT are similar to the values for combined EBRT/HDR-BT (Table 5.1). Additionally, for stool frequency the \( n \) values for EBRT are similar to the values for combined EBRT/HDR-BT (Table 5.1). For all non-bleeding toxicities, the \( TD50 \) values for EBRT are larger than those for combined EBRT/HDR-BT (Table 5.1). For most toxicities and radiotherapy techniques, including the dose fractionation correction did not significantly increase the maximum log-likelihood for the model (p-value > 0.05 in Table 5.2). The exception is urgency/tenesmus after combined EBRT/HDR-BT where including a dose fractionation correction significantly increased the maximum log-likelihood. Inclusion of the dose fractionation correction for urgency/tenesmus was associated with an optimum alpha-beta ratio towards 10 Gy and a slight increase in the \( n \) parameter (Tables 5.1 and 5.2).
5.7 Discussion

5.7.1 Rectal bleeding is associated with a late and serial response of the rectum

The $n$ parameter was less than 0.16 and 0.19 for moderate severity (G2) of rectal bleeding after EBRT and combined EBRT/HDR-BT respectively. Additionally, the $n$ and $TD_{50}$ parameters for rectal bleeding decreased and increased respectively with increasing severity of bleeding (G2 to G3). Consequently, a greater severity of rectal bleeding is more strongly associated with higher doses as maximum doses dominate when the $n$ value is zero and the $TD_{50}$ value is high. The low values of $n$ for proctitis after EBRT indicate proctitis is also associated with high doses. Additionally, the results for dose fractionation correction indicate that severe rectal bleeding (G3) after combined EBRT/HDR-BT is related to a late response of the rectum as the optimum alpha-beta ratio was 3.1 Gy.

As illustrated in Figure 5.2, the identified late serial response for rectal bleeding is consistent with published LKB NTCP studies where high doses are important [3, 17, 26, 28, 31, 34–36]. It is also consistent with dose-volume studies finding that bleeding is associated with high-dose metrics [42, 58, 59] and that an appropriate alpha-beta ratio is around 3 Gy [3, 26, 54]. The finding also supports the suggestion that rectal bleeding is associated with epithelial damage and mucositis as a result of exposure of parts of the rectal wall to near-maximum doses [60]. The confirmation of the expected importance of high doses after registration for combined EBRT/HDR-BT is important as the GEC/ESTRO recommendation is to limit the $D_{2cc}$ to 75 Gy [61] and a previous study without registration did not find any significant association of bleeding with near-maximum doses [18].

The smallest value for $n$ was obtained for severe rectal bleeding (G3) after combined EBRT/HDR-BT. The importance of high doses (small $n$ values) for combined EBRT/HDR-BT could be related to the steepness of dose gradients in HDR-BT treatments, as it has been proposed that a focused high-dose region could aid healing of the vascular sclerosis in high-dose regions via cell migration from the low-dose region [62]. Consequently, it would be useful to determine if optimum constraints on rectal dose for combined EBRT/HDR-BT after registering and accumulating dose
Figure 5.2: A comparison of the $m$, $n$, TD50 and alpha-beta ratio ($\alpha/\beta$) parameters for rectal bleeding in this study with other published studies. The $m$, $n$, TD50 and $\alpha/\beta$ parameters are in (A), (B), (C) and (D) respectively. Late rectal bleeding was dichotomised (thresholded) at either grade 2 or 3 with thresholds subsequently abbreviated as G2 and G3 respectively. Parameters from this study for bleeding include those for external beam radiotherapy (EBRT) and combined EBRT/high-dose-rate brachytherapy (HDR-BT).

include intermediate- and low-dose metrics.

5.7.2 The importance of mean dose for non-bleeding toxicities varies according to radiotherapy technique

The two radiotherapy techniques (EBRT and combined EBRT/HDR-BT) were associated with some differences in the values of the LKB NTCP parameters, which is expected as the $n$ parameter should depend on treatment technique. The $n$ and TD50 parameters for diarrhoea, anorectal pain and proctitis after combined EBRT/HDR-BT are larger and smaller respectively than the corresponding values after EBRT. Consequently, high doses have less influence on diarrhoea, anorectal
pain and proctitis after combined EBRT/HDR-BT than they do on toxicities after EBRT. For combined EBRT/HDR-BT, an influencing factor for the importance of intermediate-high doses rather than low doses could be that the combined treatments were subject to the constraint that the maximum rectal dose from HDR-BT should not exceed 80% of the 19.5 Gy prescription dose for HDR-BT. This constraint in the context of the total dose for combined EBRT/HDR-BT effectively applies more to the lower end of the intermediate-dose range after adjusting for dose fractionation than it does to the high-dose region. Similarly, the constraints on the volume of the rectum receiving near prescription doses for EBRT could contribute to the finding that intermediate dose and less than maximum dose ($n > 0$) are important for toxicities after EBRT.

The intermediate to mean doses are also important for stool frequency, urgency/tenesmus and completeness of evacuation symptoms after EBRT and combined EBRT/HDR-BT as the $n$ parameter values range from 0.31 to 0.80. Additionally, intermediate to mean doses are also important for diarrhoea, anorectal pain and proctitis after combined EBRT/HDR-BT as the $n$ parameter ranges from 0.37 to 0.78. The association of urgency/tenesmus with $TD_{50}$ values from 33-39 Gy in this study is consistent with the finding from another study where violation of the $V_{40\text{Gy}}$ dose constraint was important for urgency [63]. As mentioned above, the constraints on the high doses for EBRT and the effective constraint on the lower end of the intermediate-dose range for combined EBRT/HDR-BT could contribute to the importance of intermediate to mean doses for various toxicities.

The dose fractionation correction resulted in intermediate to mean doses becoming more important for urgency/tenesmus after combined EBRT/HDR-BT relative to the case without the correction, as the value of the $n$ parameter increased after the correction. The results for dose fractionation correction indicate that urgency/tenesmus after combined EBRT/HDR-BT could be associated with early response of the rectum, as the optimum alpha-beta ratio for dose fractionation correction was towards 10 Gy. However, an isolated finding of significance should be considered with respect to toxicity event rates, sample size and the potential of random discovery. A larger sample size containing patients from a variety of institutions would allow a more extensive investigation of the significance of the dose
fractionation correction, given the lack of significance for all other toxicities.

The concept of a dose constraint in one dose region leading to other dose regions becoming important is consistent with a previous study focusing on dose-volume constraints for patients within this trial who received EBRT only [42]. The study indicated the low-intermediate dose range was important for stool frequency, urgency and tenesmus in the presence of high-dose constraints [42]. More optimised dose constraints for the intermediate-high dose range based on accumulated dose could be useful for reducing the toxicities associated with these doses. Such constraints could be relatively more important for urgency/tenesmus compared to stool frequency, given the higher toxicity rate in this patient sample compared to the other toxicities.

5.7.3 A comparison of rectal bleeding parameters with other studies

Late rectal bleeding has been a popular endpoint for LKB NTCP analysis [3, 17, 26, 28, 31, 34–36]. Figure 5.2 shows that the \( n \) parameters for late rectal bleeding in this study are generally low (0.16-0.19 for at least grade 2 bleeding and 0.09-0.13 for at least grade 3 bleeding). As such, the low \( n \) parameters are consistent with the ranges for other studies, i.e. Figure 5.2 indicates the ranges for other studies are 0.07-0.23 for at least grade 2 bleeding and 0.06-0.18 for at least grade 3 bleeding. The other studies also indicate the \( TD_{50} \) parameters for late rectal bleeding are high as the ranges are 68-81 Gy for at least grade 2 bleeding and 78-79 Gy for at least grade 3 bleeding (Figure 5.2). The \( TD_{50} \) parameters for late rectal bleeding in this study are in most cases consistent with the high-dose range in other studies (Figure 5.2). The exception is the \( TD_{50} \) value for at least grade 3 bleeding after combined EBRT/HDR-BT, which is relatively higher than other studies with a value of 97 Gy in Figure 5.2. The \( TD_{50} \) value may be relatively high for at least grade 3 bleeding in this study due to potential for HDR-BT to result in high peak rectal doses when the anterior rectal wall is located close to the HDR-BT catheters in the prostate and the expectation that higher doses are required for damage to lead to more severe grades of bleeding. The low \( n \) and high \( TD_{50} \) values reported in this study and other studies [3, 17, 26, 28, 31, 34–36] supports the concept of a serial response for rectal bleeding.

Figure 5.2 reveals that the \( m \) parameter values for rectal bleeding are in all cases
larger than those in other studies (including those with similar conformal EBRT techniques such as the study by Gulliford et al.) [3, 17, 26, 28, 31, 34–36]. Factors which could be contributing to the flatter or more blurred dose-response relationship (larger $m$) for this study include: (1) the treatment quality at centres improving with the escalation of prescription dose [43]; (2) the effect of inter-fractional and intra-fractional movement for EBRT [64] and catheter displacement with HDR-BT [45, 65]; and (3) the additional uncertainty associated with registrations [50] and contouring [66, 67] for combined EBRT/HDR-BT. In this study, the $m$ parameter values are larger for combined EBRT/HDR-BT compared to EBRT only (Figure 5.2). The dose-response relationship may be more blurred for combined EBRT/HDR-BT compared to EBRT only due to the uncertainty associated with registrations for combined EBRT/HDR-BT. The $m$ parameter value for at least grade 2 bleeding after combined EBRT/HDR-BT in this study stands out as it is considerably larger than other studies (Figure 5.2). The earlier mentioned registration uncertainty could contribute to it standing out; however, there is also the potential additional blurring of the dose-response relationship when a less severe grade of bleeding is considered as other factors including the general incidence of bleeding in the population may confound the occurrence of a lower level bleed when sample sizes are not large.

Consequently, it is important to validate the findings in other contexts using a variety of registration algorithms as well as standardised contouring, implanting and inter/intra-fraction motion guidelines for EBRT and HDR-BT.

5.7.4 Parameters for studies on non-bleeding toxicities

It is less common for studies to analyse late non-bleeding toxicities using LKB NTCP models than it is for studies to analyse late rectal bleeding. Studies have reported the LKB NTCP parameters for urgency, proctitis and stool frequency as well as other endpoints which were not assessed in this study, such as loose stools [16, 17, 37]. Figure 5.3 shows that the $m$ parameter values for stool frequency, urgency/tenesmus and proctitis in this study are larger than those in other studies, which is consistent with the finding for late rectal bleeding and subject to the same reasoning.

Figure 5.3 also shows that the $n$ parameter for proctitis after EBRT in this study is consistent with the low values reported in other studies [16, 17] and that the $n$
Figure 5.3: A comparison of the $m$, $n$ and $TD_{50}$ parameters for non-bleeding toxicities in this study with other published studies. The $m$, $n$ and $TD_{50}$ parameters are in (A), (B) and (C) respectively. The parameters included from this study are for diarrhoea, stool frequency (frequency), urgency/tenesmus (urgency) and proctitis. The parameters included from other studies are for stool frequency (frequency), loose stools, urgency and proctitis. The late toxicities were dichotomised (thresholded) at either grade 1 or 2 with thresholds subsequently abbreviated as G1 and G2 respectively. The parameters included for this study include those for external beam radiotherapy (EBRT) and combined EBRT/high-dose-rate brachytherapy (HDR-BT).

parameter value for diarrhoea after EBRT in this study is best approximated by the values for loose stools and urgency reported in the study by Gulliford et al. [17]. Additionally, Figure 5.3 shows that the $TD_{50}$ values for proctitis after EBRT in this study are similar to 58.2 Gy value reported by Gulliford et al. [17], which may be driven by both studies having a similar conformal EBRT technique. The $n$ parameter values for stool frequency and urgency/tenesmus for both radiotherapy techniques in this study as well as proctitis after combined EBRT/HDR-BT are larger than those in other studies [16, 17, 37]. This reduced influence of high dose compared to other studies could be related to the observation of a more conformal
dose as the prescription dose was escalated in the RADAR trial [43].

5.7.5 It is important to validate modelling in a variety of radiotherapy populations and registration contexts

This study is the first to apply deformable registration prior to obtaining the LKB NTCP model parameters for gastrointestinal toxicities observed after combined EBRT/HDR-BT. Additionally, it is the first study to use Australian and New Zealand multi-centre trial data to obtain LKB NTCP model parameters for a variety of gastrointestinal toxicities observed after prostate 3D conformal EBRT. The context of the application of LKB NTCP in this study leads to a number of confounding factors such as patient characteristics, treatment techniques, inter/intra-fraction motions, registration algorithms, registration circumstances and contouring circumstances. For dose-toxicity modelling, the accuracy of DVHs is important and the accuracy in this study is confounded by contouring, registration and intra/inter-fraction motion uncertainties. Consequently, it is important for dose-toxicity modelling to be published for a variety of registration contexts and it would be useful to validate the findings of such studies in a variety of radiotherapy populations, registration applications and treatment contexts.

In this study, a comparison of the parameters for combined EBRT/HDR-BT with the parameters for EBRT does not provide any definitive information on the adequacy of registrations for combined EBRT/HDR-BT as the confidence intervals for one generally include the estimates of the other. However, the proximity of the HDR-BT rectum to the HDR-BT catheters means the parameters obtained after registration are sensitive to small localised variations in contouring and/or registration accuracy across the prostate/rectum interface. Consequently, software developers and treatment-planning vendors have the opportunity to greatly improve the reliability of dose-toxicity modelling after registration by improving contouring and registration accuracy for combined EBRT/HDR-BT. A general structure overlap of 70% is considered to be the starting point for satisfactory structure-correspondence in radiotherapy [68, 69]; however, ongoing improvements in the contouring and registration accuracy would allow more registrations to be included in sample sizes. Increasing the sample size is important for increasing the reliability of predictive
dose-toxicity models. There will always be a trade-off between increasing sample size and tightening registration quality criteria as there is no known ground truth for registering two different clinical images.

5.7.6 Interesting future directions

- Validate the findings for combined EBRT/HDR-BT in the context of other registration algorithms, registration circumstances, contouring applications, treatment techniques and inter/intra-fraction motion constraints.

- Investigate whether including spatial information on non-homogeneous dose distributions in toxicity modelling improves the predicative capability, e.g. including dose-shape toxicity modelling [70] and analysis on doses registered to a common template [69].

- Use large sample sizes to explore other methods of assessing toxicity, e.g. models that incorporate multiple toxicity events over the follow-up period [71] or include the persistence of toxicity rather than peak late toxicity [72].

- Assess whether image-guided radiotherapy or further imaging improves the reliability of accumulated dose-histogram metrics [32] and LKB NTCP parameters in terms of the predictive ability of subsequent dose-toxicity models.

- Consider prostate and urethra doses for combined EBRT/HDR-BT by developing registration algorithms which are accurate in the presence of catheters within the HDR-BT prostate or by undertaking analysis on data for treatments with fewer artefacts in the prostate, e.g. plastic HDR-BT catheters.

5.8 Conclusions

The $m$, $n$ and $TD_{50}$ parameters for the Lyman-Kutcher-Burman model of normal tissue complication probability varied across the various late gastrointestinal toxicities. Including a dose fractionation correction only significantly improved the model for urgency/tenesmus. Rectal bleeding was influenced by late response to high doses with optimum $m$, $n$, $TD_{50}$ and alpha-beta ratio values of 0.24, 0.09, 97 Gy and 3.1 Gy respectively for grade 3 bleeding after combined EBRT/HDR-BT.
Non-bleeding toxicities were influenced less by high doses than rectal bleeding. A comparison of the parameters for EBRT and combined EBRT/HDR-BT indicated smaller $TD_{50}$ values for non-bleeding toxicities after combined EBRT/HDR-BT. It was found that the $n$ and $TD_{50}$ estimates from other studies are consistent with most of the values in this study. However, the slope of the dose-response curve ($1/m$) for non-bleeding toxicities was smaller than some published studies. The parameter values for combined EBRT/HDR-BT are confounded by uncertainties related to registrations and contouring, and discrepancy between initial planning CT scans and actual dose delivered. Validation studies on parameters for combined EBRT/HDR-BT and additional toxicity modelling for combined EBRT/HDR-BT are encouraged as this is the first study for such analysis involving registrations.

5.9 Supplements 5A-5D

5.9.1 Supplement 5A

This supplement provides information on patient characteristics and treatment protocol for combined EBRT/HDR-BT.

The 167 prostate cancer patients were initially treated with neoadjuvant androgen deprivation therapy at Sir Charles Gairdner Hospital in the period 2004 to 2008. Then they received external beam radiotherapy (EBRT) followed by high-dose-rate brachytherapy (HDR-BT). Patient criteria and treatment methodology were as specified for the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [38, 39]. The standard HDR-BT planning and treatment process has previously been described [45]. The important details are:

- The EBRT prescription dose to the prostate for the 167 patients was 46 Gy to the International Commission on Radiation Units and Measurements 50 reference point (23 daily fractions of conventional fractionation over five weeks).
- The four-field three-dimensional EBRT plan was created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden) based on the planning CT with the patient in the supine position.
• The prescription dose to the prostate was 19.5 Gy for HDR-BT delivered by Iridium-192 after-loading catheters (Varian Oncology Systems).

• The HDR-BT prescription dose covered the prostate gland and any extracapsular extensions.

• The HDR-BT was delivered in three fractions of 6.5 Gy across two days with the trial guidelines stipulating a maximum delivery time of 90 minutes for each fraction and a minimum of six hours between fractions.

• The dose to the rectum from HDR-BT was limited to a maximum of 80% of the 19.5 Gy prescription dose.

• The HDR-BT was typically started two to five weeks after the end of EBRT.

• The temporary metal needle HDR-BT catheters were inserted with trans-rectal ultrasound, fluoroscopy and perineal template guidance while the patient was in the lithotomy position.

• Needle catheters were inserted and cystoscopy was used to ensure proper tenting of the bladder wall mucosa by catheters.

• A plastic template was sutured to the skin to hold the needles in place.

• The patient was then taken to have a HDR-BT planning CT and a three-fraction HDR-BT plan was created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US) based on this CT.

• The HDR-BT doses were based on the standard TG43 format [44].

• Patients were in the lithotomy position for HDR-BT treatment with cushions used to keep the patients’ legs in the abducted position between fractions.

• No patient had artificial hip joints.

• Reproducibility of needle positions before each fraction was ensured via reference to fiducial markers implanted before the first fraction [45].
- The EBRT planning target volume (PTV) and HDR-BT source definition volume (SDV) were obtained by expanding the corresponding clinical target volume (CTV) by a 10 mm margin. The HDR-BT SDV was used to restrict dwell positions to the lengths of identified catheters covered by the SDV.

Table S5.1 summarises the patient characteristics at baseline.

**Table S5.1:** The baseline clinical characteristics of 167 patients who underwent external beam radiotherapy followed by high-dose-rate brachytherapy for prostate cancer. Abbreviations: PSA = Prostate-specific antigen; HDR-BT = High-dose-rate brachytherapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspect of characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median</td>
<td>66.6</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>62.1-71.4</td>
</tr>
<tr>
<td>PSA</td>
<td>PSA &lt; 10</td>
<td>43 (25.8%)</td>
</tr>
<tr>
<td></td>
<td>10 ≤ PSA &lt; 20</td>
<td>58 (34.7%)</td>
</tr>
<tr>
<td></td>
<td>PSA ≥ 20</td>
<td>66 (39.5%)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>&lt; 7</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>= 7</td>
<td>61 (36.5%)</td>
</tr>
<tr>
<td></td>
<td>≥ 8</td>
<td>104 (62.3%)</td>
</tr>
<tr>
<td>Tumour classification</td>
<td>T2a</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>17 (10.2%)</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>30 (18.0%)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>118 (70.6%)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Risk group</td>
<td>Medium</td>
<td>44 (26.3%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>123 (73.7%)</td>
</tr>
<tr>
<td>Number of HDR-BT catheters</td>
<td>12</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>136 (81.4%)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>21 (12.6%)</td>
</tr>
</tbody>
</table>
This supplement provides additional detail on the treatment protocol for patients who received EBRT only.

The 724 prostate cancer patients who received external beam radiotherapy (EBRT) only were treated at 23 centres across Australia and New Zealand in the period 2003 to 2008. All patients were initially treated with neoadjuvant androgen deprivation therapy. Patient criteria and treatment methodology were as specified for the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [38, 39]. The planning, treatment, patient and quality assurance details for EBRT have previously been discussed in detail [38–43]. Appendix II in the Ebert et al. [42] study provides figures for important details. The details relevant to this study are:

- The EBRT prescription dose to the prostate for the 724 patients was allowed to be 66, 70, 74 or 78 Gy to the International Commission on Radiation Units and Measurements 50 reference point.

- No patients were treated with a prescribed dose 78 Gy.

- The prescription dose could be delivered in up to two phases.

- The prescription dose was delivered in daily conventional fractions.

- Beam energy was required to be 6 MV or greater (with most delivered using 18 MV).

- Patient setup orientation could be prone or supine (with most in the supine position).

- Treatment was delivered with at least three fields (with most delivered using four fields).

- The dose calculation algorithms were mostly convolution, generalised pencil-beam and collapsed-cone convolution.
- The volume of the rectum receiving at least 65, 70 and 75 Gy was constrained to at most 40%, 30%, and 5% respectively.
5.9.3 Supplement 5C

This supplement provides information on the criteria for grading the different types of toxicities.

**Table S5.2:** Toxicity grading system for clinician-assessed rectal bleeding, stool frequency, diarrhea, completeness of evacuation, anorectal pain, urgency and tenesmus, and CTC proctitis (Note: the table continues on the next page). Source: [1], Creative Commons CC-BY.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>Never</td>
<td>Occult</td>
<td>&gt; 2/week</td>
<td>Daily</td>
<td>Gross haemorrhaging</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>&lt; 2/day</td>
<td>2-4/day</td>
<td>5-8/day</td>
<td>&gt; 8/day</td>
<td>Uncontrolled diarrhea</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>None</td>
<td>Increase &lt; 4</td>
<td>Increase of 4-6</td>
<td>Increase of ≥ 7</td>
<td>Physiologic consequences requiring intensive care; haemodynamic collapse</td>
</tr>
<tr>
<td>Complete</td>
<td>Complete</td>
<td>Occasional multiple evacuations (“about once a week feel like you’re not ‘all done’” or it takes more than one movement to “you’re all done”)</td>
<td>Frequent multiple evacuations (“more than once a week feel like you’re not ‘all done’” or it takes more than one movement)</td>
<td>Requires enema to obtain complete emptying</td>
<td>–</td>
</tr>
</tbody>
</table>

186
<table>
<thead>
<tr>
<th>Anorectal pain</th>
<th>Never</th>
<th>Occasional and mild</th>
<th>Intermittent and tolerable</th>
<th>Persistent and intense</th>
<th>Refractory and excruciating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency and tenesmus</td>
<td>Never</td>
<td>Occasional</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Refractory</td>
</tr>
<tr>
<td>CTC proctitis</td>
<td>None</td>
<td>Increased stool</td>
<td>Increased stool</td>
<td>Increased stool</td>
<td>Perforation, bleeding or necrosis or other life threatening complication requiring surgical intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>frequency, occasional blood-streaked stools or rectal discomfort not requiring medication</td>
<td>frequency, bleeding mucous discharge or rectal discomfort requiring medication, anal fissure</td>
<td>frequency/diarrhoea requiring parenteral support, rectal bleeding requiring transfusion, or persistent mucous discharge necessitating pads</td>
<td></td>
</tr>
</tbody>
</table>
5.9.4 Supplement 5D

This supplement provides an example of the visual check on registration alignment.

Figure S5.1: Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images for combined EBRT/HDR-BT. The EBRT images are in the background. Regions of the HDR-BT images after a rigid plus multi-pass deformable image registration are contained within the yellow outlined rectangular spyglass box. This box can be resized and moved around (e.g. left image versus right image). The EBRT clinical target volume, planning target volume and rectal structures are in purple, red and green respectively. Source: [1], Creative Commons CC-BY.
5.10 References


Stage III:
Using novel methods to relate spatial features of dose distributions to symptoms
Chapter 6:
Spatial analysis
6.1 Foreword for manuscript

The previous two chapters determined which dose regions were important for gastrointestinal complications observed after combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT). However, these regions were extracted from dose-volume histograms, which are degenerate to the underlying dose distribution. The question is then: what additional information is obtained by analysing the shape of the distribution of dose? Consequently, the manuscript in this chapter relates regional (voxel-wise) features of dose-surface maps and parameterised spatial patterns to gastrointestinal complications observed after combined prostate EBRT/HDR-BT. The findings can then be compared with the previous two chapters to reveal sub-regions of the rectum or arrangements of dose to the rectum that may be associated with gastrointestinal complications. Additionally, the findings can be compared with published studies on the spatial features important for gastrointestinal complications after EBRT. The above comparisons will allow future treatments to include a better consideration of important regions of the rectum for reducing dose and the potential spatial-based metrics for constraining spatial features associated with complications.
Spatial features of dose-surface maps from deformably-registered plans correlate with late gastrointestinal complications.


Publication status: Published. The manuscript in this chapter (including supplements) is a typeset of the version submitted to the journal for peer review. The inclusion of published material in this chapter is allowed by the copyright agreement for the final published article [1]. Additionally, Sections 6.5.1, 6.5.2, 6.5.3, 6.10.1, 6.10.2, 6.10.3 and 6.10.4 are based on the publication for Chapter 4 [2].

6.3 Abstract

6.3.1 Background

This study investigates the associations between spatial distribution of dose to the rectal surface and observed gastrointestinal toxicities after deformably registering each phase of a combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) prostate cancer treatment.

6.3.2 Methods

118 patients received EBRT in 23 fractions of 2 Gy and HDR-BT (TG43 algorithm) in three fractions of 6.5 Gy. Results for the Late Effects of Normal Tissues - Subjective, Objective, Management and Analytic (LENT-SOMA) toxicity assessments were available with a median follow-up of 72 months. The HDR-BT CT was deformably-registered to the EBRT CT. The EBRT and registered HDR-BT TG43 dose distributions in a reference 2 Gy/fraction were summed. Rectal dose-surface maps (DSMs) were obtained by virtually unfolding the total rectal surface dose slice-by-slice. Patients were classed into toxicity or no toxicity groups if they did or did not have a grade LENT-SOMA toxicity from the period three months after radiotherapy onwards. The toxicities were rectal bleeding, stool frequency, diarrhoea, urgency/tenesmus, anorectal pain, proctitis and completeness of evacuation. Associations with late peak gastrointestinal toxicities were investigated using voxel-wise DSM analysis as well as parameterised spatial patterns. The latter were obtained by thresholding DSMs from 1-80 Gy (increment=1) and extracting inferior-superior extent, left-right extent, area, perimeter, compactness, circularity and ellipse-fit parameters. Logistic regressions and Mann-Whitney U-tests were used to correlate features with toxicities.

6.3.3 Results

Rectal bleeding, stool frequency, diarrhoea and urgency/tenesmus were associated with greater lateral and/or longitudinal spread of the high doses near the anterior rectal surface. Rectal bleeding and stool frequency were also influenced by greater low-intermediate doses to the most inferior 20% of the rectal length and greater
low-intermediate-high doses to 40-80% of the rectal length respectively. Greater low-intermediate doses to the superior 20% and inferior 20% of the rectal length were associated with anorectal pain and urgency/tenesmus respectively. The low doses to the posterior side of the rectum were greater for patients with diarrhoea, completeness of evacuation and proctitis events. Spatial features for the intermediate-high dose regions such as area, perimeter, compactness, circularity, eccentricity of ellipse fits and confinement to ellipse fits were strongly associated with toxicities other than anorectal pain.

6.3.4 Conclusions

The shape of isodoses and dose coverage were found to be associated with toxicity. The findings indicate that spatial constraints on the intermediate-high doses to the superior/inferior ends of the rectum may be important for reducing gastrointestinal toxicities. The features of DSMs revealed specific regions and spatial characteristics for each toxicity that may be useful for dose optimisation.
6.4 Introduction

The side effects associated with irradiation of organs at risk are clinically managed by constraining the dose-volume histograms (DVH) and/or dose-surface histograms (DSH) for the 3D dose to the organ at risk (OAR) [3]. DVHs and DSHs have been used to associate dose ranges with late gastrointestinal (GI) toxicities, e.g. high doses are important for rectal bleeding [3]. However, analysis based on a DVH for a whole OAR assumes homogeneous radio-sensitivity, lacks spatial accuracy and does not incorporate radio-sensitive sub-regions of the OAR [4, 5].

A variety of methods have improved on the standard DVH-based analysis to identify important sub-regions of OARs for toxicity prediction. One improvement on the standard DVH-based analysis is to perform the analysis for DVHs calculated over sub-regions of the OAR [5, 6] or to parameterise the OAR prior to dose-line histogram analysis [7]. Another method involves relating distance-from-dose metrics to observed toxicity [8, 9] or relating the size of simulated clustering of damage from dose to observed toxicity [10]. The patient data can also be registered to a common template followed by voxel-wise analysis [4, 11] or voxel-based principal component analysis [12]. A parameterised alternative to this 3D analysis is to reduce the 3D surface dose for tubular-like organs (e.g. rectum) to a 2D dose-surface map [10, 13–18].

The DSM method is appropriate for associating dose distribution with rectal bleeding, as studies on recto-sigmoidoscopy [19], voxel-based analysis of registered doses [4, 12], normal tissue complication probability [20–22], dose constraints [6] and dose-distance metrics [8, 9] have identified the importance of high doses close to the wall/surface of the rectum. Additionally, supplementing DVH-based analysis with rectal dose shapes from DSMs has been shown to result in significantly improved predictions for various late GI toxicities [15]. DSMs also identify differences in accumulated doses that are not revealed by DVH-based analysis [23]. Consequently, DSMs have been useful for explaining GI toxicity in terms of spatial distribution of dose [10, 13–18].

One issue when considering the dose for combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) is that the phases are typically planned separately [24]. The planned dose/constraints applied for each phase [25]
are consequently susceptible to anatomical differences between the planning CTs. Hence, it would be preferable to consider GI toxicity by accumulating dose for the two phases using image registration and constraining the total planned dose [26]. The DSM should then be calculated on the total planned dose after applying the registration, as the DSMs for each phase may not be aligned due to deformations, shrinkage and contouring errors [27–30]. Consequently, a rigid registration should be used to align the reference coordinate systems and then deformable image registration (DIR) should be applied to adjust for deformations and shrinkage [27–30]. Additionally, the doses for different fraction schedules should be converted to equieffective doses given in a reference $X\text{Gy per fraction (}EQDX_{\alpha/\beta}\text{ Gy)}$, as this adjusts for the biologically non-equivalent fractionation schedules [31–33].

Studies in other contexts have adjusted for the earlier mentioned factors; however, deformable image registration has rarely been used to accumulate the rectal dose from phases of a combined EBRT/HDR-BT prostate treatment, as the typical approach is to use rigid registration or DVH-based parameter-adding to estimate accumulated dose. This study will be the first to calculate registered DSMs for combined EBRT/HDR-BT prostate treatment delivered according to multicentre trial guidelines. This study will examine the regional correlation of rectal dose-surface maps with late gastrointestinal toxicities, for the purpose of confirming whether spatial analysis reported for prostate EBRT applies to prostate combined EBRT/HDR-BT after applying deformable registration. Additionally, the spatial distribution of dose will be characterised by features and these will be related to observed toxicities.

6.5 Methods

6.5.1 Patient data

This study included 118 prostate cancer patients (tumour T stage $\geq 2a$) who were treated with EBRT followed by HDR-BT at Sir Charles Gairdner Hospital in the period 2004 to 2008. These patients were treated as part of the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [34, 35]. The patient criteria and treatment methodology for the RADAR trial have previously been detailed [34, 35]. Aspects of the
combined EBRT/HDR-BT treatment process have previously been described [36]. The four-field 3D conformal EBRT plans for a prescription dose of 46 Gy in 23 daily fractions were created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden). The HDR-BT plans for a prescription dose of 19.5 Gy in three fractions across two days were created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US). The doses for the HDR-BT plans were calculated using the TG43 formalism [37]. Supplementary details on patient characteristics and treatment protocol are provided in Supplement 6A.

The external wall of the rectum was manually delineated by treating-clinicians in the HDR-BT CTs using BrachyVision and in the EBRT CTs using the Elekta Focal contouring system (Elekta AB, Stockholm, Sweden). Author with initials MK reviewed outlines of rectums for consistency among patients. For contouring of the rectum, the inferior-superior limits of the rectum were the rectosigmoid flexure and the last slice where the ischial tuberosities were visible. Patients did not commonly require bowel preparation. Supplementary examples of the planning CTs and structures for EBRT and HDR-BT TG43 physical dose plans are provided by Figures S6.1 and S6.2 in Supplement 6B.

### 6.5.2 Toxicity outcomes

Patients were assessed for various gastrointestinal toxicities at baseline (randomisation) and subsequent time points after randomisation (e.g. 3, 6, 9, 12, 15, 18, 24, 30, 36, 42, 48, 54, 60, 72, 84, 96, 108 months). The median of the most recent follow-ups was 72 months (range 12-96 months). The Late Effects of Normal Tissue - Subjective, Objective, Management and Analytic (LENT-SOMA) scales were used to assess rectal bleeding, urgency/tenesmus, stool frequency, diarrhoea, anorectal pain and completeness of evacuation [38]. Proctitis was scored by clinicians according to the Common Toxicity Criteria for Adverse Events (CTCAE version 2) [39]. A supplementary description of the grading systems is provided by Table S6.2 in Supplement 6C.

Late peak toxicity was calculated for the period onwards from three months after radiation therapy. Figure 6.1 provides a summary of the late peak toxicity event rates for the follow-up period. Patients were classified to a toxicity group if the
late peak toxicity was at least a certain grade (threshold for dichotomisation). In the interest of modelling a moderate severity of toxicity, the threshold was grade 2 for rectal bleeding, stool frequency and completeness of evacuation. The threshold was grade 1 for diarrhoea, anorectal pain, urgency/tenesmus and proctitis due to low sample sizes and/or similar dose-response for groups formed by thresholding at grade 2. The thresholds used to dichotomise the toxicities for each symptom are illustrated in Figure 6.1.

![Figure 6.1: Late peak toxicity grades for various toxicity types over the follow-up period for 118 patients. The toxicity types (abbreviation) are rectal bleeding (bleeding), CTC proctitis (proctitis), stool frequency (frequency), diarrhoea, urgency/tenesmus (urgency), anorectal pain (pain) and completeness of evacuation (evacuation). The toxicity rates are reported as cumulative percentages of the 118 patients. The thresholds for subsequently grouping patients into toxicity/no toxicity groups are indicated by the red dashed lines. Source: [2], Creative Commons CC-BY.](image)

### 6.5.3 Registration process

The HDR-BT CT was registered to the EBRT CT using rigid registration followed by a B-splines multi-pass DIR in Velocity Advanced Imaging 2.8.1 (Varian Medical Systems, Palo Alto, US) [40]. The registration process has been described in detail previously [40, 41]. The registrations were quantitatively evaluated for each patient in this study using the overlap of the EBRT rectum and registered HDR-BT rectum.
(expressed as a percentage of the volume of the registered HDR-BT rectum). The median overlap is 80.4% for alignment of EBRT/registered HDR-BT rectal structure volumes (Figure 6.2). A general structure overlap of 70% has been used by other studies as the starting point for satisfactory registrations in the radiotherapy context [4, 42]. Visual inspections by authors (initials CRM, VL and CIT) for the 118 patients did not identify any major registration misalignments (e.g. Figure S6.3 in Supplement 6D). The registrations have also previously been extensively evaluated using structure-correspondence metrics and image similarity metrics [41].

Figure 6.2: Illustration of the structure overlap-metric used to assess major misalignment of rectal volume (Top). Overlap of the external beam radiotherapy (EBRT) rectum/registered high-dose-rate brachytherapy (HDR-BT) rectum was expressed as a percentage of the volume of the registered HDR-BT rectum (i.e. an increasing overlap metric indicates increasing correspondence of the two rectal structures). Structure overlap results for the 118 patients after the rigid plus multi-pass deformable image registration (DIR) are provided (Bottom). Source: [2], Creative Commons CC-BY.
6.5.4 Obtaining dose-surface maps

The EBRT and registered HDR-BT 3D-doses were imported into MATLAB™ R2010a (The MathWorks Inc., Massachusetts, US) and the Computational Environment for Radiotherapy Research (CERR, version 4.1) [43]. The voxel doses were converted to equieffective doses given in a reference 2 Gy per fraction using the linear-quadratic model [32, 44] with an alpha-beta ratio (α/β) of 3 Gy for the rectum [45]. The dose-surface maps were also produced for an alpha-beta ratio of 5.4 Gy to check the sensitivity of results to the upper limit published for the rectum [46]. However, the maps were similar and hence the results for an alpha-beta ratio of 5.4 Gy are not reported in further detail. The EBRT dose was summed voxel-by-voxel with the registered HDR-BT dose. MATLAB code was created to virtually unfold the 3D rectal surface slice-by-slice by cutting through the posterior of the rectum and unfolding the dose onto a 2D dose-surface map using a similar method to Tucker et al. [10]. The posterior cut-point was the lateral component of the centroid. The DSM voxels were equally spaced by finding points at which regularly-separated rays from the contour centroid intercepted the contour. As recommended by previous DSM studies [14, 16, 17], the DSMs were normalised in the anterior-posterior-anterior and inferior-superior directions to allow voxel-wise comparisons from patient to patient. The x and y axes were normalised as percentages of 180 degrees and the length of rectum respectively. Additionally, the anterior-posterior-anterior dose and location were normalised onto 45 voxels on the x-axis and the inferior-superior dose and location were normalised onto 51 voxels on the y-axis. These dimensions for the DSMs were chosen to maintain the resolution of the planned dose distributions. Figure S6.4 in Supplement 6E provides an illustration of the virtual unfolding process for obtaining a DSM.

6.5.5 Features of the spatial distribution

To characterise the spatial distribution of dose each DSM was thresholded at dose levels from 1-80 Gy in 1 Gy increments. Binary masks (clusters) were generated from voxels of the DSM where dose was at least the thresholded dose. Typically, one large cluster was formed at each dose as the highest rectal dose in EBRT and HDR-BT is located on the anterior rectal wall. The gradual decrease in dose around the hot-
spot on the anterior rectal wall is suited to the use of elliptical fits for extracting features of the spatial distribution. Consequently, an ellipse was fitted to the cluster for each thresholded DSM following the method of Buettner et al. [14]. Figure S6.5 in Supplement 6E provides an example of an ellipse fitted to a thresholded DSM. The major and minor axes of the ellipse were projected onto the DSM axes to obtain lateral and longitudinal extent of the ellipse. Additionally, the eccentricity and rotation of the ellipse were obtained. Table 6.1 describes the features of clusters and ellipse fits which were used to parameterise the spatial distribution.

### 6.5.6 Response modelling

Voxel-wise comparisons between the maps for patients with and without symptoms were performed and summarised via dose difference of the median maps. Additionally, voxel-wise Mann-Whitney U-tests [47] were used to obtain voxel-wise p-values for such comparisons across the two toxicity groups. For each type of toxicity, univariate ordinal logistic regression was applied at each DSM voxel across all patients to obtain an odds ratio (OR) for the increase in toxicity probability per 2 Gy increase in dose. Similarly, logistic regression was undertaken for each DSM feature across all patients to obtain an odds ratio for the increase in toxicity probability per 1 unit increase in the normalised value of the feature. The feature values were normalised so that there is a consistent maximum possible value of 100 for all features.

P-values for odds ratios were calculated using bootstrapping with 10,000 resamples from the toxicity and no toxicity groups [48]. P-values which demonstrate a trend across regions or dose levels and do not appear random are important for associating regions or dose levels with elevated symptoms [5]. Consequently, we identify potentially important dose levels or regions by finding p-values from 0 to 0.05 and looking at the p-value trend of 0.05 to 0.2 in the neighbouring regions/dose levels. The logistic regressions, bootstrapping and Mann-Whitney U-tests were performed in MATLAB® R2015a (The MathWorks Inc., Massachusetts, US).
Table 6.1: Features used to parameterise the spatial distribution.

<table>
<thead>
<tr>
<th>Name (label)</th>
<th>Description</th>
<th>Format</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sup limit (S_limit)</td>
<td>Maximum superior extent of the cluster</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Inf limit (I_limit)</td>
<td>Maximum inferior extent of the cluster</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Sup-inf range (SI_range)</td>
<td>Longitudinal spread of the cluster = Sup limit - Inf limit</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Left limit (L_limit)</td>
<td>Maximum posterior-left extent of the cluster</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Right limit (R_limit)</td>
<td>Maximum posterior-right extent of the cluster</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Left-right range (LR_range)</td>
<td>Lateral spread of the cluster = Left limit - Right limit</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Centroid lateral (Cen_lat)</td>
<td>Lateral component of the centroid for the cluster</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Centroid longitudinal (Cen_lon)</td>
<td>Longitudinal component of the centroid for the cluster</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Area (Area)</td>
<td>Normalised area of the cluster = Area of cluster / Area of DSM</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Perimeter (Perimeter)</td>
<td>Perimeter of the cluster normalised by the maximum perimeter calculated across all dose levels and patients</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Compactness (Compactness)</td>
<td>Scaled discrete compactness of the cluster ( = 100 \left( \frac{\text{Area} - \text{Perimeter}}{4} \right) / \left( \text{Area} - \text{Area}^{1/2} \right) ) [49]</td>
<td>Raw</td>
<td>0 (fully disjoint) 100 (solid square)</td>
</tr>
<tr>
<td>Circularity (Circularity)</td>
<td>Scaled circularity of the cluster ( = 400\pi \frac{\text{Area}}{\text{Perimeter}^2} ) [49]</td>
<td>Raw</td>
<td>0 (elongated) 100 (perfect circle)</td>
</tr>
<tr>
<td>Ellipse eccentricity (Ell_ecc)</td>
<td>Scaled eccentricity of ellipse fitted to cluster [14]</td>
<td>Raw</td>
<td>0 (circle) 100 (ellipse)</td>
</tr>
<tr>
<td>Ellipse rotation (Ell_rot)</td>
<td>Angle between the major axis from the ellipse fit of the cluster and the DSM x-axis as percentage of 360° [14]</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Ellipse lateral (Ell_lat)</td>
<td>Maximum projection of the axes from the ellipse fit of the cluster onto the DSM x-axis [14]</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Ellipse longitudinal (Ell_lon)</td>
<td>Maximum projection of the axes from the ellipse fit of the cluster onto the DSM y-axis [14]</td>
<td>%</td>
<td>0-100</td>
</tr>
<tr>
<td>Ellipse filled (Ell_fill)</td>
<td>Percentage of the cluster that is contained within the ellipse fitted to the cluster = Area of cluster within ellipse / Area</td>
<td>%</td>
<td>0-100</td>
</tr>
</tbody>
</table>
Clinical risk factors were not included in dose-response modelling as a previously published analysis determined that clinical covariates did not significantly influence late toxicities for patients in the RADAR trial [2, 50]. An equivalent dose-volume analysis for the 118 patients in this study confirmed that clinical covariates did not significantly influence late toxicities and are thus not reported any further [2]. The clinical factors considered were age, tumour T stage, Gleason score, initial PSA, risk group, number of HDR-BT catheters, colorectal disorders, hypertension, diabetes, smoking, use of statins, ACE inhibitors and anti-coagulants [2].

6.6 Results

Unless it is stated otherwise, all figures and tables in this section report dose values in a reference 2 Gy per fraction using an $\alpha/\beta$ of 3 Gy. In general, doses to various regions of the rectum were associated with toxicities as shown by visual comparisons of dose-surface maps (Figure 6.3 and Figure S6.6 in Supplement 6F), voxel-wise dose differences for dose-surface maps (Figures 6.4 and 6.5), voxel-wise odds ratios for dose-surface maps (Figures 6.4 and 6.5) and odds ratios (OR) for features used to characterise thresholded dose-surface maps (Table 6.2 or, alternatively, figures in Supplement 6G). As detailed in the following sections, each symptom displayed some unique association with dose to certain regions. Comparisons of dose regions are reported in terms of the low/intermediate/high dose for patients with toxicity being greater/lower than the corresponding low/intermediate/high dose for patients without toxicity.

6.6.1 Rectal bleeding

Figure 6.3 shows greater lateral spread of the intermediate-high dose regions (50-80 Gy) near the anterior side of the rectum for patients with bleeding (this group is subsequently referred to as bleeders). Figure 6.3 also shows greater longitudinal spread of the intermediate-high dose region (50-80 Gy) near the anterior side of the rectum for bleeders, with the 70 Gy isodose extending more superiorly for bleeders (about an additional 5% of the rectal length). Table 6.2 indicates bleeding is strongly associated (OR $>1.1$) with the area of the intermediate-high isodoses (49-80 Gy) and perimeter of the low-intermediate-high isodoses (8, 10-13, 27-29, 56, 63-65, 67 Gy).
Additionally, the compactness and circularity of the intermediate isodoses (38-47 Gy) and the confinement of intermediate doses (38-40 Gy) to ellipse fits is strongly associated with bleeding (Table 6.2). The dose differences in Figure 6.4 indicate greater low-intermediate doses to the last (inferior) 20% of rectum for bleeders and greater low doses along the posterior section of the rectum for bleeders. Additionally, Figure 6.4 indicates the greatest dose-response (OR > 1.1) is for the low-dose region on the posterior side of the rectum at about 80% of the rectal length.

6.6.2 Stool frequency

Figure 6.3 shows greater lateral spread of the intermediate-high dose regions (50-80 Gy) near the anterior side of the rectum for patients with stool frequency events. Figure 6.3 also shows greater longitudinal spread of the high-dose region (70-80 Gy) near the anterior side of the rectum for stool frequency events, with the 70 Gy isodose extending more superiorly for patients with events (about an additional 5% of the rectal length). Additionally, the dose differences in Figure 6.4 indicate greater low-intermediate-high doses to the rectal surface at about 40-80% of the rectal length. Figure 6.4 indicates the greatest dose-response (OR > 1.1) is for the low-intermediate dose region on the posterior side of the rectum in a section of 60-80% of the rectal length. Additionally, Table 6.2 identifies stool frequency events are strongly associated (OR > 1.1) with compactness of the intermediate doses (44-49 Gy) and perimeter of the low-intermediate isodoses (28-32 Gy). Table 6.2 also provides some evidence of stool frequency being associated with the eccentricity of ellipse fits and the confinement of clusters to ellipse fits at intermediate doses.

6.6.3 Completeness of evacuation

Figure 6.3 shows greater sparing of the superior end of the rectum to the 10 Gy isodose (an inferior shift of at least 5% of the rectal length) for patients with completeness of evacuation events. Additionally, the dose differences in Figure 6.4 reveal greater low doses along the posterior side of the rectum for patients with completeness of evacuation events. Figure 6.4 also shows some protective low-intermediate dose effect for the superior 40% of the rectal length with most of the effect located at the anterior side of the rectum. Figure 6.4 indicates that most of the low-
intermediate dose-response (OR>1.1) is located along the posterior side of the rectum. Additionally, most of the low-intermediate protective dose-response (OR<1) is along the anterior side of the most superior 40% of the rectal length (Figure 6.4). Table 6.2 indicates that there is some association (OR>1.1) of completeness of evacuation with the compactness, circularity and lateral extent of ellipse fits at low doses.

6.6.4 Anorectal pain

The dose differences in Figure 6.5 reveal greater low-intermediate doses to the superior 20% of the rectal length for patients with anorectal pain events. Figure 6.5 reveals greater low-intermediate doses to the left and right sides of the rectum from 0-60% of the rectal length. Additionally, most of the low-intermediate dose-response (OR>1.1) is located between 20-60% of the rectal length on the left-posterior-right section of the rectum (Figure 6.5). Table 6.2 indicates anorectal pain is not associated with any spatial measures for the intermediate-high doses.

6.6.5 Diarrhoea

Figure S6.6 in Supplement 6F shows greater lateral spread of the high-dose regions (70-80 Gy) near the anterior side of the rectum for patients with diarrhoea events. Additionally, Figure 6.5 indicates greater low doses to the posterior side of the rectum along the middle 60% of the rectal length. Figure 6.5 indicates that most of the low-intermediate dose-response (OR>1.1) is located along the posterior side of the rectum. Table 6.2 details some association (OR>1.1) of diarrhoea with the perimeter of the intermediate isodoses (30-32, 59-60 Gy) and the eccentricity of ellipse fits at high doses (69-70 Gy).

6.6.6 Urgency and tenesmus

Figure S6.6 in Supplement 6F shows greater longitudinal spread of the high-dose region (70-80Gy) near the anterior side of the rectum for patients with urgency/tenesmus events. Additionally, Figure 6.5 indicates that the spread of 20-30 Gy dose range near the left and right sides of the rectum in the inferior 20% of rectal length is important.
Figure 6.3: Median dose-surface maps for groups of patients assigned as having and not having a rectal bleeding, stool frequency and completeness of evacuation event. The peak late toxicities for rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2 whereas diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1. The green lines identify isodose contours. Figure S6.6 in Supplement 6F provides the maps for diarrhoea, anorectal pain, proctitis and urgency/tenesmus. Abbreviations: $EQD_2$ Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy; S, superior; I, inferior; P, posterior; L, left; A, anterior; R, right.
Figure 6.4: Voxel-wise dose differences and odds ratio maps for rectal bleeding, stool frequency and completeness of evacuation. Dose difference maps are calculated based on the median dose-surface maps for groups of patients with and without a toxicity event. The odds ratio maps are the increase in toxicity probability per 2 Gy increase in dose. The maps include only those voxels where the p-value from voxel-wise Mann-Whitney U-tests for differences or voxel-wise bootstrapped logistic regressions for odds ratios are less than 0.2. The peak late toxicities for rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2 whereas diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1. Figure 6.5 provides the corresponding maps for diarrhoea, anorectal pain, proctitis and urgency/tenesmus. Abbreviations: EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy; S, superior; I, inferior; P, posterior; L, left; A, anterior; R, right.
Figure 6.5: Voxel-wise dose differences and odds ratio maps for diarrhoea, anorectal pain, proctitis and urgency/tenesmus. Dose difference maps are calculated based on the median dose-surface maps for groups of patients with and without a toxicity event. The odds ratio maps are the increase in toxicity probability per 2 Gy increase in dose. The maps include only those voxels where the p-value from voxel-wise Mann-Whitney U-tests for differences or voxel-wise bootstrapped logistic regressions for odds ratios are less than 0.2. The peak late toxicities for diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1 whereas rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2. Abbreviations: EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy; S, superior; I, inferior; P, posterior; L, left; A, anterior; R, right.
Table 6.2: Summary of DSM features which had considerable odds ratios. A full set of odds ratio results for DSM features is provided in Supplement 6G. Abbreviations: DSM, dose-surface map; OR, odds ratio is the increase in toxicity probability per 1 unit increase in the normalised value of the DSM feature; p-value, p-value from bootstrapping the logistic regression; Sup, superior; Inf, inferior; Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy; $\alpha/\beta$, alpha-beta ratio.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Low dose</th>
<th>Intermediate dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>Inf limit (4-5 Gy)</td>
<td>Area (49-59 Gy)</td>
<td>Area (60-80 Gy)</td>
</tr>
<tr>
<td></td>
<td>Sup-Inf range (3-5 Gy)</td>
<td>Perimeter (56 Gy)</td>
<td>Perimeter (63-65, 67 Gy)</td>
</tr>
<tr>
<td></td>
<td>Area (2-3 Gy)</td>
<td>Compactness (37-49 Gy)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Perimeter (8, 10-13, 27-29 Gy)</td>
<td>Circularity (38-47 Gy)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Circularity (1 Gy)</td>
<td>Ellipse filled (38-40 Gy)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Ellipse longitudinal (2 Gy)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>Left limit (24 Gy)</td>
<td>Perimeter (30-32 Gy)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Perimeter (28-30 Gy)</td>
<td>Compactness (44-49 Gy)</td>
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<tr>
<td></td>
<td>Compactness (20 Gy)</td>
<td>Ellipse eccentricity (48-50 Gy)</td>
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<tr>
<td></td>
<td>Ellipse lateral (27 Gy)</td>
<td>Ellipse filled (39-40 Gy)</td>
<td>-</td>
</tr>
<tr>
<td>Completeness of evacuation</td>
<td>Compactness (19-21 Gy)</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>Circularity (20-22 Gy)</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>Ellipse eccentricity (19 Gy)</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>Ellipse lateral (18, 24-27 Gy)</td>
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<td>-</td>
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<tr>
<td></td>
<td>Ellipse filled (19 Gy)</td>
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<td>Anorectal pain</td>
<td>Sup-Inf range (3 Gy)</td>
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<tr>
<td></td>
<td>Area (2 Gy)</td>
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<td>-</td>
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<tr>
<td></td>
<td>Compactness (4 Gy)</td>
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<td>-</td>
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<tr>
<td></td>
<td>Ellipse longitudinal (2 Gy)</td>
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<td>-</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Left-right range (23 Gy)</td>
<td>Perimeter (30-32, 59 Gy)</td>
<td>Perimeter (60 Gy)</td>
</tr>
<tr>
<td></td>
<td>Compactness (20 Gy)</td>
<td>-</td>
<td>Ellipse eccentricity (69-70 Gy)</td>
</tr>
<tr>
<td></td>
<td>Circularity (20-21 Gy)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urgency and tenesmus</td>
<td>Compactness (18-20 Gy)</td>
<td>Perimeter (30-32 Gy)</td>
<td>Ellipse eccentricity (77 Gy)</td>
</tr>
</tbody>
</table>

320
Figure 6.5 also indicates that most of the low-intermediate dose-response (OR>1.1) for urgency/tenesmus is located in the left-posterior-right section of the rectum. Table 6.2 details a strong association (OR>1.1) of urgency/tenesmus with the perimeter of the high isodoses (67-68, 70-76 Gy).

6.6.7 Proctitis

Figure 6.5 identifies greater low doses to the middle 60% of the rectal length along the posterior side of the rectum for increased proctitis symptoms. Additionally, Figure 6.5 indicates that most of the low-intermediate dose-response (OR>1.1) is located along the left-posterior-right section of the rectum. Table 6.2 indicates some association (OR>1.1) of compactness, perimeter and eccentricity of ellipse fits with proctitis symptoms.

6.7 Discussion

The rectal dose for combined EBRT/HDR-BT prostate cancer treatment has previously been accumulated without applying deformable registration [18, 24]. In line with the recommendations of a previous study [33], this is the first study to more accurately obtain total planned dose via deformably registering the phases of combined EBRT/HDR-BT prostate cancer treatment. This is also the first study for combined EBRT/HDR-BT prostate cancer treatment to publish dose-surface maps and correlate the maps with multiple individual gastrointestinal toxicities. It is important to publish dose-surface maps for this application as it is uncertain how valid dose-surface maps published for other treatment contexts involving EBRT alone are for combined EBRT/HDR-BT [10, 13–18]. It is also important for registration-based dose-toxicity modelling, including DSM analysis, to be published for a variety of studies, as this would allow a multi-institutional comparison of findings to include the confounding factors associated with different registration algorithms, registration circumstances and diversity in treatment techniques.

In agreement with other studies [4, 6, 8, 9, 12, 19–22, 45, 51], rectal bleeding was significantly correlated with high-dose metrics and consistent with a serial response. As this is a study of dose to the surface of the rectum, it supports the suggestion that rectal bleeding is associated with near-maximum doses causing epithelial damage.
and mucositis in parts of the rectal wall [52]. This confirmation in the context of deformable registration is important as a previous study without registration did not find a correlation with near-maximum doses [24]. The finding that rectal bleeding is associated with the lateral and longitudinal spread of the high-dose region (70-80 Gy) near the anterior side of the rectum and the area/perimeter of the high isodoses (70-80 Gy) supports the GEC/ESTRO recommendation of limiting the $D_{2cc}$ to 75 Gy [26]. This recommendation may also help with reducing the incidence of diarrhoea, urgency/tenesmus and stool frequency, as the results indicate these toxicities were associated with greater lateral, longitudinal and lateral/longitudinal spread of the high-dose regions respectively. The associations for perimeter at some dose levels and area at other dose levels indicate the shape of the high isodoses as well as the coverage may be important for reducing toxicity.

It has been suggested that the intermediate-dose region (> 30 Gy) is important for rectal bleeding [6, 53–55] and that specifically the lateral spread of the 39-61 Gy isodoses is important [14]. This study confirms the importance of the intermediate-dose region as greater low-intermediate doses to the last (inferior) 20% of rectum and greater low doses along the posterior section of the rectum were associated with the most sensitive dose-response for bleeding (OR > 1.1). Additionally, the findings of this study support the influence of the intermediate-dose region (> 30 Gy) on rectal bleeding as the areas of the 49-59 Gy isodoses and the perimeter of the 56 Gy isodose were strongly associated (OR > 1.1) with bleeding. Additionally, the compactness and circularity of the 38-47 Gy isodoses and the confinement of 38-40 Gy doses to ellipse fits were strongly associated with bleeding. The finding that more compact, circular and confined intermediate isodoses were correlated with bleeding supports the idea that cell migration from the low-dose region could aid healing of the vascular sclerosis in high-dose regions [9]. In regard to cell migration, cells in some low-dose areas could experience a closer approach to the high-dose region when the intermediate isodoses are less compact, circular and confined. The role of the low-dose region could explain why spatial features such as compactness, perimeter and eccentricity for intermediate-high doses were associated with stool frequency, diarrhoea, urgency/tenesmus and proctitis symptoms. Consequently, it would be useful to determine constraints for combined EBRT/HDR-BT based on
accumulated dose-volume metrics and spatial metrics or to explore cluster models of damage [10]. A larger sample size containing patients from a variety of institutions or advanced registration algorithms for registering all data to a common template would allow for a feasible application of multivariate, cut-point and dose constraint analysis.

Low and intermediate doses were associated with anorectal pain, diarrhoea, proctitis, urgency/tenesmus and completeness of evacuation. These findings are consistent with previous findings that the violation of $V_{40\text{Gy}}$ dose constraints is important for controlling urgency [54, 56] and that the low doses are important for controlling loose stools [14]. Additionally, the findings agree with a previous study focusing on patients within this trial who received EBRT only [6]. In that study the low-intermediate dose range was important for incidence of stool frequency, urgency and tenesmus [6]. In this current study the most sensitive dose-responses (OR $> 1.1$) for anorectal pain, diarrhoea, urgency/tenesmus, stool frequency and proctitis were found in the low-intermediate dose region near the left-posterior-right section of the rectum. The various toxicities did demonstrate some difference in terms of the importance of the inferior-superior location of low and intermediate doses. Anorectal pain appears to be associated with greater low-intermediate doses to the superior 20% of the rectal length, whereas greater low doses in the inferior 20% of the rectal length were associated with urgency/tenesmus. The latter is consistent with previous findings that dose to the inferior rectum can be indicative of effects on pelvic floor muscles with consequent control-like toxicity effects [57]. For diarrhoea and proctitis, the importance of low doses was in the middle 60% section of the rectal length. For stool frequency, the importance of low-intermediate doses was at 60-80% of the rectal length. The importance of low-intermediate dose-regions is reasonable as a low or intermediate dose to a large area would be expected to be associated with some detriment.

In contrast to the above and standard dose-response expectations, the occurrence of completeness of evacuation events was associated with greater sparing of the superior end of the rectum to the 10 Gy isodose. Specifically, a low-intermediate protective dose-response (OR $< 1$) was identified along the anterior side of the rectum within the superior 40% of the rectal length. However, this finding and other isolated
findings of association in low-dose regions should be considered with respect to likely correlations with other dose regions, event rates, sample size and the potential of random discovery. Analysis for the low-dose region resulted in a number of isolated findings of features being associated with toxicity. However, some associations were not important in the context of the trend across dose levels.

In this study and other studies applying registrations, the correlations with toxicity are confounded by errors in contouring and registration accuracy. Studies applying registrations in the radiotherapy context have indicated that a general structure overlap of 70% is considered to be the starting point for satisfactory registrations [4, 42]. In comparison, the median overlap was 80.4% for the rectal volume correspondence across all patients in this study. We recommend close monitoring of small localised variations in contouring and/or registration accuracy across the prostate/rectum interface, as parameters obtained after registration of EBRT/HDR-BT data are sensitive to such variations given the proximity of the HDR-BT rectum to the HDR-BT catheters.

Given this is the first deformable-registration-based spatial analysis study for combined EBRT/HDR-BT, additional studies using a variety of registration algorithms in a variety of contexts would be useful and could benefit from exploring: (1) the use of multiple toxicity events over the follow-up period [58] or the inclusion of the persistence of toxicity rather than peak late toxicity [59]; (2) the impact of additional imaging on the reliability of accumulated doses [60, 61]; (3) customised registration algorithms to allow accurate registration to a common template in the presence of catheters within the HDR-BT prostate as prostate and urethra doses are key clinical concerns in the RADAR trial [34, 35, 50]; and (4) constraints based on including a variety of dose-toxicity modelling methods [7, 10, 13–18, 23].

6.8 Conclusions

A number of significant dose-response and spatial effects were confirmed or revealed for gastrointestinal toxicities after applying deformable registration to adjust for the anatomical differences between planning CTs for each phase of a combined EBRT/HDR-BT prostate cancer treatment. Analysis on the features of DSMs revealed specific regions and spatial features for each toxicity that may be useful
for further reducing toxicity rates. The intermediate-high dose range and near-
maximum doses were important for rectal bleeding. The high-dose range was
also important for stool frequency, diarrhoea and urgency/tenesmus. Greater low-
intermediate doses to the last (inferior) 20%, superior 20% and inferior 20% of rectal
length were associated with rectal bleeding, anorectal pain and urgency/tenesmus
respectively. Consequently, reducing dose to the superior and inferior ends of the
rectum may also be important for reducing anorectal pain and urgency/tenesmus
respectively. We encourage other studies from a variety of registration contexts to
report on important spatial aspects of accumulated dose distributions for combined
EBRT/HDR-BT, as this study provides the first findings on dose-surface maps for
HDR-BT registered to EBRT.

6.9 Declarations

6.9.1 Conflict of interest disclosure

The Trans-Tasman Radiation Oncology Group trial 03.04 was supported by grants
from Australian and New Zealand Governments and non-governmental sources. No
financial benefits were paid to trial investigators or listed authors.

6.9.2 Acknowledgements

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at Sir Charles Gairdner Hospital and Annette Haworth for their considerable ef-
forts in generation of the data. We also appreciate the support of the RADAR
investigators and the Trans-Tasman Radiation Oncology Group.
6.10 Supplements 6A-6G

6.10.1 Supplement 6A

This supplement provides additional detail on patient characteristics and treatment protocol.

The 118 prostate cancer patients were initially treated with neoadjuvant androgen deprivation therapy at Sir Charles Gairdner Hospital in the period 2004 to 2008. Then they received EBRT followed by HDR-BT. Patient criteria and treatment methodology were as specified for the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [34, 35]. The standard HDR-BT planning and treatment process has previously been described [36]. The important details are:

- The EBRT prescription dose to the prostate for the 118 patients was 46 Gy to the International Commission on Radiation Units and Measurements 50 reference point (23 daily fractions of conventional fractionation over five weeks).
- The four-field 3D conformal EBRT plan was created in the Elekta XiO treatment planning system (Elekta AB, Stockholm, Sweden) based on the planning CT with the patient in the supine position.
- The prescription dose to the prostate was 19.5 Gy for HDR-BT delivered by Iridium-192 after-loading catheters (Varian Oncology Systems).
- The HDR-BT prescription dose covered the prostate gland and any extracapsular extensions.
- The HDR-BT was delivered in three fractions of 6.5 Gy across two days with a maximum delivery time of 90 minutes for each fraction and a minimum of six hours between fractions.
- The dose to the rectum from HDR-BT was limited to a maximum of 80% of the 19.5 Gy prescription dose.
- The HDR-BT was typically started two to five weeks after the end of external beam radiotherapy.
• The temporary metal needle HDR-BT catheters were inserted with trans-rectal ultrasound, fluoroscopy and perineal template guidance while the patient was in the lithotomy position.

• Needle catheters were inserted and cystoscopy was used to ensure proper tenting of the bladder wall mucosa by catheters.

• A plastic template was sutured to the skin to hold the needles in place.

• The patient was then taken to have a HDR-BT planning CT and a three-fraction HDR-BT plan was created in the BrachyVision treatment planning system (Varian Medical Systems, Palo Alto, US) based on this CT.

• The HDR-BT doses were based on the standard TG43 format [37].

• Patients were in the lithotomy position for HDR-BT treatment with cushions used to keep the patients’ legs in the abducted position between fractions.

• No patient had artificial hip joints.

• The EBRT planning target volume (PTV) and HDR-BT source definition volume (SDV) were obtained by expanding the corresponding clinical target volume (CTV) by a 10 mm margin. The HDR-BT SDV was used to restrict dwell positions to the lengths of identified catheters covered by the SDV.

Table S6.1 summarises the patient characteristics at baseline.
Table S6.1: The baseline clinical characteristics of 118 patients who underwent external beam radiotherapy followed by high-dose-rate brachytherapy for prostate cancer. Abbreviations: PSA = Prostate-specific antigen; HDR-BT = High-dose-rate brachytherapy. Source: [2], Creative Commons CC-BY.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspect of characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median</td>
<td>66.6</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>61.0-71.4</td>
</tr>
<tr>
<td>PSA</td>
<td>PSA &lt; 10</td>
<td>31 (26.3%)</td>
</tr>
<tr>
<td></td>
<td>10 ≤ PSA &lt; 20</td>
<td>42 (35.6%)</td>
</tr>
<tr>
<td></td>
<td>PSA ≥ 20</td>
<td>45 (38.1%)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>&lt; 7</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>= 7</td>
<td>41 (34.7%)</td>
</tr>
<tr>
<td></td>
<td>≥ 8</td>
<td>75 (63.6%)</td>
</tr>
<tr>
<td>Tumour classification</td>
<td>T2b</td>
<td>14 (11.9%)</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>16 (13.6%)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>87 (73.7%)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Risk group</td>
<td>Medium</td>
<td>29 (24.6%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>89 (75.4%)</td>
</tr>
<tr>
<td>Number of HDR-BT catheters</td>
<td>12</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3 (2.5%)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>96 (81.4%)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>13 (11.0%)</td>
</tr>
</tbody>
</table>
This supplement provides examples of planning CTs and planned doses.

**Figure S6.1:** A four-field EBRT physical dose plan with dose displayed as a colourwash up to the prescription dose of 46 Gy. The EBRT clinical target volume, planning target volume and rectal structures are in yellow, red and green respectively. Source: [2], Creative Commons CC-BY.

**Figure S6.2:** A HDR-BT TG43 physical dose plan with dose displayed as a colourwash up to the prescription dose of 19.5 Gy. The HDR-BT clinical target volume, source definition volume and rectal structures are in yellow, red and green respectively. Source: [2], Creative Commons CC-BY.
### 6.10.3 Supplement 6C

This supplement provides information on the criteria for grading the different types of toxicities.

**Table S6.2**: Toxicity grading system for clinician-assessed rectal bleeding, stool frequency, diarrhoea, completeness of evacuation, anorectal pain, urgency and tenesmus, and CTC proctitis (Note: the table continues on the next page). Source: [2], Creative Commons CC-BY.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>Never</td>
<td>Occult</td>
<td>&gt; 2/week</td>
<td>Daily</td>
<td>Gross haemorrhaging</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>&lt; 2/day</td>
<td>2-4/day</td>
<td>5-8/day</td>
<td>&gt; 8/day</td>
<td>Uncontrolled diarrhoea</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>None</td>
<td>Increase &lt; 4</td>
<td>Increase of 4-6</td>
<td>Increase of ≥ 7</td>
<td>Physiologic consequences requiring intensive care; parenteral support haemodynamic collapse</td>
</tr>
<tr>
<td>Completeness of evacuation</td>
<td>Complete</td>
<td>Occasional multiple evacuations (“about once a week feel like you’re not ‘all done’ completely empty bowel or feel you’re all done”)</td>
<td>Frequent multiple evacuations (“more than once a week feel like you’re not ‘all done’ or it takes more than one movement to finish”)</td>
<td>Requires enema to obtain complete emptying</td>
<td>–</td>
</tr>
</tbody>
</table>

380
<table>
<thead>
<tr>
<th>Anorectal pain</th>
<th>Never</th>
<th>Occasional and mild</th>
<th>Intermittent and tolerable</th>
<th>Persistent and intense</th>
<th>Refractory and excruciating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency and tenesmus</td>
<td>Never</td>
<td>Occasional</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Refractory</td>
</tr>
<tr>
<td>CTC proctitis</td>
<td>None</td>
<td>Increased stool frequency, occasional blood-streaked stools or rectal discomfort not requiring medication</td>
<td>Increased stool frequency, bleeding mucous discharge or rectal discomfort requiring medication, anal fissure</td>
<td>Increased stool frequency/diarrhoea requiring parenteral support, rectal bleeding requiring transfusion, or persistent mucous discharge necessitating pads</td>
<td>Perforation, bleeding or necrosis or other life threatening complication requiring surgical intervention</td>
</tr>
</tbody>
</table>
6.10.4 Supplement 6D

This supplement provides an example of the visual check on registration alignment.

Figure S6.3: Use of the spyglass box tool in Velocity Advanced Imaging to check the anatomical alignment between images. The EBRT images are in the background. Regions of the HDR-BT images after a rigid plus multi-pass deformable image registration are contained within the yellow outlined rectangular spyglass box. This box can be resized and moved around (e.g. left image versus right image). The EBRT clinical target volume, planning target volume and rectal structures are in purple, red and green respectively. Source: [2], Creative Commons CC-BY.
This supplement provides an example of the process for obtaining a dose-surface map and a subsequent thresholded dose-surface map.

**Figure S6.4:** The process for constructing a 2D dose-surface map from a 3D surface dose. For each superior-inferior slice the contour is cut at the longitudinal component of the centroid and then the contour is unfolded. The same process is repeated for the other superior-inferior slice levels and the unfolder contours are stacked. The resulting 2D map is normalised in the superior-inferior direction by the length of the rectum and in the axial directions by posterior point from the longitudinal component of the centroid. The surface dose at the normalised points is then interpolated from the planned dose. The result is a 2D dose-surface map with the colourwash indicating surface dose.
Figure S6.5: Example of an ellipse fit on a dose-surface map thresholded at 57 Gy. Dose-surface maps voxels with doses of at least 57 Gy become 1-value pixels in the thresholded dose-surface maps. The 1-valued pixels are coloured in black and form a cluster. The ellipse outline is coloured in blue and the major/minor axes are coloured in red.
6.10.6 Supplement 6F

This supplement provides the toxicity and no toxicity group DSMs for diarrhoea, anorectal pain, proctitis and urgency/tenesmus.

![Median dose-surface maps for groups of patients assigned as having and not having a diarrhoea, anorectal pain, proctitis and urgency/tenesmus event. The peak late toxicities for diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1 whereas rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2. The green lines identify isodose contours. Abbreviations: E\(\text{QD}2\) Gy, equivalent dose in 2-Gy fractions using \(\alpha/\beta = 3\) Gy; S, superior; I, inferior; P, posterior; L, left; A, anterior; R, right.](image)

**Figure S6.6:** Median dose-surface maps for groups of patients assigned as having and not having a diarrhoea, anorectal pain, proctitis and urgency/tenesmus event. The peak late toxicities for diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1 whereas rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2. The green lines identify isodose contours. Abbreviations: E\(\text{QD}2\) Gy, equivalent dose in 2-Gy fractions using \(\alpha/\beta = 3\) Gy; S, superior; I, inferior; P, posterior; L, left; A, anterior; R, right.
6.10.7 Supplement 6G

This supplement provides the odds ratios for measures calculated on dose-surface maps thresholded at various dose levels.

Figure S6.7: Odds ratios for measures calculated on dose-surface maps thresholded at various dose levels with patients assessed according to rectal bleeding, stool frequency and completeness of evacuation symptoms. The odds ratio is the increase in toxicity probability per 1 unit increase in the value of the DSM feature. Only those odds ratios where the bootstrapped p-values from logistic regressions are less than 0.2 are displayed. The peak late toxicities for rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2 whereas diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1. Abbreviations: EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy.
Figure S6.8: Odds ratios for measures calculated on dose-surface maps thresholded at various dose levels with patients assessed according to diarrhoea, anorectal pain, proctitis and urgency/tenesmus symptoms. The odds ratio is the increase in toxicity probability per 1 unit increase in the value of the DSM feature. Only those odds ratios where the bootstrapped p-values from logistic regressions are less than 0.2 are displayed. The peak late toxicities for diarrhoea, anorectal pain, proctitis and urgency/tenesmus were dichotomised at grade 1 whereas rectal bleeding, stool frequency and completeness of evacuation were dichotomised at grade 2. Abbreviations: EQD2 Gy, equivalent dose in 2-Gy fractions using $\alpha/\beta = 3$ Gy.
6.11 References


Chapter 7:
General discussion
7.1 Foreword for discussion

The studies described in the previous chapters include improvements on previously published studies [1–3]. Prior to the studies in this thesis, the rectal dose for combined external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) prostate cancer treatment had been accumulated without applying deformable registration [1, 2]. One of the main improvements in this thesis is the application of deformable registration as recommended by Kikuchi et al. [3]. Additionally, the studies contain novel analyses such as distribution-adding versus parameter-adding for combined prostate EBRT/HDR-BT and correlating dose-surface maps for combined prostate EBRT/HDR-BT with various types of late gastrointestinal complications. The main findings of previous chapters are compared and discussed in this chapter with a view towards future research directions. It is acknowledged that the studies in this thesis are subject to confounding factors and their relevance is discussed, which leads to recommendations.
7.2 Quality control of registrations

In Chapter 2, the deformable registration of high-dose-rate brachytherapy (HDR-BT) and external beam radiotherapy (EBRT) planning CTs was evaluated using structure-correspondence metrics, image-similarity metrics, displacement-vector-field metrics and visual assessments [4–9]. A key finding was that the use of a single structure-correspondence metric (e.g. an overlap statistic such as the Dice similarity coefficient) can be misleading as visual assessments were also important. Consequently, registrations were checked before being included in the studies described in other chapters of this thesis. The importance of visual assessments for evaluating deformable registrations is well known and forms the basis for approving the clinical use of deformed images [6, 10].

The registration evaluations in Chapter 2 determined that the B-splines deformable registration algorithm in Velocity Advanced Imaging was the best of the available registration algorithms for registering the rectums in EBRT and HDR-BT CTs. However, alternatives do exist as there has been a focus on developing additional registration algorithms for radiotherapy [4, 8, 11–19]. Consequently, the types of algorithms and settings for registering the rectum are expansive and it is expected that such developments will continue to improve the reliability and accuracy of deformable registration applied to EBRT and HDR-BT CTs. The continuing development of customised and new algorithms will also be associated with existing and new methods for evaluating such algorithms [4–8, 14, 20–29]. The challenge for clinicians and medical physicists is keeping an up-to-date knowledge of what software and algorithms are most appropriate for certain registration applications and image characteristics as well as appropriate methods for quality control. With increased clinical implementation the quality control of the registration process is expected to become risk-assessment orientated in accordance with the risk control process that has been applied for the safe delivery of radiotherapy [30]. Future considerations of such risks will be influenced by a future report from Task Group Number 132 of the American Association of Physicists in Medicine (AAPM), which was formed to investigate and provide recommendations on clinical validation and quality assurance of image registration.
7.3 Options for accumulating rectal dose

There are risks associated with using deformable registration to accumulate rectal dose as the registrations may be inaccurate. One way of considering such risks is to compare the accumulated rectal dose obtained using deformable registration with the dose obtained using alternative methods which do not require deformable registration [28, 31–36]. Chapter 3 provided such an evaluation for combined prostate EBRT/HDR-BT by comparing rectal dose after registration-based distribution-adding with rectal dose after parameter-adding of dose-volume histograms (DVH). The key finding from Chapter 3 was that it is possible for registration-based distribution-adding to provide greater rectal high-dose metrics than DVH-based parameter-adding if there are contouring, registration and inter/intra-fraction motion uncertainties near the anterior rectal wall. Across the sample of patients the differences were small for the $D_{20\%}$; however, in some patients the differences were large enough to warrant clinical consideration.

Some studies on registration-based distribution-adding for gynaecological cancer treatments have also reported results where conservative rectal dose estimates were provided by registration-based distribution-adding in the presence of inter-fraction motion, contouring inconsistencies or inhomogeneous dose distributions [31, 36]. The finding in this thesis highlights the importance of inter/intra-observer contouring consistency and accurate deformable registrations in regions of an organ at risk where dose gradients are high. Assessing such discrepancies in accumulated rectal dose for realistic applications of the two methods to combined EBRT/HDR-BT is important. However, the ultimate consideration of discrepancies between the methods for accumulating rectal dose in the context of dose-response modelling in subsequent chapters of this thesis was whether the methods identify the same dose regions as important for complications.

7.4 Dose-volume analysis

The study in Chapter 4 correlated DVH parameters after parameter-adding and distribution-adding with late gastrointestinal complications. It was found that the mid-high dose range and near-maximum doses were important for rectal bleeding
while the distribution-adding mid-high dose range was important for stool frequency and urgency/tenesmus. The finding for the importance of near-maximum doses after registration was important as a previous study without registration did not find any significance for near-maximum doses [1] and the GEC/ESTRO recommendation is to limit the $D_{2cc}$ to 75 Gy [37]. Additionally, urgency/tenesmus was also associated with distribution-adding doses at the lower end of the mid-dose range and this finding was consistent with the finding from another study where the violation of the $V_{40Gy}$ dose constraint was important for urgency [38]. Overall, the dose regions identified as important using distribution-adding were in most cases consistent with those identified as important using parameter-adding.

To obtain additional dose-response information the study in Chapter 5 applied the Lyman-Kutcher-Burman model of normal tissue complication probability [39–43] using doses obtained by distribution-adding. Application of the Lyman-Kutcher-Burman model confirmed the earlier findings that rectal bleeding was influenced by high doses and that non-bleeding toxicities were influenced less by high doses than rectal bleeding. The parameter values obtained for the Lyman-Kutcher-Burman model were in most cases consistent with values reported for other studies [43–50]. The notable exception was the slope of the dose-response curve, which was consistently smaller than as found in other studies [43–50]. Contributing factors for the flatter or more blurred dose-response relationship for this study include the treatment quality at centres improving with the escalation of prescription dose [51] and the added uncertainty associated with inter/intra-fraction motions, registrations and contouring for combined EBRT/HDR-BT.

The analysis for the Lyman-Kutcher-Burman model also included an estimation of the appropriate alpha-beta ratio for dose fractionation correction via the linear-quadratic model [52, 53]. The optimum alpha-beta ratio for late rectal bleeding was determined to be 3.1 Gy for patients receiving combined prostate EBRT/HDR-BT. This finding for the optimum alpha-beta ratio agrees with the value of 3 Gy used by other published studies [44, 45, 54]. However, inclusion of the dose fractionation correction via the alpha-beta ratio from the linear-quadratic model only significantly improved the fit of the Lyman-Kutcher-Burman model for late urgency/tenesmus symptoms. Other studies have also found that a dose fractionation correction is not
useful for improving the model [45, 55]. The analysis based on DVH parameters and the Lyman-Kutcher-Burman model was useful for obtaining information on the importance of dose regions for gastrointestinal complications; however, the limitation is that it is not possible to obtain information on the importance of the shape of dose regions from such methods.

7.5 Spatial information from the dose distribution

The study in Chapter 6 investigated the arrangement of dose across the rectum as an additional influence on gastrointestinal complications. The dose-surface map analysis found that the intermediate-high dose range and near-maximum doses were important for rectal bleeding. This finding is consistent with findings from analyses of DVH parameters and the Lyman-Kutcher-Burman model as well as other published studies [56–59]. Other dose regions also influence late gastrointestinal complications as the dose-surface map analysis indicated that the high-dose range was also important for stool frequency, diarrhoea and urgency/tenesmus.

The results for spatial analysis indicated that the shape of isodoses and dose coverage also influence late gastrointestinal complications. Rectal bleeding, stool frequency, diarrhoea and urgency/tenesmus were associated with greater lateral and/or longitudinal spread of the high doses near the anterior rectal surface. The importance of the lateral spread of high doses for rectal bleeding confirms the findings of the study by Buettner et al. [60]. The spatial analysis also found that greater low-intermediate doses to the last (inferior) 20%, superior 20% and inferior 20% of rectal length were associated with rectal bleeding, anorectal pain and urgency/tenesmus respectively. The importance of inferior parts of the rectum for urgency/tenesmus is consistent with another study where dose to the inferior rectum was found to be indicative of effects on pelvic floor muscles with consequent control-like toxicity effects [61]. Diarrhoea, completeness of evacuation and proctitis were also related to greater low doses to the posterior side of the rectum. The findings above indicate that constraints on the intermediate-high doses as well as doses to the superior/inferior ends of the rectum may be important for reducing gastrointestinal toxicities.

In Chapter 6, a number of spatial features for clusters formed by thresholding dose-surface maps at mid-high dose levels were confirmed or revealed as important
for gastrointestinal toxicities. The spatial features for clusters of intermediate-high dose regions, such as area, perimeter, compactness, circularity, eccentricity of ellipse fits and confinement to ellipse fits, were strongly associated with toxicities other than anorectal pain. For rectal bleeding, the areas of the 49-59 Gy isodoses and the perimeter of the 56 Gy isodose were important. Additionally, the compactness and circularity of the 38-47 Gy isodoses and the confinement of 38-40 Gy doses to ellipse fits were strongly associated with bleeding. The findings of more compact, circular and confined intermediate isodoses correlating with bleeding events support the suggestion in another study that cell migration from the low-dose region could aid healing of the vascular sclerosis in high-dose regions [62]. The findings above and the additional findings detailed in Chapter 6 reveal specific regions and spatial characteristics for each toxicity that may be useful for dose optimisation. We acknowledge that this study is the first to report findings on dose-surface maps for HDR-BT registered to EBRT and is subject to confounding factors which are discussed below. Consequently, we encourage other studies from a variety of registration contexts to report on important spatial aspects of accumulated dose distributions for combined EBRT/HDR-BT.

### 7.6 Confounding factors

The studies in this thesis were in general confounded by contouring uncertainties [63, 64], registration uncertainties [4, 8] and intra/inter-fraction motion [65–68]. The uncertainties associated with contouring and registration can not be completely removed, even for strict study protocols, due to difficulties in establishing ground truth for patient images. In the presence of such uncertainties the dose regions indicated as being important for toxicity after distribution-adding were in most cases still consistent with those indicated as important after parameter-adding. However, the proximity of the HDR-BT rectum to the HDR-BT catheters makes parameters and dose regions obtained by registration and distribution-adding sensitive to small localised variations in contouring and/or registration accuracy across the prostate/rectum interface.

In addition to contouring and registration uncertainties, the treatments were subject to inter-fraction motion [65–68]. Consequently, institutions are increasingly
using repeat imaging over the course of treatment to improve the correspondence between planned dose and delivered dose [67, 69]. However, the data for the studies in this thesis do not contain repeat imaging due to the retrospective nature of the analysis, where long follow-up is required to correlate dose with late toxicities, and the subsequent treatment protocol that was in existence at the time of the trial. Given these limitations, studies have previously identified rectal motion and variable rectal contents as confounding factors for the accuracy of rectal dose distributions obtained from single static planning CTs [66, 70, 71]. The discussion in Chapter 4 included estimates from published studies for the influence of intra/inter-fraction motion on doses. A published study applying the same registration software and registration algorithm as used in this thesis was identified [66]. The identified study reported that estimates of the $D_{2\%}$ and equivalent uniform dose for EBRT using a single CT were larger than registration-based estimates by 3.9% and 5.8% respectively [66]. With respect to the brachytherapy phase, studies have identified inter-fraction movement of the anterior rectal wall relative to the prostate as important [68, 72]. As described in Chapter 4, a study with larger mean caudal catheter displacements than those for patients in this thesis indicated that displacements were associated with mostly systematic increases to the $D_{2\text{cc}}$ of 0.69 Gy ($\approx 6.6\%$) and 0.76 Gy ($\approx 7.2\%$) for fractions 2 and 3 respectively [68]. However, the displacement of catheters for patients included in this thesis were checked prior to each of the three fractions using an anterior-posterior radiograph and corrected for using a rigid external holding device as described by Tiong et al. [73]. Consequently, the earlier estimates for the impact of catheter displacements are expected to be conservative.

It is possible that the above mentioned confounding factors could remove significance found in the various analyses. Such influences are likely to be more important when proposing dose constraints as they could systematically shift dose regions. Consequently, for the method accumulating dose using deformable registration it would be important to investigate dose-volume constraints and/or spatial-based constraints for a variety of registration, contouring and treatment contexts. It is also possible to pursue other avenues in future research, as described below.
7.7 Future directions

7.7.1 Validation studies

This is the first reported study to apply deformable registration prior to correlating rectal dose from combined prostate EBRT/HDR-BT with toxicity. Consequently, it is important that the findings in this thesis be validated in the context of other registration algorithms, registration circumstances, contouring applications and treatment techniques with standardised contouring, implanting and planning guidelines for EBRT and HDR-BT. Such validations could also include larger sample sizes which would allow a consideration of models that incorporate multiple toxicity events over the follow-up period [74] or include the persistence of toxicity rather than peak late toxicity [75]. An increased sample size and external validation would also allow robust analysis of whether constraints based on a variety of dose-response models, which include spatial information and DVH parameters, provide improved predictive capability [2, 44, 60, 76–84]. Another benefit of validation and larger sample size is the context it would provide for findings in this thesis in terms of the trial specific toxicity event rates and the potential of random discovery.

7.7.2 Alternative registrations and toxicity modelling

Given the developments that have occurred over the duration of the studies in this thesis, it would be useful to explore a variety of registration algorithms that have been developed for different uses [4, 8, 11–19]. Registration algorithms that may improve the alignment of the EBRT/HDR-BT CTs include those that include a penalty term for minimising the volume of missing information [13], methods that exclude rectal discrepancies [12, 15] and methods with contour guidance [11, 19]. Additionally, it would be beneficial, in those programs that allow it, to investigate the optimum settings for registering HDR-BT CTs to EBRT CTs, e.g. customise DIRART to use other image-similarity metrics [85]. The different registration algorithms and settings would have to be evaluated. Such evaluations for patient images are difficult as there is no direct measure of registration error and a variety of methods have been proposed [4–8, 20, 21, 25–29]. Additionally, the information from other evaluation methods such as landmarks, phantoms and deformed dose
uncertainty [14, 22–24, 86] may be useful.

An alternative to registering the HDR-BT CT to the EBRT CT for each patient is to register all CTs to a common template [87]. The potential benefit of such registrations is the ability to undertake dose-response modelling in a common rectal structure with a potentially increased power to resolve spatial differences [87]. Additionally, the incidence of toxicity may be further explained by associations between toxicity and doses to organs other than the rectum (e.g. doses to the bowel and gastrointestinal tract could be associated with toxicity [76, 83]). A project is currently being undertaken at the University of Western Australia to register CTs to a common template and to explore the correlation between dose in other anatomy and late complications.

It is also possible to include clinical factors when correlating dose metrics with late complications [50, 83, 84, 88, 89]. The predictive capability of such models may be improved by using advanced methods including machine learning type methods [90, 91].

7.7.3 Additional imaging

An alternative to using more recent registration algorithms is to improve the quality of registrations by acquiring images immediately prior to the HDR-BT insertion of needles, as this may allow changes over the preceding weeks to be separated from changes due to HDR-BT needles, tissue oedema and treatment positioning. Additionally, image-guided radiotherapy or further imaging during the EBRT and HDR-BT phases may allow better management of inter-fraction motion and improve the reliability of accumulated dose-histogram metrics [44, 83, 84, 92, 93] and dose-surface maps [2, 60, 76–80, 94, 95].

7.7.4 Treatment planning

The HDR-BT plans for patients included in this thesis were planned using the AAPM TG43 algorithm [96]. However, more advanced dose calculation algorithms have been developed and implemented for HDR-BT and EBRT planning, which has included model-based and Monte Carlo type dosimetry algorithms [97, 98]. It would be useful to assess the variations in accumulated rectal doses for the different
dosimetry algorithms. A project is currently being undertaken at the University of Western Australia to assess differences between planned doses for the Acuros model-based dosimetry algorithm [97] and the TG43 formalism [96].

7.7.5 Accumulating prostate and urethra doses

Another difficult application of deformable registration is to register the urethra, bladder, prostate and seminal vesicles in the EBRT and HDR-BT CTs as it would require dealing with considerable image issues (e.g. HDR-BT needles in the prostate and the urethra catheter balloon in the bladder). Advances in deformable registrations for such areas are important as accumulated doses for the urethra and prostate are important considerations in the RADAR trial [51, 99–101]. Registrations of the prostate may be easier for data from treatments which used plastic HDR-BT catheters.

7.8 References


268


Chapter 8:
General conclusion
8.1 Foreword for conclusion

The general aim for the thesis was to model how the distribution of dose to the rectum from combined prostate external beam radiotherapy/high-dose-rate brachytherapy relates to observed late gastrointestinal complications. The findings in previous chapters indicate the general aim has been achieved. This final chapter provides last remarks on the main findings of all studies in this thesis.
8.2 Important findings

Dose-response modelling is difficult for combined prostate external beam radiotherapy (EBRT)/high-dose-rate brachytherapy (HDR-BT) as separate treatment plans for each phase of the combined treatment have to be accumulated. The previous sections of this thesis provided findings for the first reported application of deformable registration to accumulate the rectal dose for combined prostate EBRT/HDR-BT. The findings from the three stages for associating rectal dose with observed gastrointestinal toxicities are summarised below.

8.2.1 Stage 1: Advanced methods to accumulate the planned dose for EBRT followed by HDR-BT

The aim of the first study in the thesis was to comparatively evaluate deformable registration methods that were available to our research group for registering the rectums in EBRT and HDR-BT CTs of prostate cancer patients. The analysis in the first study confirmed that structure correspondence, image similarity and visual assessments are useful tools for evaluating registrations. The application of such tools resulted in successful achievement of the aim of the study as the deformable registration methods in Velocity Advanced Imaging were found to provided optimum registrations for the rectum. It was recommended that a single structure-correspondence metric should not be used as a sole indicator of rectal alignment as other metrics and visual assessments provided contrasting information. Additionally, the use of image-similarity and displacement-vector-field metrics should be confined to a restricted region covering the organ of interest rather than calculated globally. It was acknowledge that accumulating the rectal dose is only one aspect as an important future application of registrations for combined prostate EBRT/HDR-BT would include accumulating the prostate and urethra dose as such doses are key clinical concerns in the RADAR trial.

This thesis also explored an alternative method to deformable registrations for accumulating the rectal dose. That is, the aim of the second study was to compare rectal doses for deformable registration followed by 3D-summation (distribution-adding) with those from simple addition of dose-volume histogram (DVH) param-
eters (parameter-adding). This aim was successfully achieved as it was determined that parameter-based addition resulted in smaller (larger) median $D_{0.1cc}$, $D_{1cc}$ and $D_{2cc}$ ($D_{10cc}$) values compared to distribution-based addition. Additionally, for patients with the greatest 25% of differences, the method for obtaining the $D_{0.1cc}$, $D_{1cc}$ and $D_{2cc}$ warrants clinical consideration. However, comparisons of the accumulation methods were confounded by heterogeneously distributed high-dose, inter/intra-observer rectal contouring errors, inter/intra-fraction motions and registration accuracy around the anterior rectal wall. Given such differences and confounding factors, it is important to compare how doses from both methods correlate with gastrointestinal toxicities.

8.2.2 Stage 2: Associating dose-volume metrics from planned dose with symptoms

The aim of the third study was to correlate the rectal DVH after deformable registration with gastrointestinal toxicities observed after combined EBRT/HDR-BT. The findings of the third study went beyond the aim as the rectal doses from both distribution-adding and parameter-adding were correlated with late gastrointestinal toxicities. A number of significant dose-histogram effects were revealed for gastrointestinal toxicities after rectal dose was obtained via distribution-adding. The findings for distribution-adding were also in most cases consistent with those for parameter-adding. For rectal bleeding, the mid-high dose range and near-maximum doses were important. For stool frequency and urgency/tenesmus, the distribution-adding mid-high dose range was important. The results are influenced by inter-fraction motion, contouring uncertainties and registration accuracy. Consequently, it is important for findings to be verified by other studies using similar dose-histogram analysis and other methods that may provide additional information.

The Lyman-Kutcher-Burman (LKB) model of normal tissue complication probability (NTCP) is one alternative to directly correlating DVH parameters with toxicities. Consequently, the aim of the fourth study was to obtain estimates of the LKB NTCP fitting parameters for various types of gastrointestinal complications observed after combined EBRT/HDR-BT or EBRT only in Australian and New Zealand populations. The aim was achieved as the $m$, $n$ and $TD50$ parameters
for the LKB NTCP model were obtained with and without adjustments for dose fractionation. The parameter values varied across the various late gastrointestinal toxicities. Consistent with the previous DVH-based analysis, rectal bleeding was influenced by high doses. Additionally, rectal bleeding demonstrated a late response with an optimal alpha-beta ratio of 3.1 Gy. Non-bleeding toxicities were influenced less by high doses than rectal bleeding. Additionally, the \( n \) and \( TD_{50} \) estimates from other studies were consistent with most of the values in this thesis. However, the slope of the dose-response curve \( (1/m) \) for some published studies was smaller than the values in this thesis. One limitation of the above findings for DVH-based analysis and LKB NTCP modelling is that more complete methods should include spatial information on the dose distribution.

### 8.2.3 Stage 3: Using novel methods to relate spatial features of dose distributions to symptoms

The influence of the arrangement of dose across the rectum is an additional factor for gastrointestinal complications. Consequently, this thesis explored a number of novel ways of characterising the shapes of rectal dose-surface maps after applying deformable registration as the aim of the fifth study was to relate regional (voxel-wise) features of dose-surface maps and parameterised spatial patterns to gastrointestinal complications observed after combined prostate EBRT/HDR-BT. Consistent with the DVH-based analysis and LKB NTCP modelling, such analysis confirmed the intermediate-high dose range and near maximum doses were important for rectal bleeding. The high-dose range was also important for stool frequency, diarrhoea and urgency/tenesmus. Spatial analysis revealed that greater low-intermediate doses to the last (inferior) 20%, superior 20% and inferior 20% of rectal length were associated with rectal bleeding, anorectal pain and urgency/tenesmus respectively. Additionally, a number of spatial features for clusters formed by thresholding dose-surface maps at mid-high dose levels were confirmed or revealed as important for gastrointestinal toxicities (e.g. cluster area, perimeter, compactness, circularity, eccentricity of ellipse fits of clusters and confinement of clusters to the ellipse fits). Consequently, the aim of the fifth study and the general aim of the thesis were completed.

As a last remark, we encourage other studies from a variety of registration
contexts to report DVH-based and spatial-based analysis on accumulated dose distributions for combined EBRT/HDR-BT as this thesis details the first findings for prostate HDR-BT registered to prostate EBRT.

THE END